

Phage Therapy in Medical Microbiology: Diagnostic and Therapeutic Implications for the Clinical Laboratory

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Abstract

The increasing prevalence of multidrug-resistant bacterial infections places medical microbiology laboratories at the frontline of therapeutic decision-making. In this context, bacteriophage therapy is re-emerging as a targeted anti-infective strategy that directly integrates laboratory expertise into clinical management. This systematized literature review synthesizes current biological and clinical evidence on phage therapy, with a specific focus on its relevance for medical microbiologists. Particular attention is given to the phagogram as a diagnostic tool analogous to the antibiogram, enabling strain-specific selection of therapeutic bacteriophages. Technical, organizational, and regulatory challenges associated with implementing phage therapy within routine laboratory workflows are discussed. Overall, phage therapy represents an emerging extension of precision microbiology, reinforcing the central role of the clinical laboratory in personalized anti-infective strategies.

Keywords: Phage Therapy; Medical Microbiology; Phagogram; Antimicrobial Resistance

Introduction

Antimicrobial resistance has become one of the most pressing challenges facing global public health. In 2019 alone, it was associated with nearly 4.95 million deaths worldwide, including 1.27 million directly attributed to drug-resistant bacterial infections [1]. This growing burden is largely driven by the extensive and often inappropriate use of antibiotics, combined with the declining development of new antimicrobial agents [2,3].

Against this backdrop, phage therapy, based on the therapeutic use of lytic bacteriophages, has regained considerable scientific and clinical interest. These viruses possess several unique biological properties, including high host specificity, self-replication at the site of infection, and activity against bacterial biofilms [4,5].

Although phage therapy was historically sidelined in Western medicine, recent experimental and clinical findings have contributed to its renewed emergence as a potential alternative or adjunct to conventional antimicrobial strategies [6,7]. This approach is increasingly aligned with the principles of personalized medicine and places the clinical microbiology laboratory at the center of therapeutic decision-making, particularly through the implementation of phagogram testing [8].

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Despite this renewed interest, the integration of phage therapy into routine clinical practice remains limited. Several challenges persist, including the lack of standardized methodologies, restricted accessibility to therapeutic phages, and uncertainties regarding its precise role within current anti-infective treatment strategies.

Therapeutic interest in the clinical setting

Phage therapy has emerged as a promising therapeutic approach for the management of complex infections caused by multidrug-resistant bacteria.

Osteoarticular infections and infections associated with implanted medical devices represent major indications for phage therapy due to the critical role of bacterial biofilms in their pathogenesis [13]. In cystic fibrosis, chronic infections caused by *Pseudomonas aeruginosa* also constitute an important target, with encouraging outcomes reported following inhaled phage administration [14].

Cases involving severe systemic infections, particularly those caused by *Acinetobacter baumannii*, have demonstrated significant clinical improvement in patients with limited or no remaining therapeutic options [15].

Recent data suggest clinical improvement rates ranging from 70% to 85% in certain case series, especially when phages are combined with antibiotics, highlighting a potential synergistic effect [6,11,16]. However, these findings remain heterogeneous and are predominantly derived from non-randomized studies, which still limits their broader generalization and clinical implementation.

The phagogram: A diagnostic tool in medical biology

The phagogram constitutes a central component of phage therapy. It is an *in vitro* assay designed to evaluate the susceptibility of a bacterial strain to bacteriophages, based on a principle analogous to that of the antibiogram [8].

The most commonly used methods include the spot test, which provides a rapid qualitative assessment within 18-24 hours, and the double-layer agar technique, which offers a semi-quantitative approach through the enumeration of lysis plaques [17].

However, unlike the antibiogram, the phagogram has not yet benefited from international standardization. The absence of interpretive thresholds, inter-laboratory variability, and dependence on experimental conditions represent major limitations to its reproducibility [18].

In clinical practice, these constraints may delay patient management, particularly in acute infections, and restrict access to this approach to specialized centers. To date, few studies have robustly evaluated the correlation between *in vitro* phagogram results and *in vivo* clinical efficacy, making this a priority area for future research.

Therefore, although the phagogram represents a promising diagnostic tool, its routine clinical implementation remains dependent on further standardization efforts and comprehensive clinical validation.

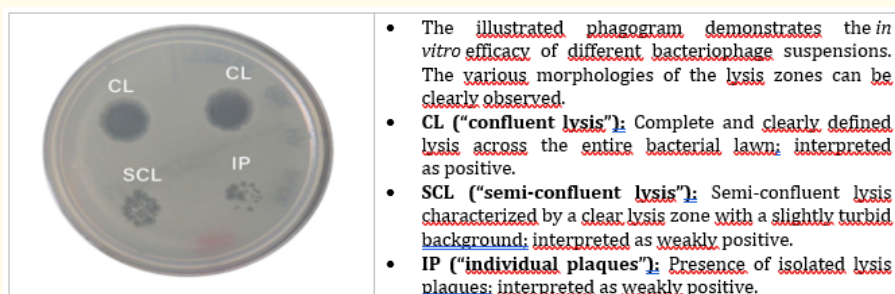


Figure 1: Phagogram performed on TS agar using the overlay agar method on *Pseudomonas aeruginosa* (PHAGOGRAMS*).*

Criteria	Antibiogram	Phagogram
Primary objective	Evaluate bacterial susceptibility to standard antibiotics	Assess the activity of a specific bacteriophage against a bacterial strain
Type of targets	Broad spectrum: Gram-positive and Gram-negative bacteria	Narrow target range: specific to a bacterial strain or species
Methodology	Agar diffusion (Kirby-Bauer), automated MIC determination (VITEK, Phoenix, etc.)	Spot test, double-layer agar assay, MPA (Microscopic Phage Adsorption)
Turnaround time	24-48 hours	24-72 hours depending on the method used
Standardization	Established standards (EUCAST, CLSI)	No universal standards; methods still undergoing validation
Spectrum of activity	Broad (variable depending on the antibiotic)	Narrow, dependent on phage adsorption to the targeted strain
Degree of personalization	Limited: standardized testing according to bacterial species	Very high: testing performed strain by strain and phage by phage
Risk of secondary resistance	Moderate to high (well-known selective pressure)	Low to moderate (although bacterial escape mutations may occur)
Impact on the microbiota	Often negative (dysbiosis and collateral effects)	Negligible: phages act only on their specific target
Clinical interpretation	Based on MIC values and S/I/R categories	Qualitative or semi-quantitative (lysis zones, PFU counts)
Routine clinical use	Yes, widely used in medical biology laboratories	No, still experimental or restricted to regulated compassionate use

Table 1: Comparison between the antibiogram and the phagogram. Adapted from Achour I. (2024).

Limitations and challenges

Despite its promising therapeutic potential, phage therapy still presents several limitations.

The high specificity of bacteriophages requires the performance of an individualized phagogram, which may delay patient management, particularly in emergency situations [9]. In addition, access to phages produced according to pharmaceutical-grade standards remains limited and depends on a small number of specialized facilities [19].

The emergence of bacterial resistance to phages may also occur, necessitating the use of phage cocktails (combining multiple viral strains against the same bacterial target) or combined therapeutic strategies [11]. More recently, genetically engineered phages have been developed, including:

- CRISPR-Cas phages, capable of delivering a CRISPR system into bacteria in order to cleave essential genetic sequences or resistance plasmids.
- Chimeric phages, combining optimized binding or lytic domains.
- Phages carrying therapeutic or vaccine-related payloads, such as enzymes, antimicrobial agents, or immunomodulatory molecules [19].

Furthermore, the host immune response may lead to partial neutralization of phages, particularly during repeated administrations [20].

Finally, the absence of a harmonized regulatory framework remains a major obstacle to the integration of phage therapy into routine clinical practice, limiting its use in many settings to compassionate or experimental indications [21].

Perspectives in medical biology

The growing development of phage therapy is redefining the role of the medical biologist, who is becoming a key contributor to personalized anti-infective strategies.

Their involvement extends from the identification of bacterial strains to the interpretation of phagogram results, in close collaboration with clinicians [8,18].

The development of phage banks, the standardization of methodologies, and the integration of phagogram results into laboratory information systems are expected to facilitate a broader and more structured implementation of this therapeutic approach [19].

In this context, the phagogram appears to be a crucial component governing the effective integration of phage therapy into clinical practice. Its optimization could represent a major driver in the transition toward precision microbiology.

Strengths

This review presents several strengths. It provides an up-to-date synthesis of current data regarding phage therapy, incorporating recent studies focused on clinical applications and combination strategies involving antibiotics.

It also highlights the central role of the phagogram, which remains insufficiently explored in the literature, by emphasizing its practical implications in diagnostic microbiology and personalized medicine.

Conclusion

Phage therapy represents a promising alternative in response to the growing prevalence of infections caused by multidrug-resistant bacteria. Its potential efficacy, particularly in complex infections, makes it an attractive complement to conventional antibiotic-based strategies.

However, its integration into routine clinical practice remains dependent on several challenges, foremost among them the standardization of the phagogram and improved access to therapeutic phages.

In this context, the medical biologist occupies a pivotal position at the core of the development of this approach, which could ultimately transform the management of resistant bacterial infections.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest related to this work.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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