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Bacteriophage therapy in infection after fracture fixation (IAFF) in orthopaedic surgery

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ABSTRACT

Infection after fracture fixation (IAFF) in orthopaedic surgery is a significant complication that can lead to disability due to chronic infection and/or relapsing disease, non-union necessitating revision surgery. Management of IAFF is a major challenge facing orthopaedic surgeons across the world due to two key pathogenic mechanisms of Biofilm formation and antimicrobial resistance (AMR) against traditional antibiotics. Advanced prophylactic and treatment strategies to help eradicate established infections and prevent the development of such infections are necessary. Bacteriophage therapy represents an innovative modality to treat IAFF due to multi-drug resistant organisms. We assess the current role and potential therapeutic applications of the novel bacteriophage therapy in the management of these recalcitrant infections to achieve a successful outcome.

1. Introduction

Infection after fracture fixation (IAFF) in orthopedics is a well-known complication after trauma surgery with a quoted incidence of 1%–2% after closed fractures and reaching up to 30% in open fractures.[1,2] The real incidence of IAFF is probably misjudged due to a lack of precise definition and universally accepted classification. Metsemakers et al. classified IAFF into early (less than 2 weeks), delayed (between 2 and 10 weeks), and late (more than 10 weeks) infections based on the formation and maturation of biofilm and the severity of invasion of pathogens into bone and soft tissues.[2] Implant-associated infection is predominantly due to surface-adhering bacteria that form biofilms and the emergence of antimicrobial resistance (AMR) against conventional antibiotics.[3] Though the reasons for antibiotic resistance are complex such as inappropriate use of antibiotics in the management of infections, failure to eradicate IAFF can lead to non-union, osteomyelitis, loss of function, and increased socio-economic burden.[1] Biofilm formation makes eradication of infection difficult owing to inherent endurance to host defense mechanisms and AMR resulting from biofilm embedded bacterial organisms which also propagate resistance due to altered cell signaling systems such as 'Quorum sensing'.[4] Gram-positive organisms such as *Staphylococcus aureus (20%–30%), coagulase-negative staphylococci (CoNS) (18%–40%), Streptococci (1%–10%), and Enterococci (3%–7%)* are commonly encountered organisms after fracture fixation. However, increasingly Gram-negative bacilli, including *Pseudomonas aeruginosa, Enterobacteriaceae, Acinetobacter, Klebsiella, and Propionibacterium acnes* species have been associated with IAFF and orthopaedic device-related infection (ODRI) with issues of significant AMR.[5] Consequently, to combat this AMR crisis, a few innovative and targeted therapies like nanomedicine, bacteriophage (phage) therapy, antimicrobial peptides (AMP), silver iontophoresis, and sonic therapies have been introduced. Increasing clinical data supports the use of bacteriophage therapy for infections of prosthetic joints due to bacteriophages' capacity to dissolve biofilms, multiply themselves, and induce bacteriolysis.

2. Bacteriophage therapy

Bacteriophages (phages) are ubiquitous viruses that infect bacteria and can be used against specific bacterial species. Phage replication within the infected bacterium can occur as a lytic cycle (virulent phages) or a part of the lysogenic (temperate phages) cycle.[6] Lytic phages lead to the destruction of the host bacteria and release newly formed phage particles to continue as potent

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antimicrobial agents, especially against multi-drug resistant infections.

The main bacteriophage attachment receptor for *S. aureus* is teichoic acid. Temperate phages act by integrating their genome with the host's genome and are not used in the anti-microbial activity, lying dormant till the host's stress response leads to them entering a lytic phage cycle. The portals of the approach of Bacteriophage therapy are through phage cocktails ['prêt-à-porter' approach (the production of fixed/phage cocktails to have at least one that will be effective on the bacteria)[7] and "Sur-mesure" approach (patients are administered a few specific phages that are active on the strain or species responsible for their AMR infection)][8] and synergistic approach (phage cocktails are used synergistically with complementary antibiotics to combat AMR infection).

The pharmacokinetics of phages differ greatly from antibiotics in terms of tissue uptake and diffusion. Phages are composed of agglomerated proteins whereas antibiotics are small molecules.[9] Due to this low mobility of phages, local delivery (intramuscular, intradermal, subcutaneous, intravenous, intraperitoneal, or topical) is plausible at the site of infection.[10] The ideal phage delivery systems must possess biomaterials, biomaterial constructs, and a mode of phage incorporation.[11] The therapeutic phages should be lytic and hence those phages must be screened for lysogeny and antibiotic resistance genes.[12,13] No serious side effects have been reported in the literature.

3. Applications of bacteriophage therapy in orthopaedic implant and prosthesis-related infections

The understanding of phage-antibiotic synergy (PAS) is crucial in the usage of bacteriophage therapy in eradicating osteoarticular infections. Various studies have shown PAS reduces the development of multi-drug resistant organisms by bactericidal mechanisms. The proteolytic enzymes of bacteriophages destroy the polysaccharides present in the biofilms. Phages possess anti-biofilm properties and hence it is used in IAFFs. The forms of phage therapy are a combination of antimicrobial agents and phages, phage cocktails (combination of different phages), and genetically engineered phages as shown in Fig. 1.

A few animal studies [1 rabbit, 1 rat, and 4 mouse studies] have been published on the usage of bacteriophages in treating osteo-articular infections. In-vitro studies on the orthopaedic implant with a preformed biofilm model support the prophylactic and therapeutic usage of bacteriophages alone or in combination with antimicrobials in eradicating multidrug-resistant infections.[14] Pre-clinical studies have established the role of bacteriophage therapy in patients undergoing immunosuppressant therapy to prevent microbial colonization.[15] Wroe et al. demonstrated hydrogel scaffold-based phage (ΦPaer4, ΦPaer14, ΦPaer22, ΦW2005A) delivery to treat local osteoarticular infections caused by *P.aeruginosa* in a mouse model.[16] Phages loaded scaffolds produce a bactericidal effect in planktonic and biofilm forms in vitro without disturbing the metabolic activity of human mesenchymal stromal cells. Bacteriophages-loaded hydrogel significantly decreases the bacterial counts in mouse model osseous defect at 1-week post-implantation.[16] The prospect of scaffold-based phage delivery is used as a prophylactic modality in established osteoarticular infections as they need a continuous supply of antibiofilm agents to curb the infections.

Barros et al. reported lytic phages against MDR *S. aureus, E. faecalis,* and *E. coli* from implant-associated osteoarticular infections.[17] These phages demonstrate higher efficacy towards MRSA and VRE.[17] Patey et al. reported the disappearance of organisms with negative cultures in 7 cases of osteoarticular infections and concluded that a combination of phages and appropriate antibiotics helps in eradicating antibiotic-resistance or difficult-to-treat infections.[18] Few clinical studies demonstrated that bacteriophage therapy has successfully eradicated extremely drug-resistant *P.aeruginosa* and multi-drug resistant *A.baumannii* in sacroiliac joint osteomyelitis and postoperative infection followed by traumatic brain injury and craniotomy respectively.[19,20] The results of bacteriophage therapy are safe without any complications with rapid clinical improvement. The combination of ϕAbKT21phi3 and ϕKpKT21phi1 phages were used to treat *A.baumannii* and *K.pneumoniae* infections in left tibial bicondylar fracture. By the end of the 8th-month follow-up, the patient was reported with a

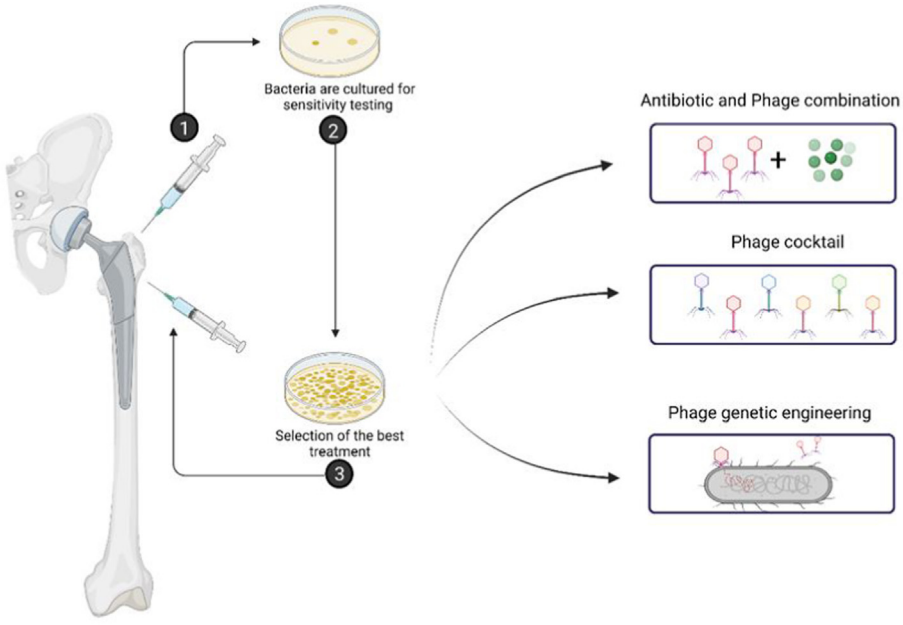

Fig. 1. Forms of Phage therapy techniques studied for the management of osteo-articular infection shown on a Total Hip Replacement associated infection.

Table 1
Evidence of clinical studies of phage therapy in osteoarticular infections.

Author (Year)	Model	Bacteria	Phage used	Results
Fish et al.[25] (2016)	Diabetic toe ulcers (n = 6)	*S.aureus*	Staphylococcal phage Sb-1	Despite the antibiotic failure, topical Sb-1 phage curbs off diabetic toe ulcers
Fish et al.[26] (2018)	Staphylococcal osteomyelitis (n = 1)	MRSA	Staphylococcal phage Sb-1	Phage therapy treatment offers the potential for improved outcomes in this era of escalating antibiotic resistance.
Ferry et al.[19] (2018)	Right sacro-iliac joint osteomyelitis (n = 1)	Extremely drug resistant (XDR) *P.aeruginosa*	Phage cocktail (1450, 1777, 1792 and 1797)	Eradication of XDR-*P.aeruginosa* within 14 days
Ferry et al.[27] (2018)	Periprosthetic joint infection of right hip (n = 1)	Methicillin-sensitive *S.aureus*	Phage cocktail (1493, 1815, and 1957)	Phage act as antibiofilm producer in relapsing *S.aureus* periprosthetic joint infection
Onsea et al.[28] (2019)	Osteomyelitis of pelvis and femur (n = 4)	*S.aureus* *S.epidermidis* *S.agalactiae* *E.faecalis* *P.aeruginosa*	Staph species and *P.aeruginosa* - BFC1; *E.faecalis* - *Pyo*	A single course of phage therapy prevents recurrence of infection ranging from 8 to 16 months
LaVergne et al.[20] (2019)	Postoperative infection followed by traumatic brain injury and craniotomy (n = 1)	MDR *A.baumannii*	104 *A.baumanii* bacteriophages from the NMRC's phage-Biolog system	Absence of infection in the craniotomy site
Patey et al.[18] (2019)	Pelvic bone infection (n = 1)	*S. aureus*; *P. aeruginosa*	Anti S.aureus and anti-*P.aeruginosa* suspension	Complete resolution of infection in 24 months
	Complex fracture of right foot (n = 1)	*S.aureus*	Anti *S.aureus* suspension	Clearance of infection within 6 months
	Mandibular fracture, osteosynthesis, and fistulised infection (n = 1)	MRSA	Tbilisi phage therapy and anti *S.aureus* suspension	Clearance of infection within 6 months
	Femoral fracture under hip prosthesis (n = 1)	MRSA	Anti *S.aureus* suspension	Clearance of *MRSA* infection within 12 months
	Left knee prosthesis infection (n = 1)	*P.aeruginosa*	Phage cocktail	Clearance of *P.aeruginosa* infection within 2 years
	Osteomyelitis of the left tibia (n = 1)	MRSA	Anti *S.aureus* suspension	Clearance of infection within 6 months
	Left tibia fracture, followed by reopened bone infection (n = 1)	*S.aureus*	Anti *S.aureus* suspension	Clearance of *S.aureus* infection within 12 months
Nir-Paz et al.[21] (2019)	Left bicondylar tibial plateau fracture (n = 1)	*A.baumannii;* *K.pneumoniae*	Combination of ϕAbKT21phi3 and ϕKpKT21phi1	Tissue healing along with negative bacterial culture observed at the end of the 8th-month follow-up
Tkhilaishvili et al.[29] (2019)	Right knee periprosthetic infection and chronic osteomyelitis of the femur (n = 1)	MDR *P.aeruginosa*	*P.aeruginosa* specific phage cocktail	Phage act as an adjuvant to antimicrobial in curbing MDR *P.aeruginosa* infection
Ferry et al. (2020)[30]	Megaprosthesis joint infection (n = 1)	*S.aureus*	Phage cocktail [PP1493 and PP1815] loaded onto DAC hydrogel	Phage therapy exhibit potential antimicrobial effect in megaprosthetic joint infections.
Ferry et al.[31] (2020)	Left knee relapsing PJI (n = 1) Right knee relapsing PJI (n = 2)	*S. aureus*	Phage cocktail [PP1493, PP1815, and PP1957]	Clearance of *S.aureus* infections were achieved in all 3 cases ranging from 3 months to 3 years
Aslam et al.[32] (2020)	Cranial osteomyelitis with subdural and epidural empyema (n = 1)	*MDR A.baumannii*	Single phage	Patient expired due to ventilator-associated pneumonia
	Sternal osteomyelitis due to ventricular assist device infection (n = 1)	*MDR P.aeruginosa*	GD-1 phage	Developed bacteremia 1 week after starting phage therapy which resolved with change in antibiotics indicated failure of phage therapy
	Sternal osteomyelitis due to ventricular assist device infection (n = 1)	*S.aureus*	AB-SA 01 phage	Infection resolved with phage therapy and antibiotics
	PJI (n = 1)	*S.aureus*	AB-SA01 phage and SaGR51øK phage	Re-treated almost 6 months later with surgical revision, systemic antibiotics, and phage therapy with resolution of *S. aureus* infection
Nadareishvili et al.[33] (2020)	Recurrent sternal osteomyelitis (n = 1)	*S.aureus*	Per os infiltration of staphylococcal bacteriophage, and SES bacteriophage; Local infiltration of Pyo bacteriophage	Wound covered with fresh granulation tissue in first 20 days of the treatment
	Right tibial chronic osteomyelitis (n = 1)	*S.aureus*	Per os infiltration of staphylococcus bacteriophage and Intesti bacteriophage	Complete closure of wound attained at 18 weeks of phage therapy
	Diabetic ulcer left foot (n = 1)	*Burkholderia cepacia, S. aureus,* and *Enterococcus faecalis*	Per os infiltration of staphylococcus bacteriophage and Intesti bacteriophage; Topical infiltration of Intesti bacteriophage	Resolution of osteomyelitis in CT after 6 weeks of phage therapy
	Post surgical infection of skin graft over left thigh (n = 1)	*Pseudomonas aeruginosa*	Per os infiltration of Pyo bacteriophage and Intesti bacteriophage	Complete wound resolution attained after 3 months of phage therapy
Ramirez-Sanchez	Right knee PJI (n = 1)	Methicillin sensitive *S.aureus*	1st treatment - AB-SA01 cocktail [J-Sa36, Sa83, Sa87]	Bacteriophage therapy is an adjunct modality along with routine surgery and antibiotics in curbing MSSA.

(*continued on next page*)

Table 1 (*continued*)

Author (Year)	Model	Bacteria	Phage used	Results
et al.[34] (2021)			2nd treatment – Single lytic phage SaGR51ø1	
Cano et al.[35] (2021)	Right knee relapsing PJI (n = 1)	*K.pneumoniae*	KpJH46Φ2	Recommended further clinical studies on evaluating safety and efficacy of phage therapy in PJI
Ferry et al.[36] (2021)	Left knee relapsing PJI (n = 1)	*P.aeruginosa*	Phage cocktail [PP1450, PP1777, and PP1792]	Phage therapy act as a salvage therapy for patients with *P. aeruginosa* relapsing PJI along with antibiotics

negative culture of the organisms and with good tissue healing.[21] A recent study evaluated the in vitro activity of a group of bacteriophages against clinical *S. aureus* prosthetic joint infection (PJI) isolates; more than 95% of these isolates demonstrated adequate growth inhibition of the predominate planktonic colonies by at least one bacteriophage strain, suggesting the therapeutic utility of bacteriophage therapy.[22]

Clinical reports have shown the successful role of adjuvant personalized intravenous bacteriophage therapy in recalcitrant MRSA prosthetic infection with failed conventional surgical and medical treatment.[23,24] The evidence of clinical studies of phage therapy in osteoarticular infections from 2016 till date is tabulated in Table 1.

The potential limitation of bacteriophage therapies are a) absence of specific activity for a particular bacterial strain, b) plausible emergence of bacterial resistance against bacteriophages, c) decreased activity due to immunological response against bacteriophages, and d) technical difficulties in pharmaceutical preparation of bacteriophages. To overcome the emergence of phage resistance, phage engineering is being developed to make genetically engineered bacteriophages that are less immunogenic to eradicate the infection. To validate these ATMPs, technologies such as next-generation sequencing have emerged as a powerful tool to analyze the phage and bacteria utilized, however, it could not be implemented as a GMP-compliant assay due to the lack of a strong validation framework that needs to be developed.

US-FDA approved phage therapy via the "Emergency Investigational New Drug Scheme" through the Centre for Innovative Phage Applications and Therapeutics (IPATH).[37] In the case of genetically modified phages (GMPs), some additional requirements such as environmental risk assessment need to be analyzed before clinical use. These products are considered advanced therapeutic medicinal product (ATMP) by the European Medical Agency and needs a centralized authorization procedure.[38]

4. Conclusion

The future relies on bacteriophage therapy for eradicating MDR organisms, especially in IAFFs. The development of various phage cocktails to eradicate MDR organisms is the prime area for further research in orthopedics. Due to the lack of preclinical and clinical evidence, further research on bacteriophage therapy is warranted. Studies on the development and evaluation of the delivery of multiple microbe-specific bacteriophages to combat chronic IAFF are advocated. To overcome the emergence of phage resistance, phage engineering is being developed to make genetically engineered bacteriophages that are less immunogenic, and target-specific with CRISPR repeats to eradicate the infection. The ideal phage release kinetics with phage-specific and patient-specific phages must be developed for the future.

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Declaration of competing interest

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