Bacteriophage Therapy in Intensive Care Units: A Targeted Strategy to Combat Multidrug-Resistant Infections – A Review

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ABSTRACT

The rise of multidrug-resistant (MDR) bacterial infections, particularly in intensive care units (ICUs), poses a grave threat to global health, severely compromising the effectiveness of conventional antibiotics. This crisis has been further exacerbated by the COVID-19 pandemic, which led to the indiscriminate use of broad-spectrum antimicrobials and heightened susceptibility to secondary infections. In this context, bacteriophage (phage) therapy has re-emerged as a promising, targeted alternative capable of addressing MDR infections in critical care settings. Unlike traditional antibiotics, phages exhibit narrow host specificity, the ability to penetrate biofilms, and self-replicating potential at the infection site, making them ideal candidates for ICU integration. This review explores the therapeutic promise of phage therapy in ICU protocols, emphasizing strategies such as phage-antibiotic synergy (PAS), personalized phage cocktails, and engineered phages. It also highlights clinical evidence supporting phage efficacy, regulatory and infrastructural challenges, and the diagnostic tools required for effective implementation. Finally, the review argues for the integration of phage therapy as part of a forward-looking, One Health–aligned strategy to mitigate antimicrobial resistance and improve patient outcomes in ICU environments.

Keywords: Phage-antibiotic synergy, Personalized phage cocktails, Engineered bacteriophages, Carbapenem-resistant enterobacteriaceae, ICU multidrug-resistant infection management

Key Message

- Bacteriophage therapy targets multidrug-resistant ICU infections when antibiotics fail.
- Personalized and combination phage strategies show clinical potential.
- Regulatory, diagnostic, and trial design challenges remain for widespread adoption.
- Phage therapy preserves beneficial microbiota and adapts to bacterial resistance.

Introduction

The emergence and global spread of multi-drug-resistant (MDR) bacterial pathogens represent one of the most pressing challenges in contemporary clinical medicine, especially within the high-risk environment of intensive care units (ICUs).[1] MDR organisms are defined as strains that are non-susceptible to at least one agent in three or more antimicrobial categories, and their proliferation compromises the efficacy of available therapeutic options.[2] ICU settings, characterized by a high density of vulnerable patients and the routine use of invasive devices and broad-spectrum antibiotics, provide an ideal environment for the emergence and transmission of MDR organisms.[3] In this context, the search for alternative, more effective treatment modalities is not merely a scientific ambition but an urgent medical necessity.

Historically, antibiotics have been the basis of infection control in critical care. However, the relentless overuse, misuse, and inappropriate prescription of antimicrobials in both hospital and community settings have accelerated the natural evolution of resistance mechanisms.[4] The result has rendered many first-line and even last-resort antibiotics, such as colistin and carbapenems, ineffective against a growing number of pathogens. Further, COVID-19 exacerbated the MDR. The pandemic led to widespread overuse of antibiotics in hospitals and ICUs, despite low actual rates of bacterial co-infections among COVID-19 patients.[5] According to the World Health Organization (WHO), antimicrobial resistance (AMR) is among the top ten global public health threats facing humanity, with MDR infections contributing to increased morbidity, mortality, and healthcare costs.

ICUs serve as epicenters for the acquisition and dissemination of antimicrobial resistance. The occurrence of MDR bacterial infections in ICUs has increased dramatically over the past two decades, driven by several interrelated factors.[6] These include prolonged hospital stays, the frequent use of broad-spectrum antibiotics, invasive procedures, and immunosuppression due to underlying diseases or therapeutic interventions.

Among the most worrisome MDR organisms in ICU environments are:

- **Carbapenem-resistant Enterobacteriaceae (CRE)**: These bacteria are resistant to most beta-lactams, including carbapenems, which are considered last-line antibiotics.[7]
- **MDR *Acinetobacter baumannii*:** Known for its persistence in hospital environments and resistance to desiccation and disinfectants.[8]
- **MDR *Pseudomonas aeruginosa*:** Exhibits complex resistance mechanisms, including efflux pumps, enzyme production, and biofilm formation.[9]
- **Methicillin-resistant *Staphylococcus aureus*:** Continues to cause severe ICU-related infections, particularly ventilator-associated pneumonia and bloodstream infections.[10]

To counter these Infections, phage therapy has re-emerged as an alternative to antibiotics, which shows promise as a targeted and effective antimicrobial

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strategy. Phages are natural viruses that selectively infect and lyse bacteria and are gaining renewed attention as a precision weapon against MDR infections, especially in complex cases where conventional antibiotics fail.[11]

The potential of phage therapy in ICU settings remains underutilized. Unlike antibiotics, which exert broad-spectrum pressure on microbial communities and promote dysbiosis, phages offer high specificity, targeting only the pathogenic strains without harming the beneficial microbiota.[12] Additionally, they can self-amplify at the site of infection and evolve alongside bacterial hosts, thus maintaining efficacy even in the face of resistance development. These advantages position phage therapy as a powerful adjunct or alternative to antibiotics in the clinical management of MDR infections.[13] Figure 1 shows a diagrammatic representation of bacteriophage therapy in hospital settings.

The process begins with MDR pathogen infection in patients, followed by isolation and purification of MDR pathogens from clinical samples. Environmental sources such as wastewater are used for bacteriophage sample collection, from which phages are screened and subjected to bacteriophage isolation against the target pathogen. The isolated phages undergo morphological analysis and whole genome sequencing to ensure safety and therapeutic potential. Selected phages are then formulated into a bacteriophage cocktail, which is subsequently applied as a treatment strategy against MDR infections.

Methodology

A comprehensive literature search was performed in PubMed, Scopus, and Google Scholar, covering publications from January 2020 to 10th August 2025. The following structured search string was applied across databases: ("bacteriophage therapy" or "phage therapy"), ("ICU" or "intensive care unit" or "critical care"), and ("multidrug-resistant" or "antimicrobial resistance"). Additional terms such as *phage-antibiotic synergy* and *personalized phage cocktails* were also used to refine results. A total of 859 records were initially identified. After removing 31 duplicates, 828 records remained for screening. 261 records were excluded based on the title and abstract screening, leaving 567 full-texts for eligibility assessment. Based on the inclusion and exclusion criteria, 414 records were excluded and resulting in 153 records taken for the study. 59 articles included in the final synthesis. Details of the workflow are depicted in the literature search and study selection flow diagram in Figure 2.

Inclusion/Exclusion Criteria

- Inclusion: Studies on bacteriophage therapy for MDR infections in ICUs, human research, Preclinical animal, and exvivo studies directly relevant to ICU pathogens (included as supportive evidence, synthesized separately from human ICU data). English-language, peer-reviewed publications.
- Exclusion: Non-ICU studies and non-ICU pathogens, non-peer-reviewed, inadequate methodology.

The Promise of Bacteriophage Therapy in ICU Settings

Building on the advantages already outlined, the relevance of phage therapy in ICU settings becomes increasingly evident. Importantly, bacteriophages can disrupt bacterial biofilms, a critical advantage given that biofilm-associated infections are highly prevalent in ICU patients with catheters, ventilators, or surgical implants and are typically recalcitrant to antibiotics. Furthermore, phages do not harm the commensal microbiota, thus minimizing the risk of dysbiosis and secondary infections commonly associated with broad-spectrum antibiotics.[14]

In addition to their biological appeal, phages can be personalized to match the specific bacterial strains infecting a patient. This is especially important in ICUs, where pathogens can vary in resistance mechanisms and virulence profiles.[15] Personalized phage therapy involves isolating the bacterial pathogen from the patient, screening phage libraries for effective lytic activity, and formulating a customized cocktail. This approach has gained significant clinical attention and is increasingly being incorporated into compassionate-use cases and pilot clinical trials.[16] Notably, Hospitals and critical care units are exploring the

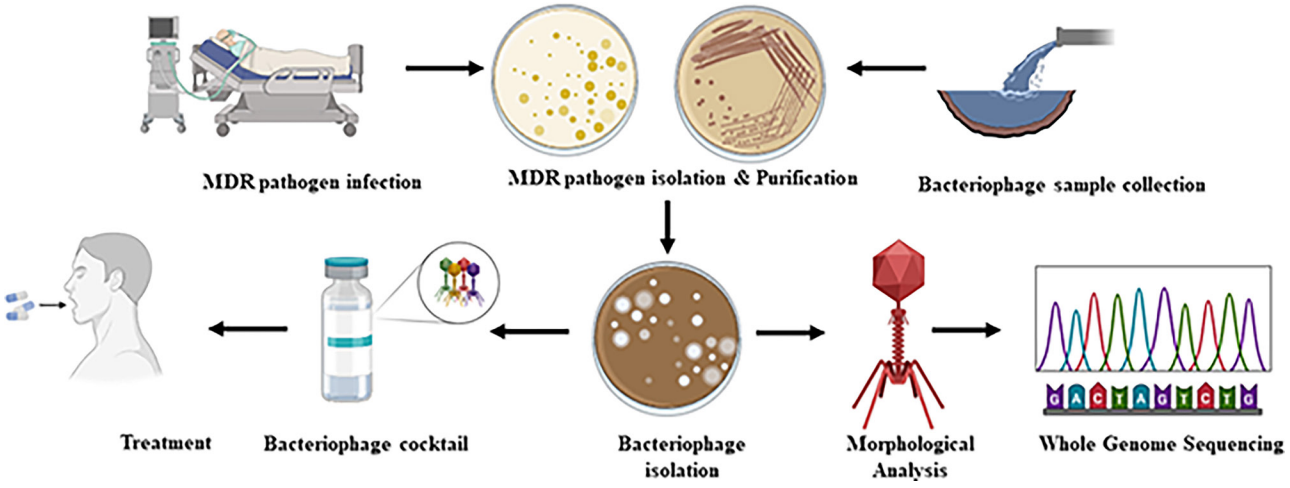

Fig 1 | Combating MDR bacteria using bacteriophages in hospital settings

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potential of integrating phage banks, rapid diagnostic tools, and in-house phage formulation units to support timely and targeted therapy.[17] Despite regulatory challenges and limited commercialization, growing evidence from clinical settings underscores the transformative potential of bacteriophage therapy, particularly when administered in tandem with antibiotics or engineered for enhanced efficacy. This synergy between phages and antibiotics, termed phage-antibiotic synergy (PAS), can not only increase bacterial killing but, in some cases, reverse resistance to antibiotics, making previously ineffective treatments viable again.[18]

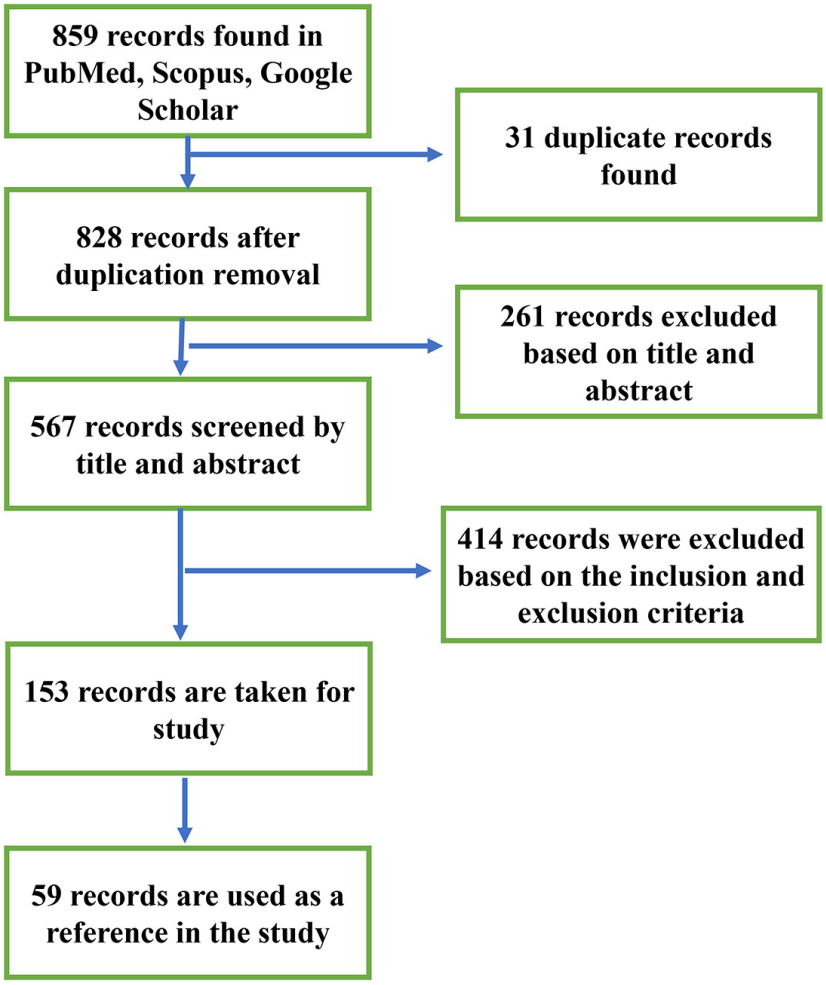

Fig 2 | Details of the workflow are depicted in a flow diagram of the literature search and study selection process

A wealth of clinical cases has begun to validate the efficacy of phage therapy in real-world ICU scenarios. One of the most comprehensive studies to date, conducted by,[19] examined the outcomes of 100 consecutive patients treated with personalized bacteriophage therapy across multiple centers. This retrospective multicenter observational study, published in Nature Microbiology, included a substantial number of ICU patients suffering from severe MDR infections, including ventilator-associated pneumonia, bloodstream infections, osteomyelitis, and prosthetic joint infections. The study reported clinical improvement in 77.2% of cases, with microbiological eradication achieved in 61.3% of patients. No serious phage-related adverse events were recorded, and outcomes were particularly encouraging in patients infected with *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Table 1A summarizes the phage therapy against MDR bacteria, and Table 1B summarizes the preclinical evidence for phage therapy against MDR bacteria. These findings offer compelling evidence that phage therapy, when appropriately matched to the infecting pathogen, can serve as a safe and effective last-resort treatment for ICU patients unresponsive to traditional antibiotics.

Beyond individual cases, several pilot trials and compassionate-use frameworks have laid the groundwork for broader clinical acceptance of phage therapy. While randomized controlled trials are limited, the growing success of personalized applications and the establishment of international phage consortia are accelerating clinical validation. Moreover, recent advances in synthetic biology now enable the engineering of phages to overcome host defense mechanisms, expand host range, or deliver CRISPR-based genetic payloads to silence resistance genes.[20] These engineered phages are being explored as next-generation antimicrobials

Table 1A | Phage therapy against MDR bacteria in ICUs

Sl.No	Bacteria	Phage	Outcome	References
1	*Klebsiella pneumoniae*	Phage -antibiotic synergy	Patient clinical outcomes significantly improved, and phage-antibiotic synergy (PAS) demonstrated high therapeutic efficacy against multidrug-resistant infections.	22
2	*Acinetobacter baumannii*	vB_AbaM_Acibel004 b	The treatment promotes faster recovery, reduces lung burden, reduces inflammation, and causes no adverse events in an ex vivo human lung model.	23
3	*Pseudomonas aeruginosa*	Personalized phage	Severe reduction of bacteria in a Cystic fibrosis patient	24

Table 1B | Preclinical evidence for phage therapy against MDR bacteria

Sl.No	Bacteria	Phage	Outcome	References
1	*Klebsiella pneumoniae*	Phage cocktail	Suppresses bacteria levels and attenuates liver Inflammation and disease severity in hepatobiliary injury-prone SPF mice.	25
2	*Pseudomonas aeruginosa*	PEV31- Phage	Phage-treated groups exhibited a significant reduction in pulmonary bacterial load by 1.3-1.9 $\log_{10}$	26
3	*Acinetobacter baumannii*	Phage (Bϕ-R2096)	In mouse model, phage Bϕ-R2096 improved survival (30% at MOI 0.1 to 100% at MOI 10 over 12 days), cleared lung bacteria by day 3, reduced histologic lung damage, and caused no mortality or serious side effects.	27

for ICU use, particularly in environments where pathogen evolution outpaces drug development.

Despite these encouraging outcomes, phage therapy in ICUs is not without challenges. Regulatory barriers persist, especially in countries lacking compassionate-use frameworks or tailored approval pathways for biologics. Additionally, the need for rapid pathogen identification, timely phage matching, and stringent GMP manufacturing standards remains a critical bottleneck.[21]

Synergistic Approaches and Personalization Strategies

The clinical deployment of bacteriophage therapy has gained substantial interest in ICU settings. However, to maximize its therapeutic potential and clinical relevance, phage therapy is increasingly being optimized through advanced strategies that include synergistic phage-antibiotic combinations, personalized phage cocktails tailored to individual pathogens, and molecular engineering of phages to expand their functionality.[28]

Phage-Antibiotic Synergy

The concept of PAS is one of the most innovative and practically valuable strategies in contemporary phage therapy. This phenomenon refers to the enhanced bactericidal effect observed when bacteriophages are co-administered with antibiotics, often leading to outcomes superior to either agent alone.[29] Unlike antagonistic drug interactions, PAS occurs when the sub-lethal activity of antibiotics induces physiological stress in bacterial cells, thereby enhancing phage adsorption, replication, or host lysis. In ICU settings, where time-sensitive infections are frequently unresponsive to monotherapies, PAS represents a strategic intervention capable of not only improving survival but also restoring sensitivity to previously ineffective antibiotics.[30]

Several in vitro and in vivo studies have demonstrated this synergy. For instance, phage application alongside aminoglycosides or beta-lactams has been shown to destabilize bacterial membranes, allowing for increased phage penetration.[31] Moreover, in the case of biofilm-associated infections such as ventilator-associated pneumonia or catheter-related bloodstream infections, PAS has shown significant promise.[32] Antibiotics can disrupt the outer matrix of the biofilm, exposing deeper bacterial layers to phage attack. Simultaneously, phage activity can degrade extracellular polymeric substances and weaken the biofilm's structural integrity, allowing antibiotics to reach their targets more effectively.[14] Clinical reports further validate these findings; for example, in compassionate-use cases of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* infections in ICU patients, PAS protocols resulted in faster bacterial clearance, reduced inflammation, and decreased ICU stay duration.[18,33] This dual-agent approach also appears to reduce the risk of resistance development, as the evolutionary pressure from both phages and antibiotics may constrain the pathogen's mutational pathways. Collectively, PAS is being recognized not only as a theoretical concept but also as a tangible therapeutic modality warranting further clinical exploration and institutional adoption.

Personalized Phage Cocktails

Another pillar of modern phage therapy is the formulation of personalized phage cocktails, designed to match the specific bacterial strains isolated from individual patients.[34] This precision-based approach counters one of the key limitations of traditional antibiotics: their inability to discriminate between pathogenic and commensal bacteria. In contrast, phages can be selected or engineered to target narrow-spectrum microbial populations with high specificity, a critical feature for immunocompromised or critically ill ICU patients, where microbiome preservation is essential.[35]

Personalized phage therapy begins with the isolation of the pathogen from clinical specimens (e.g., blood, sputum, urine, or wound swabs), followed by phagogram analysis similar to an antibiotic susceptibility test to identify the most effective lytic phages.[36] These phages are then combined into a cocktail to broaden the host range and prevent the rapid emergence of phage-resistant bacterial mutants. Studies have shown that using multiple phages with overlapping but distinct receptor targets can reduce the likelihood of resistance and increase therapeutic success.[37] Moreover, personalized phage cocktails are adaptable to polymicrobial infections, a frequent occurrence in ICU patients, where multiple pathogens coexist and complicate treatments.

Clinical outcomes from personalized phage therapy have been promising. In a study conducted by the Eliava Institute and collaborating hospitals, patients suffering from severe infections unresponsive to antibiotics showed complete resolution after receiving tailored phage formulations.[38] Similarly, in post-COVID ICU cases involving *Acinetobacter baumannii* and carbapenem-resistant Enterobacteriaceae, personalized cocktails were able to achieve bacteriological clearance within days, with no observed adverse effects.[7,8] The process of generating such cocktails has been accelerated by the establishment of phage bank repositories that maintain a wide library of pre-characterized phages available for rapid deployment. Emerging bioinformatics tools, AI-driven host range prediction models, and real-time sequencing technologies are further enhancing the speed and efficiency of personalized phage selection.[39]

Phage Engineering

Beyond natural phage-host interactions, the field of synthetic biology has revolutionized how bacteriophages are designed and deployed in therapeutic settings. Engineered phages can be modified to enhance their lytic capabilities, expand their host range, evade bacterial defense systems (such as CRISPR-Cas), or deliver therapeutic payloads such as antimicrobial peptides or CRISPR-Cas nucleases to disrupt resistance genes.[40] These advances are particularly relevant in ICU infections, where conventional phages may not possess the necessary attributes to overcome complex resistance barriers or intracellular persistence.

For example, researchers have engineered phages to express biofilm-degrading enzymes like

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depolymerases, enabling deeper penetration into chronic biofilm-associated infections common in ventilated or catheterized ICU patients.[41,42] Others have incorporated CRISPR-based systems into phage genomes, allowing for the targeted cleavage of plasmid-borne resistance genes within bacterial cells, effectively curing them of their drug resistance.[43,44] Some engineered phages have even been modified to overcome bacterial mutations in phage receptors, thus reducing the frequency of therapeutic failure due to resistance.[45]

Clinical Evidence and Challenges

While the clinical potential of bacteriophage therapy has been increasingly recognized in recent years, particularly in the context of MDR infections in ICUs, its integration into mainstream medical practice still faces a complex landscape of challenges. Emerging evidence from both observational studies and compassionate-use cases strongly supports phage therapy's efficacy, safety, and relevance in critical care. However, these promising outcomes are tempered by practical constraints related to standardization, regulation, scalability, and real-time implementation.[46] An infographic summary showing the pathways of clinical evidence shown in Figure 3.

Current Limitations and Regulatory Concerns

Despite growing enthusiasm, bacteriophage therapy continues to struggle with several unresolved limitations, particularly in regulatory and pharmacological domains. A primary issue is that the inherent biological complexity of phages, which defies conventional pharmaceutical classification.[47] Unlike small-molecule drugs with fixed molecular structures and predictable pharmacokinetics, phages are living entities that evolve, replicate within the host, and exhibit narrow host ranges. These characteristics challenge traditional models of drug development, quality control, and standardization.

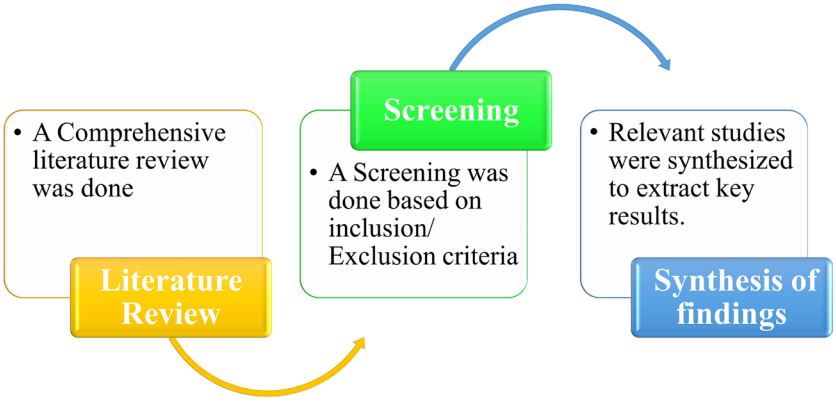

Fig 3 | An infographic summarising clinical evidence pathways

In most regulatory frameworks, including those governed by the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and India's Central Drugs Standard Control Organization (CDSCO), there is no formal classification for bacteriophages as therapeutic agents.[48] As a result, phages fall into a gray area regulated either as biologics or as investigational new drugs under case-by-case considerations. The regulatory landscape for bacteriophage therapy differs considerably between the United States and the European Union, resulting in unique challenges and outstanding gaps. In the United States, the Food and Drug Administration (FDA) currently regulates phage-based therapies as biological drugs via the Investigational New Drug (IND) pathway; this approach requires standard preclinical data, phased clinical trials, and GMP manufacturing. The FDA allows extended access to the INDs of phage therapy under exceptional situations for patients when they cannot enroll in clinical trials.[49] In contrast, the European Medicines Agency (EMA) treats phage therapies as either biological medicinal products or considers them under advanced therapy medicinal product (ATMP) guidelines. The centralized EMA procedure is the primary route for approval in the EU, but there is significant ambiguity about the classification of phages, and no phage products have obtained full EMA authorization. Some member states (like Belgium and France) allow use via national 'hospital exemption' or magistral preparation frameworks, enabling tailored phage preparations for specific patients outside the commercial market.[50] Table 2 provides a comparative analysis of the distinct regulatory pathways for therapeutic approval established by key global agencies, such as the U.S. FDA,EMA and CDSCO.

Compassionate-use frameworks have allowed some progress in addressing these hurdles, but they do not constitute a scalable model for widespread clinical use. For phage therapy to transition from experimental intervention to standardized medical care, regulatory agencies must develop novel evaluation metrics tailored to phages unique biological properties. This includes defining potency standards, pharmacodynamics, stability requirements, and post-market surveillance systems specific to phage-based products.[51]

Table 2 | Consolidated summary of regulatory pathways

Sl.No	Region/Agency	Primary Regulatory Pathway	Requirements & Notes	Special Access/Exemptions
1	FDA	Biological drugs	Requires standard preclinical data, phased clinical trials, and GMP manufacturing.	Extended access (compassionate use) is allowed for patients unable to enroll in clinical trials.
2	EMA	Biological medicinal products or considers them under advanced therapy medicinal product (ATMP) guidelines	Significant ambiguity in classification; no phage products have received full EMA authorization to date.	Some member states (e.g., Belgium, France) permit use through national 'hospital exemption' or magistral preparation frameworks for tailored, non-commercial use.
3	CDSCO	No formal classification	No guidelines	–

Infrastructure and Diagnostic Needs

Beyond regulatory and biological challenges, the successful deployment of phage therapy in ICU settings is dependent on the availability of robust infrastructure, including diagnostic platforms, phage banks, manufacturing facilities, and trained personnel.[52] Unlike antibiotics, which are readily available as off-the-shelf formulations, phage therapy often requires a customized, patient-specific approach that relies on timely identification of the causative bacterial strain and rapid matching with an appropriate lytic phage. This process is logistically intensive and time-sensitive, making it ill-suited to many healthcare systems that lack integrated diagnostic and therapeutic capabilities.

One of the most critical needs is the development of high-throughput and rapid diagnostic tools capable of identifying bacterial pathogens at the species and strain level within hours.[53] Traditional culture-based diagnostics are time-consuming, often requiring 48–72 hours of unacceptable delay in ICU settings where infection progression can be fatal. Recent advances in next-generation sequencing (NGS), multiplex polymerase chain reaction (PCR), and matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry have significantly improved the speed and accuracy of pathogen identification.[54] However, these technologies are not yet universally available, especially in low- and middle-income countries, and they require substantial investments in hardware, reagents, and skilled operators.

In addition to diagnostics, there is a critical need for well-curated and accessible phage libraries, repositories characterized by host range, lytic activity, and genomic safety. Such libraries would enable rapid screening and formulation of personalized phage cocktails.[55] Several institutions, such as the Eliava Institute (Georgia), Phage Directory (U.S.), and Phage Bank Korea, have made strides in this direction. However, most hospitals and ICUs still lack direct access to such resources, resulting in delays and inconsistencies in treatment. The establishment of regional phage banks, coupled with digital platforms that facilitate inter-institutional collaboration, could revolutionize the speed and accuracy of phage deployment in emergency care.[56]

Equally important is the establishment of in-hospital phage preparation units capable of rapidly formulating, purifying, and delivering phage therapeutics under aseptic conditions. These units would need to comply with biosafety and sterility standards while ensuring the absence of endotoxins, prophages, and resistance genes.[57] Investments in such infrastructure would not only streamline phage deployment but also enhance safety and reproducibility, two factors critical for ICU integration.

Risk and Mitigation

Despite encouraging clinical outcomes, phage therapy in ICUs is not without risks. A major concern is the endotoxin burden released during bacterial lysis, which can worsen systemic inflammation or septic shock; this can be mitigated by employing high-purity GMP-grade phage preparations with validated endotoxin removal protocols.[58] Another limitation is the development of anti-phage antibodies, particularly in prolonged or repeated dosing, which may neutralize therapeutic phages; rotating phage cocktails, limiting treatment duration, or combining phages with antibiotics can reduce this risk. The potential for horizontal gene transfer (HGT), especially with temperate phages, also poses a theoretical safety challenge; to minimize this, only strictly lytic, genomically characterized phages without virulence or resistance genes should be used.[59] Finally, bacterial resistance to phages can emerge, particularly with monophage therapy; mitigation strategies include using diverse phage cocktails, employing PAS to constrain mutational escape, or leveraging engineered phages with expanded host ranges and anti-resistance mechanisms.[18,31,35]

Future Directions: Research Priorities

The following research priorities outline critical areas for advancing the clinical application and translational development of bacteriophage therapy in intensive care and infectious disease settings. Addressing these priorities will help bridge current knowledge gaps, optimize therapeutic strategies, and accelerate safe, effective, and widely accessible use of phage therapeutics for combating multidrug-resistant infections in ICUs.

- Investigate phage pharmacokinetics and pharmacodynamics in septic and critically ill patients, including tissue distribution and clearance rates.
- Conduct cost-effectiveness analyses of phage therapy versus standard antibiotic regimens for MDR infections in ICUs.
- Develop and standardize rapid diagnostic assays and phagogram techniques to enable timely, personalized phage selection.
- Advance clinical trials on genetically engineered and synthetic phages with enhanced lytic ability and host range.
- Explore optimal dosing, administration routes (IV, inhaled, local), and combination strategies (phage-antibiotic synergy) in diverse ICU infection models.
- Assess immunological responses and anti-phage antibody development in immunocompromised and septic patients.
- Study the long-term effects of phage therapy on patient microbiome balance and risk of resistance emergence.
- Establish scalable GMP production, quality control standards, and regulatory frameworks for clinical-grade phage therapeutics.

Conclusion

MDR infections are escalating, particularly in the high-risk and resource-intensive environment of ICUs, highlighting the urgent need for novel antimicrobial strategies. Bacteriophage therapy, once sidelined by the antibiotic revolution, is now experiencing a rebirth

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as a highly promising, precision-targeted, and biologically adaptable intervention. Over the past decade, and particularly in the wake of the COVID-19 pandemic, bacteriophages have reemerged as valuable allies in the fight against pathogens that evade even the most potent antimicrobial drugs. Clinical successes across multiple compassionate-use cases and observational studies, such as the 100-case evaluation by[19] have substantiated the safety and efficacy of phage therapy in critically ill patients who have exhausted conventional treatment options.

Phage therapy offers a suite of unique advantages highly compatible with ICU settings: it is specific, self-amplifying, capable of biofilm penetration, and inherently capable of evolving to overcome bacterial resistance. When used in conjunction with antibiotics, it opens up new therapeutic paradigms through PAS, reviving the effectiveness of existing antimicrobials and slowing resistance development. Personalized phage cocktails and engineered phages further enhance their clinical applicability, providing customizable, strain-specific responses to diverse and evolving pathogens. In particular, the integration of phage therapy into ICU protocols represents a forward-looking strategy that aligns with the One Health approach, linking human medicine, microbiological innovation, and antimicrobial stewardship into a cohesive framework for sustainable disease control.

In conclusion, the mounting burden of antimicrobial resistance, particularly in ICUs, has created a critical window of opportunity to reimagine infection management through biologically intelligent therapies like bacteriophages. Phage therapy, once relegated to historical footnotes, now stands at the forefront of 21st-century infectious disease medicine. With the right convergence of clinical evidence, regulatory innovation, technological advancement, and global collaboration, phage therapy can transition from an experimental solution to a cornerstone of modern ICU infection control. It is not merely an alternative to antibiotics but a complementary and, often, superior strategy for restoring therapeutic efficacy, protecting vulnerable patients, and safeguarding the future of global health.

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