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# The Efficacy of Bacteriophage Therapy in Orthopaedic Field: A Systematic Review

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## ABSTRACT

**INTRODUCTION:** Bacterial infections are the cause of high mortality rates in the world. Antibiotics and multidrug work well together to treat the patient. The pathogens are harder to control and develop antibiotics resistance. In orthopaedic field, infections like osteomyelitis, septic arthritis, or infections of the bone, joints, or implants (periprosthetic joint infections [PJI]) can be difficult to resolve both microbiologically and clinically. Bacterial viruses (bacteriophages) are one possible substitute. Due to their great host specificity, lack of adverse effects, and safety for eukaryotic cells, these viruses provide novel advantages, such as the safe treatment of illnesses.

**MATERIAL AND METHODS:** Three databases were used for the bibliographical search: Google Scholar, PubMed, and ScienceDirect for case report related to bacteriophage therapy and antibiotic resistance in orthopaedics, which were published between 2014 and 2024, which based on PRISMA guidelines qualified 10 articles for systematic review.

**RESULT:** In orthopaedic cases biofilm formation is widely recognized as the main obstacle to effective prevention and treatment. Biofilm production is intimately related to bacteria's capacity to create chronic illnesses and the challenge of overcoming them. The biofilm-disrupting properties of certain phages make them a promising option for managing device-associated infections. The capacity of phages to enter a biofilm and then cling to the surface of the host bacteria to infect and lyse it. The effectiveness of the reticuloendothelial system's clearance and possibly the production of phage-specific antibodies, which could result in phage inactivation, determine how long phages stay in systemic therapy.

**CONCLUSION:** Bacteriophages is a safe and effective treatment option, regardless of whether it is used alone or in conjunction with antibiotics and/or surgery. Bacteriophages is particularly well-suited for inclusion in multidimensional strategies to address infections due to its adaptability and versatility. Rather than replacing antibiotics, Bacteriophages should complement their effects to enhance infection management.

***Keywords:*** Bacteriophages, Phage Therapy, Antibiotic Resistance, Orthopaedic, Biofilm

## INTRODUCTION

Bacterial infections are the cause of high mortality rates in the world. Antibiotics and multidrug work well together to treat the patient. The pathogens are harder to control and develop antibiotics resistance.[1] Since bacterial pathogens react to the severe

selection pressures exerted on them, it is not surprising that antibiotic resistance is growing quickly as a result of overuse and misuse.[2] Unfortunately, the development of new antibiotics and new classes of drugs which act differently from existing ones is both expensive and takes a long time. As a result, some of our most potent medications are losing their effectiveness.[3,4] In Indonesia, antibiotic resistance phenomena like silent pandemic because of the high mortality rate, obtained data from The Ministry of Health Republic Of Indonesia that 1.2 million patient died because of antibiotic resistance.[5] Therefore, there is an urgent need for alternate antimicrobial techniques. Bacterial viruses (bacteriophages/phage therapy) are one possible substitute.[6,7] Given their versatility and ease of manipulation, bacteriophages could have an impact on biotechnology, research, and medicine.[8]

This review article's goal is to support the varied community of researchers, scientists, and biotechnologists who are employing phages to further and expand the biotechnology field.

In 1915 and 1917, Felix d'Herrelle and Frederick Twort first described bacteriophages, which are bacterial viruses that only infect bacteria. Phages are small viruses that range in size from 20 to 200 nm.[9] Due to their great host specificity, lack of adverse effects, and safety for eukaryotic cells, these viruses provide novel advantages, such as the safe treatment of illnesses.[2] This minimizes harm to the native microflora because they only reproduce when the bacteria that are causing the infection are present. Furthermore, it is uncommon for phages to share genetic material.[2,9]

When it comes to orthopaedic surgeons, infections like osteomyelitis, septic arthritis, or infections of the bone, joints, or implants (periprosthetic joint infections [PJI], fracture-related infections [FRI] involving plates, screws, or intramedullary nails) can be difficult to resolve both microbiologically and clinically. Currently available treatments, such as antibiotics and surgery, have a 10–20% failure rate. Infection rates after elective orthopaedic surgery range from 0.7% to 4.2%, but in trauma cases, they can be significantly higher. After surgery, infection rates for closed low-energy fractures range from around 1% to over 30% for complex open tibia fractures.[10]

Phage therapy (PT), has been used to treat infections.[11] Phage flexibility would enable us to use the antibodies against the bacteria that have been exhibited on the phage surface, whereas PT can be used alone to treat a bacterial infection by lysing the bacterial cell.

This study can be used as material for reconsider and rediscover PT. By being compatible with their hosts, PT reduces the likelihood of subsequent infections. The use of antibiotics targets both pathogens and the patients' normal flora, and it may result from secondary infections or superinfections. Although no negative side effects have been documented during or following phage administration, secondary infections, allergies, and bacterial resistance are the most frequent side effects of antibiotic treatment.[2,8,9]

The effectiveness statistics from research on human patients with bacterial infections of different kinds who received phage therapy are summarized in this systematic review.

## MATERIALS & METHODS

### Materials

Three databases were used for the bibliographical search: Google Scholar, PubMed, and ScienceDirect. The terms "bacteriophage therapy" and "antibiotic resistance in orthopaedics," which were published between 2014 and 2024, were used. Boolean operators have been employed to define the search as follows: "bacteriophage therapy" OR "phage therapy AND orthopaedic antibiotic resistance."

### Study Selection and Data Collection

Full-text publications and clinical case reports or case series that were published in

English throughout the last ten years (1 January 2014 to 31 December 2024) were included in the review. This study's primary goals were to describe the use of physical therapy (PT) in human patients who were infected with different bacteria, particularly in the orthopaedic field, so that it would be possible to determine if the treatment was effective or not. The inclusion and exclusion criteria were used to choose the relevant papers.

Exclusion criteria for this study include: lack of use of PT in multidrug-resistance-based studies; metagenomics in bacteriophages without subsequent application in human patients; PT in animals; phages in foods; patients not working in orthopaedics; publications published outside of the selected time frame; and bibliographic materials such as reviews, systematic reviews, posters, conferences, book sections, and perspectives. Studies that were found to be duplicates in the search results were excluded.

The selection of publication consider to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses).

## Data Extraction

To verify for duplicate results across the three databases, the chosen citations and their titles were imported into Microsoft Office Excel. Records that were duplicates were removed.

## Data Analysis

Reviewing the abstracts and titles in order to assess the records. Everyone who didn't fit the requirements for inclusion was eliminated. The final record was included in this evaluation after the entire texts were examined to eliminate articles that did not fit the inclusion criteria.

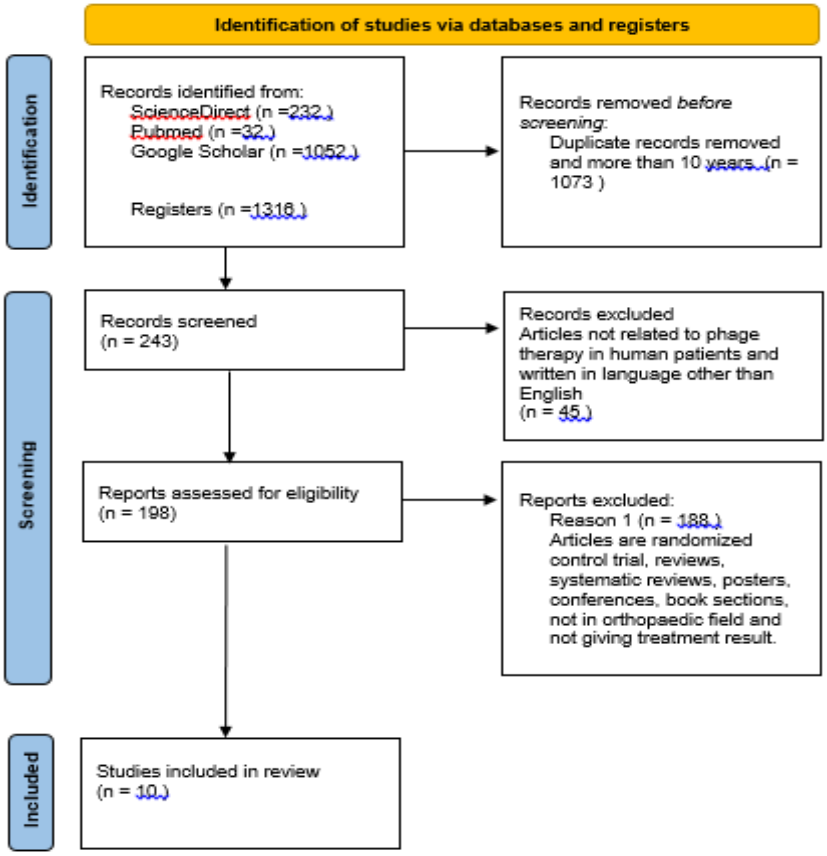


**Figure 1 PRISMA flowchart illustrating the search and selection of the articles**

## RESULT

Ten out of the 1316 documents published between 2014 and 2024 that were retrieved for screening satisfied all eligibility requirements. Publications described experiences in the United States (n = 4), Belgium (n = 2), Germany (n = 1), the Netherlands (n = 1), Latvia (n = 1), and Israel (n = 1). The ten articles comprised five male patients and five female patients. Big three bacterial species, including Pseudomonas aeruginosa (n = 2), Klebsiella pneumoniae (n = 3), and Staphylococcus aureus (n = 3), were found to be resistant to many medications. Nine of these ten patients received the phage mixtures via multiple methods of delivery, whereas one patient received them intravenously.

## DISCUSSION

Based on the outcomes of ten patients treated in ten chosen studies, it is feasible to conclude that PT produced encouraging results for the treatment of infections caused by various bacterial species, especially those that are difficult to manage, such as infections caused by bacteria resistant to multiple antibiotics. The results of nearly all of these cases in this systematic review are improved. By successfully lowering the bacterial concentration, PT enhanced results and prevented fatal infections.

Furthermore, by removing bacterial toxins and lysates, the purification process and dilution of delivered phages would further improve their safety and prevent any negative effects or immunological reaction.[3]

Combination therapy can successfully treat and prevent or reduce the development of bacterial resistance in clinical settings by having a synergistic effect. To demonstrate how sublethal antibiotic doses could increase bacterial production of lytic phages, the phage antibiotic synergy (PAS) technique was employed. This is most likely caused by the low dosage of antibiotics preventing bacterial cell division and boosting biomass, which shortens the latent period and increases the phages' burst size, enabling them to swiftly eliminate the remaining bacterial cells.[3] Nine patients in this research got combination therapy, which primarily worked in concert to dramatically lower the concentration of germs. In addition, one patient who had physical therapy without the use of antibiotics reported good results. Since phages are believed to be a part of the healthy flora, their ability to act as probiotics and immunomodulators is neither surprising nor inconvenient.[3] Investigating the impact of phage alone without infection on the human immune system is crucial since this also calls into question whether the effectiveness of PT is dependent on its antibacterial and anti-inflammatory response.

The effectiveness of PT is not solely due to the use of a single bacteriophage or in conjunction with antibiotics. When considering bacteriophages as a therapy option, a number of things need to be taken into account. First, the patient's clinical condition may determine how long the treatment will last and how effective it is; the patient's immune system is crucial to the short-, medium-, and long-term success of physical therapy. The second is phage dose and administration methods. A precise assessment of the infection's kind and severity is necessary to determine the best administration method and phage dosage.[3]

In fact, phages have a number of significant characteristics that play a role. The ability of phages to self-amplify is one of their advantages that sets them apart from traditional antibiotics and adds to their effectiveness. Second, certain phages have polysaccharide depolymerases on their tail structures, which can degrade the extracellular matrix of bacteria linked to biofilms and thus serve as an adjuvant to phage infection.[22]

| Author | Country | Patient | Bacteria | Drugs | Infection | Effect of PT | PT Route | Combination |
|---|---|---|---|---|---|---|---|---|
| Randolph Fish et al [12] | US | 63 YO F | S. aureus | MRSA | Distal phalang osteomyelitis | Quick recovery without any indication of bacteria in 14 days | inject to the infection site 0.7cc once weekly for seven weeks | not combine with other antibiotic |
| Edison J. Cano et al [13] | US | 62 YO M | K. pneumoniae | Daptomycin, penicillin, vancomycin, minocycline, linezolid, cefadroxil, meropenem | Total knee arthoplasty Dextra | observed improvements in the right lower extremity's range of motion, function, erythema, edema, and pain. | 40 intravenous doses of a single phage | combine with minocycline |
| Ran Nir-Paz et al [14] | Israel | 42 YO M | A. baumannii and K. pneumoniae | Piperacillin/tazobactam, meropenem | Both lower extremity Grade IIIA open fractures (left bicondylar tibial plateau fracture with compartment syndrome and right distal femoral fracture) | The wound is still closed and dry, and the patient did not have their limb amputated. | IV 1 ml of each phage (5x107 PFU/ml) IV tid | combine with intravenous (IV) meropenem (2 gr tid) and colistin (4.5 × 106 units/ bid), |
| Anaïs Eskenazi et al [15] | Belgium | 30 YO F | Klebsiella pneumoniae | Ampicillin, Amoxicillin-clavulanic acid, Piperacillin-tazobactam, Temocillin, Cefuroxime, Ceftazidime, Cefotaxime, Cefepime, Meropenem, Ertapenem. | Femur Fracture | Improvement of the patient's wounds in objective clinical, microbiological, radiological and overall condition | Locally to the infection for 6 days | combine with IV ceftazidime/avibactam (2 g/0.5 g, q8h); tigecycline (100 mg, q12h); moxifloxacin (400 mg, q24h); ciprofloxacin |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | (400 mg, q8h) |
| Tamta Tkhilaishvili et al [16] | Germany | 80 YO F | K. pneumoniae,P. stuartii, P. aeruginosa, S. epidermidis, S. haemolyticus | Oxacillin, piperacillin, piperacillin-tazobactam, ceftazidime, ceftazidime-avibactam, imipenem, aztreonam, cefepime, meropenem; CIP, ciprofloxacin; LEV, levofloxacin; GEN, gentamicin, tobramycin, amikacin, fosfomycin, colistin, doxycycline, rifampin, vancomycin, daptomycin, trimethoprim-sulfamethoxazole. | Chronic osteomyelitis of the femur following a gunshot injury and recurrent right knee PJI | The patient's mobility was adequate, the soft tissue at the surgery site was unremarkable, and there was no pain in the right knee. | During surgery, a 100 ml loading dose of purified bacteriophage was delivered locally. Five milliliters of bacteriophage solution were then administered every eight hours. | combine with colistin, meropenem, and ceftazidime |
| Claudia Ramirez-Sanchez et al [17] | USA | 61 YO F | Staphylococcus aureus | vancomycin, cefazolin | TKR Prosthetic Joint Infection | Numerous cultures of the patient's wounds and synovial fluid have come out negative for S. aureus. | Intra-articular and IV 12h/day 2weeks, intraoperative | combine with IV cefazoline |
| Brieuc Van Nieuwenhuyse et al [18] | Belgium | 13 YO F | C. hathewayi, P. mirabilis, F. magna | Clindamycin, rifampin, flucloxacillin, ciprofloxacin, piperacillin-tazobactam, amoxicillin, ceftriaxone, | infection of an allograft of pelvic bone following surgery to remove Ewing's sarcoma | The patient has not experienced any further infectious episodes after two years. | intraoperative | combine with clindamycin, ciprofloxacin, rifampin |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | ceftazidime, vancomycin, metronidazole | | | | |
| Ann-Sophie NEUTS et al [19] | Netherlands | 76 YO M | E. faecalis | Teicoplanin, amoxicillin, amikacin, sulfamethoxazole + trimethoprim, cefotaxime, Clarithormycin, Dalacin, Doxycycline, Erythromycin, ceftazidime, Gentamicin, Rifampicin, azithromycin, ceftriaxon, cefuroxime | infected total hip arthroplasty | Two years later, when we examined him in our outpatient clinic, he had no hip issues and no fresh cultures had been collected. | PO combination for 19 days | combine with amoxicillin, doxycycline |
| Karlis Racenis et al [20] | Latvia | 21 YO M | P. aeruginosa | Meropenem, colistin, piperacillin-tazobactam, linezolid, and fluconazole | Osteomyelitis of the femur | The patient's wounds remained dry and closed six months after treatment ended, while laboratory inflammatory markers stayed steady within typical levels. | intraoperative and IV 8h/day+via irrigation catheter for 7 days | combine with ceftadizim-avibactam, linezolid |
| James B. Doub et al [21] | USA | 72 YO M | S. aureus | Vancomycin, daptomycin, doxycycline | Prosthetic joint infection | was effective in eliminating the patient's severe persistent infection. | Daily IV phage for 3 days | combine with IV daptomycin |

For orthopedic-related cases examined in this systematic review, improved outcomes were observed, including a successful result in a patient with recalcitrant *S. aureus* prosthetic joint infection (PJI) treated with prolonged PT alongside surgery and antibiotics. In this scenario, the ability of staphylococci to form adherent, multilayered biofilms on implanted medical devices posed a significant challenge to treatment, despite the isolate's antibiotic susceptibilities. The biofilm-disrupting properties of certain phages make them a promising option for managing device-associated infections.[17] A favorable outcome for an osteomyelitis patient was also shown in this case report. Antibiotics frequently exhibit poor and insufficient penetration to such infection sites, which complicates their use in the treatment of osteomyelitis in addition to the potential for antibiotic resistance.[20] Numerous studies on animals have demonstrated the beneficial effects of bacteriophages in the treatment of osteomyelitis.[23,24] Their erythema, induration, and local edema diminished, and they became more active.

In the orthopaedic field, biofilm formation is widely recognized as the main obstacle to effective prevention and treatment. Biofilm production is intimately related to bacteria's capacity to create chronic illnesses and the challenge of overcoming them. Bacteria flourish in biofilms because they are protected from the patient's immune system and antimicrobial therapies. The expression of resistance genes, decreased bacterial growth rates, and restricted antimicrobial penetration are some of the processes that lead to antibiotic tolerance in biofilms. By binding to particular receptors on the surface of the bacterial cell and introducing their genetic material, phages fight bacteria. These strain-specific sensors could be teichoic acids or proteins found on the bacterial cell wall. Once inside, phages have two options: either they stay latent within the cell (lysogenic cycle) or they use the bacterial metabolism to multiply and eventually lyse the host cell, releasing new phage particles (lytic cycle). Important phases for PT include infection, lysis, penetration, absorption, dispersion, and phage release.[25] For phage therapy to be applied locally, absorption and distribution are typically not significant. The effectiveness of the reticuloendothelial system's clearance and possibly the production of phage-specific antibodies, which could result in phage inactivation, determine how long phages stay in systemic therapy. The capacity of phages to enter a biofilm and then cling to the surface of the host bacteria to infect and lyse it is known as penetration. These processes are called adsorption, infection, and lysis.[22]

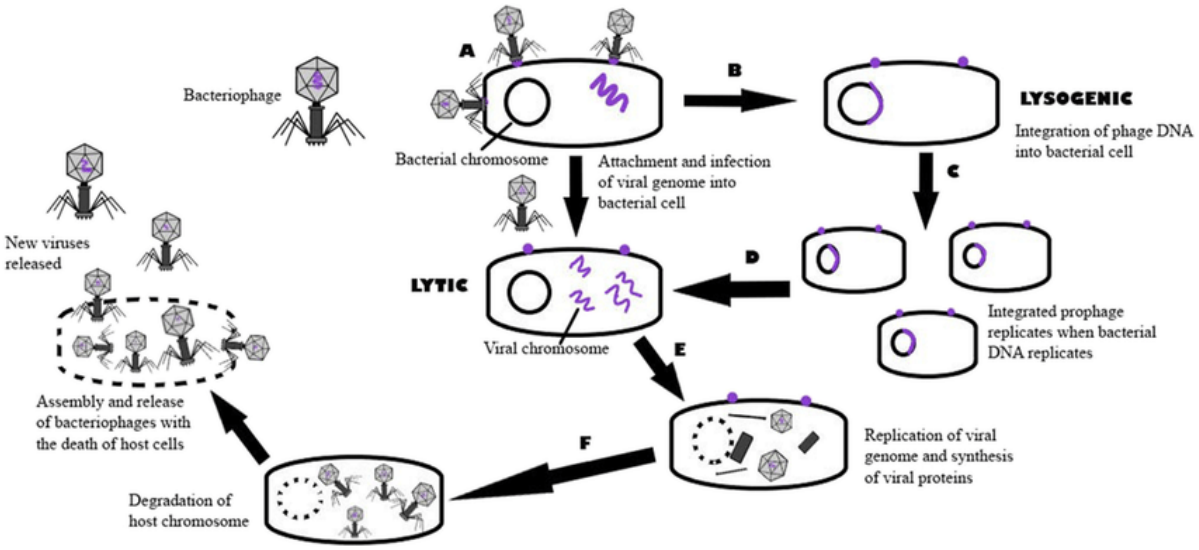


**Figure 2 Mechanism of action of bacteriophage therapy**[25]

The light of the bacterial strains' previously stated pathogenicity and the low antibiotic absorption in bone tissue. In order to tackle isolates implicated in orthopaedic implant-associated infections, orthopaedic surgeons need possess new tactics for creating innovative therapeutic techniques. PT has long been shown to be a promising antibacterial strategy, mainly due to its high specificity and effectiveness in killing targeted pathogenic bacteria. In light of the rising problem of antibiotic resistance worldwide, PT appears to be a secure and successful method of countering the effects of bacterial resistance. However, there are not enough studies that thoroughly evaluate the safety and effectiveness of PT.

There are two countries where treatment with phages is routinely available in Europe: Georgia and Poland (Russia probably also uses PT, but much less information is available). More recently, the Wound Care Center in Lubbock, Texas used PT.[1]

## CONCLUSION

According to this systematic study, PT is a safe and effective treatment option, regardless of whether it is used alone or in conjunction with antibiotics and/or surgery. PT is particularly well-suited for inclusion in multidimensional strategies to address infections due to its adaptability and versatility. Rather than replacing antibiotics, PT should complement their effects to enhance infection management. To achieve this, emphasis should be placed on evaluating safety and efficacy, standardizing protocols, and identifying suitable host ranges.

Despite the challenges associated with PT, its adoption can lead to improved treatment outcomes. Conducting clinical trials is a crucial next step to confirm its effectiveness and determine its role in cases of therapeutic failure.

### *Declaration by Authors*

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