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Letter

# PHAGE THERAPY: UNCOVERING THE CLASSICS TO TACKLE MODERN CHALLENGES

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It has been just over 100 years since Alexander Fleming discovered penicillin, a milestone that revolutionized the treatment of infectious diseases and marked the beginning of the antibiotic era. These drugs became essential allies in combating infections that were once fatal, enabling enormous advances in medicine. However, today we face an alarming reality: antibiotics are losing their clinical efficacy due to the rapid evolution of bacterial resistance, driven by the excessive and inappropriate use of antibiotics and the horizontal gene transfer mechanisms that allow antibiotic-sensitive bacteria to acquire resistance genes from resistant strains. According to the World Health Organization (WHO), this crisis is one of the greatest threats to global public health[1]. Faced with this challenge, it is imperative to reconsider therapeutic options that were once set aside, such as phage therapy. Phage therapy involves the use of bacteriophages (phages) to treat bacterial infections. Félix d'Hérelle, one of the discoverers of phages along with Frederick W. Twort, suggested the possibility of treating bacterial diseases with these viruses[2–4]. Although it was overshadowed by the rise of antibiotics, phage therapy has resurfaced as a promising solution to combat resistant bacterial infections. Phages, viruses that specifically target bacteria, offer a unique therapeutic precision that does not disrupt the microbiome[5]. This, due to initiate their infection, phages must first recognize a specific receptor on the bacteria, unlike antibiotics which target conserved molecules across different bacteria. Phages can act against infections caused by multidrug-resistant (MDR) bacteria and even bacteria capable of forming biofilms. In addition, because phages can multiply within bacterial cells, potentially, a single dose could be enough to treat an infection[4].

In recent years, phage therapy has found applications against various infections, both in experimental phases and clinical treatments. In preclinical studies, phages have demonstrated efficacy in animal models to treat infections caused by multidrug resistant bacteria such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*. Clinically, phages have been used to combat chronic respiratory infections, such as those affecting patients with cystic fibrosis, as well as prosthetic joint infections and the management of skin and soft tissue infections. Additionally, phage therapy has been applied to infections complicated by biofilms in medical devices such as catheters and prostheses. As these applications expand, studies continue to show promising results in the fight against resistant bacteria. Phage therapy has proven effective against infections resistant to conventional treatments and opened new perspectives where antibiotic resistance has reached critical levels[2–4].

Phage therapy has undergone various phases of research and application. One of the first clinical trials in the United States was conducted in 1922 to treat cases of dysentery. Although its development in the West slowed, today, with the growing bacterial resistance crisis, phage

therapy has once again garnered global interest. As of now, 61 clinical trials investigating the use of phage therapy against resistant bacterial infections are registered on ClinicalTrials.gov. Approximately 31% of these trials began between 1990 and 2020, while 69% have started since 2020, reflecting a renewed interest in exploring its application as a complement to conventional treatments[6].

However, despite the growing interest and recent advances, phage therapy still faces significant barriers to widespread adoption. One major challenge is the lack of a clear regulatory framework that allows for its generalized use in clinical practice. Although clinical trials have shown encouraging results, further research is needed to validate its safety and efficacy in a standardized manner. Moreover, mass production of phages faces technical challenges, such as ensuring purity, stability, and quality control, all of which are essential for their approval as a treatment[2–4,7].

In addition to facing these challenges, innovative strategies are being developed to make phages more efficient, such as engineering phages to express enzymes that attack bacterial exopolysaccharides, like the hydrolase DspB, which degrades the extracellular matrix, facilitating penetration into biofilms and the subsequent elimination of bacteria[8]. Another strategy involves phages that express quorum-quenching enzymes, such as the lactonase AiiA, which interferes with bacterial cell communication (quorum sensing), inhibiting biofilm formation in bacteria like *P. aeruginosa*[9]. These strategies are crucial in treating chronic and hard-to-treat infections, such as those associated with medical devices or diseases like cystic fibrosis, where biofilms play a central role in resistance to conventional treatments. Additionally, phage mutagenesis which increase their lytic activity is being explored, providing further avenues for optimizing their therapeutic potential[10].

Without a doubt, these advancements will continue to bring bacteriophages and phage therapy to the forefront as a viable alternative or complement to antibiotic treatments. Science and regulation must advance hand in hand to make this tool available on a large scale, ensuring it is safe and effective in the fight against multidrug-resistant bacterial infections.

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