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Editorial: Bacteriophage therapy in orthopedics—Key questions and emerging answers

Filippo Migliorini[1,2,3*], Fabrizio Rivera[4] and Jörg Eschweiler[1,5]

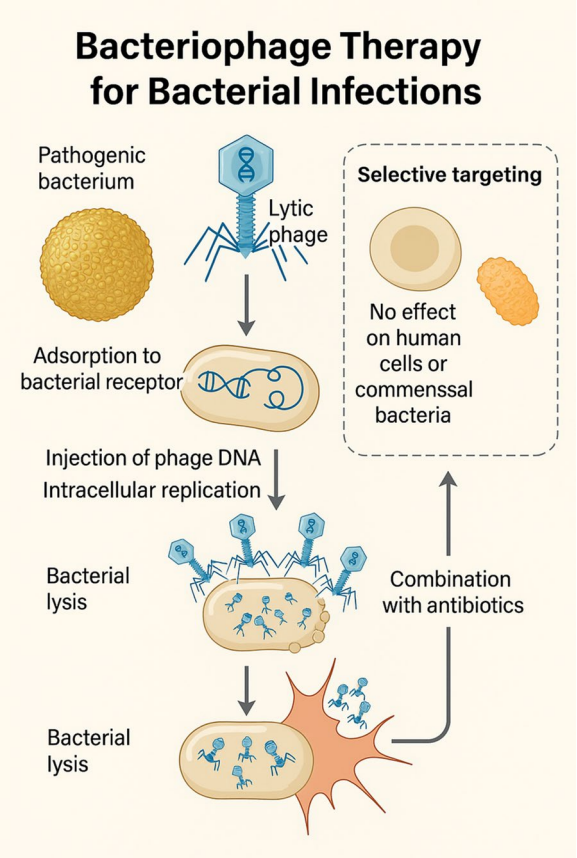
Abstract

Musculoskeletal infections remain among the most challenging conditions in orthopaedic practice, often requiring prolonged antibiotic therapy, repeated surgical interventions, and extensive rehabilitation. The emergence of antimicrobial resistance and the persistence of bacterial biofilms further complicate management, particularly in chronic osteomyelitis, infected fracture fixations, and periprosthetic joint infections. In this context, bacteriophage therapy has re-emerged as a promising adjunctive strategy. Bacteriophages offer targeted antibacterial activity, including the ability to disrupt biofilms and self-replicate at the site of infection. Contemporary approaches, such as phagograms, customised phage cocktails, and local delivery techniques, have addressed many historical limitations related to phage specificity and accessibility. A growing number of case reports and small clinical series have documented successful applications of phage therapy in orthopaedic infections, with encouraging safety profiles and infection resolution in refractory cases. Early-phase clinical trials are now systematically evaluating the feasibility, pharmacokinetics, and immunogenicity of phage therapy in musculoskeletal settings. Furthermore, synergistic effects with antibiotics and the potential to overcome biofilm-related antibiotic tolerance highlight the added therapeutic value of this approach. While regulatory and manufacturing challenges persist, the integration of bacteriophages into multidisciplinary orthopaedic care marks a paradigm shift toward precision microbiology. Rather than replacing conventional treatment, phage therapy complements surgery and antibiotics, offering a biologically rational and patient-specific adjunct in the fight against recalcitrant infections.

Keywords Infections, Bacteria, Virus, Musculoskeletal medicine, Trauma surgery, Orthopaedic surgery

*Correspondence:
Filippo Migliorini
filippo.migliorini@uk-halle.de
Full list of author information is available at the end of the article

Graphical Abstract



Introduction

Musculoskeletal infections continue to pose a challenge in clinical practice. Chronic osteomyelitis, infected fracture fixations, and periprosthetic joint infections often require multiple surgical procedures and prolonged antibiotic courses, yet outcomes are frequently unpredictable and recurrence is common [1, 2]. Difficulties extend beyond treatment alone, as non-specific clinical presentations and limitations of conventional microbiological techniques often hinder timely diagnosis [3, 4]. Prevention also remains problematic, since perioperative strategies and antibiotic prophylaxis have not eliminated the risk of infection in complex reconstructions [5, 6]. The global rise of antimicrobial resistance, combined with the intrinsic resilience of biofilms, further compromises treatment success. Against this backdrop, renewed interest in bacteriophage therapy has emerged as a potential strategy to improve outcomes through targeted, biologically adaptive mechanisms.

What are bacteriophages?

Bacteriophages, also known as phages, are viruses that selectively infect and lyse bacteria [7, 8]. Discovered before the antibiotic era, they were widely eclipsed once broad-spectrum antimicrobials became available. Phages replicate directly at the site of infection, amplifying their effect while exerting minimal systemic impact. Their capacity to degrade biofilm matrices is particularly relevant to orthopedic infections, where biofilms on implants and necrotic tissue constitute significant therapeutic barriers [9, 10]. Although their narrow host range was initially considered a limitation, modern approaches use phagograms and phage cocktails to expand coverage while minimizing collateral disruption to the microbiota. Local administration via intraoperative irrigation, phage-loaded spacers, or direct injection allows for optimized concentrations, whereas intravenous use remains mainly adjunctive [11].

Do phages replace or complement antibacterial strategies?

The potential interaction between phages and antibiotics remains an area of active investigation. Experimental studies and early clinical observations have suggested that phages may disrupt biofilms, thereby increasing bacterial susceptibility to antibiotics [12, 13]. Conversely, subinhibitory concentrations of antibiotics could, in some cases, facilitate phage penetration [14]. However, the consistency and clinical relevance of these findings are still uncertain, and it is not yet clear whether phages should be administered in isolation or systematically combined with antibiotics. Currently, phages cannot be regarded as substitutes for antibiotics or surgery; however, their potential role as complementary agents remains under exploration. Their use may represent a shift toward more individualized and ecology-based approaches to infection management, although robust evidence is still lacking.

Are there standards for phage production?

The standards for phage production and regulation remain far from established. Current approaches face multiple limitations, and it remains unclear how to ensure the best consistency, safety, and reproducibility across different preparations [15]. Issues such as quality control, regulatory classification, and host immune interactions remain insufficiently understood, and existing frameworks are only provisional [15, 16]. Further studies and collaborative efforts are necessary to refine the criteria and develop guidelines that support broader clinical translation. Immune responses to systemic phage delivery remain incompletely characterized, although local administration may reduce neutralization risks. These barriers underscore the importance of interdisciplinary collaboration among surgeons, microbiologists, and regulatory bodies in establishing practical guidelines.

What is the current clinical evidence?

Although robust trials are lacking, an increasing number of case reports and small series have described the use of bacteriophages in musculoskeletal infections. These reports include patients with periprosthetic joint infections and fracture-related infections who achieved infection control following local or combined systemic administration of phages, often in conjunction with antibiotics [17–19]. Intraoperative phage irrigation during implant retention procedures has also been associated with encouraging short-term outcomes [20]. While these experiences suggest feasibility and potential benefit in refractory cases, they remain preliminary, heterogeneous, and insufficient to draw firm conclusions.

What clinical trials are underway?

Translational momentum is now visible in Europe. The PHAGEFORCE and PHAGEinLYON programmes have implemented structured trial designs, including pharmacokinetics, biodistribution, and genomic surveillance of resistance [21]. A multicenter phase I/II trial investigating phage therapy in chronic osteomyelitis is currently recruiting, with a focus on safety, immunological response, and preliminary efficacy. In addition, several international initiatives and grant-supported projects are fostering collaborative networks and methodological development in phage research. Such efforts may help to harmonize protocols, refine regulatory pathways, and accelerate the generation of evidence that is currently still fragmentary.

What are the limitations?

Barriers to wider adoption remain substantial and multifaceted. Regulatory ambiguity continues to hinder the formal approval of phages as medicinal products, and there is no clear framework to accommodate their dynamic biological nature. Production logistics are challenging, particularly when individualized or rapidly adaptable preparations are required, and the scalability of manufacturing remains uncertain. The absence of well-designed randomized controlled trials limits the ability to conclude efficacy, durability of response, and optimal methods of administration. Concerns about the potential emergence of phage resistance add further complexity, while the lack of consensus guidelines leaves clinicians without structured recommendations. Access to phagogram testing is limited, and laboratory methods remain time-consuming and poorly standardized, restricting their routine use. Additionally, questions remain regarding pharmacokinetics, host immune interactions, long-term safety, and the reproducibility of clinical outcomes. Collectively, these limitations highlight the need for coordinated research, regulatory innovation, and the development of robust infrastructures before phage therapy can be integrated into standard orthopedic practice.

Can phages be standardized?

Unlike static chemical compounds, phages are dynamic biological entities whose behavior is shaped by multiple biological and environmental factors. Their pharmacokinetics and pharmacodynamics depend not only on bacterial density, immune status, and tissue environment, but also on the route of administration, local vascularity, and the presence of biofilm. Host immune responses, such as neutralizing antibodies or phagocytic clearance, may limit their persistence and effectiveness, and these interactions remain insufficiently characterized [22]. Although advances have been made in Good

Manufacturing Practice protocols, purification methods, and genomic characterization, achieving full reproducibility across different patients, batches, and clinical scenarios remains challenging. Variability in phage–bacteria interactions further complicates standardization, as even closely related bacterial strains may display markedly different susceptibilities. For these reasons, conventional regulatory frameworks designed for static drugs may not be adequate, and novel approaches will be required to accommodate the intrinsic variability and adaptive nature of phage-based therapies [15].

Is there a test to verify the effectiveness of phages?

Phagograms, similar to antibiograms, are currently the primary tool for assessing bacterial susceptibility to specific phages. They are generally performed through plaque assays on agar plates, in which zones of lysis indicate activity against a given bacterial strain. Variations of this method include spot tests, efficiency of plating assays, and microtiter-based formats, each with different levels of sensitivity and reproducibility. While procedures such as those pioneered at specialized institutes offer practical models, no international consensus exists on how phagograms should be standardized, interpreted, or integrated into clinical workflows [23]. Unlike antibiograms, clinical breakpoints for defining susceptibility and resistance to phages have not been established, and results are often highly strain specific. The process itself is labor intensive, time consuming, and requires specialized expertise, which limits its availability in routine microbiology laboratories [24]. Rapid molecular approaches and high-throughput systems are under exploration, but they remain experimental. Until more reliable, reproducible, and scalable methods are developed, the lack of a standardized phagogram remains a significant obstacle to the broader clinical implementation of phage therapy.

Which musculoskeletal infections are most relevant?

Most reported applications of phage therapy in orthopedics have focused on chronic osteomyelitis and periprosthetic joint infections. These conditions are notoriously difficult to eradicate because of persistent biofilms, compromised vascularity, and the presence of multidrug-resistant organisms, all of which diminish the efficacy of conventional antibiotics. Chronic osteomyelitis often requires repeated debridements and long-term antibiotic suppression [25]. At the same time, periprosthetic joint infections remain one of the leading causes of revision surgery in joint arthroplasty, with substantial morbidity and healthcare costs [1, 26]. These features make them particularly attractive targets for phage-mediated biofilm disruption and local bacterial lysis. Preliminary reports have also explored phage therapy in fracture-related infections, septic nonunions, and implant-associated infections outside the hip and knee, such as the shoulder and spine [21]. However, the total number of patients treated worldwide remains very limited, and the available evidence is based mainly on heterogeneous case reports and small series. No specific subtype of musculoskeletal infection has yet reached the level of evidence required for formal recommendation, and broader applications, including acute infections and early postoperative cases, still require rigorous validation in controlled clinical trials.

Conclusions

Bacteriophage therapy is increasingly regarded as a potential adjunct in the treatment of musculoskeletal infections, yet its role remains far from defined. Compassionate-use experiences provide early reassurance regarding feasibility and safety, but they remain anecdotal and heterogeneous. No randomized controlled trial has yet demonstrated reproducible clinical benefit, and questions persist regarding pharmacokinetics, host–pathogen interactions, and long-term outcomes. Ongoing studies will begin to address these gaps, but larger international collaborations, harmonized regulatory frameworks, and standardized diagnostic tools are still urgently needed. For now, phages should be considered an experimental but biologically promising tool. Their future integration into orthopedic practice will depend on whether current research efforts can transform preliminary signals into reliable, evidence-based protocols. In the era of antimicrobial resistance, the challenge is not only to explore phages as a novel therapy, but also to determine whether they can truly reshape the principles of infection management in orthopedics.

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Author details
[1]Department of Trauma and Reconstructive Surgery, University Hospital of Halle, Martin-Luther University Halle-Wittenberg, Ernst-Grube-Street 40, 06097 Halle (Saale), Germany. [2]Department of Orthopaedic and Trauma Surgery, Academic Hospital of Bolzano (SABES-ASDAA), via Lorenz Böhler 5, 39100 Bolzano, Italy. [3]Department of Life Sciences, Health, and Health Professions, Link Campus University, via del Casale di San Pio V, 00165 Rome, Italy. [4]Department of Orthopaedics and Traumatology, Ospedale SS Annunziata, ASL CN1, Via Ospedali, 9, 12038 Savigliano, Italy. [5]Department of Trauma and Reconstructive Surgery, BG Klinikum Bergmannstrost Halle, 06112 Halle (Saale), Germany.

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