

Bacteriophage Therapy and Current Delivery Strategies for Orthopedic Infections

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INTRODUCTION: Interest in phage therapy as an adjunctive form of infection control has grown in the last decade. However, one challenge to the therapeutic development of bacteriophages as a form of antibiosis is the ongoing uncertainty regarding optimal modes of phage delivery, optimal phage combinations and titrations, and the pharmacokinetics and pharmacodynamics of phages *in vivo*. Consequently, we conducted a SCOPING review to assess the current state of phage delivery technology and techniques to allow for a clearer assessment of ongoing knowledge gaps in bacteriophage therapeutic delivery.

METHODS: Following PRISMA-ScR guidelines, we conducted a SCOPING review through September 1st, 2023, of MEDLINE, Embase, Web of Science Core Collection, and Cochrane Central. We included all clinical and translational peer-reviewed *in vitro* or *in vivo* studies in humans or animal models presenting original data of phages or phage derivatives for treating orthopedic infections. Articles were subsequently evaluated via full-text review by two independent reviewers, and data from included articles were collected in a standardized data extraction tool.

RESULTS SECTION: In total, 77 studies were included, of which 19 (24.7%) were *in vitro* studies, 17 (22.1%) were animal studies, and 41 (53.2%) were studies in humans. Of human studies, a total of 246 patients were reported. The most studied bacterial organism was *Staphylococcus aureus* (48 studies), followed by *Enterococcus faecalis* (9 studies) and *Klebsiella pneumoniae* (8 studies). Studies most frequently involved researchers from the United States (33 studies), followed by France (12 studies) and Germany (11 studies).

DISCUSSION: Direct phage delivery remains the most studied form of phage therapy for orthopedic infections, most notably in prosthetic joint infections, osteomyelitis, and diabetic foot ulcers. Phages have been delivered in various ways, including intravenously, intraarticularly, topically, and orally, though phage pharmacokinetics, standardized regimens, and optimal dosing remain unknown. Phages are well tolerated, though they have been implicated in asymptomatic liver enzyme elevations in some cases, and are known to induce anti-phage antibody formation, though the clinical implications of this immune response are unknown. Phages are highly selective, and phage cocktails may help to broaden the range of susceptible target bacteria. Phages may work synergistically with antibiotics for many phage-antibiotic combinations. Phage delivery devices have been described to provide sustained release, including biocompatible ceramics and various hydrogels. Several barriers to phage therapy success need further investigation, including their ability to target intracellular bacteria and ways of overcoming phage resistance in target bacteria. Finally, various phage derivatives, including modified phages and phage endolysins, have also been described, though there is a limited understanding of their efficacy and toxicity *in vivo*.

SIGNIFICANCE/CLINICAL RELEVANCE: Phage therapy is an emerging therapeutic for treating orthopedic infections, and many questions remain regarding optimal indications, dosing, and modes of delivery. Our review summarizes the current state of phage delivery strategies in orthopedics, thereby enabling future hypothesis generation to advance the development phages as a future therapeutic.