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Role of Bacteriophage Therapy Against Multidrug-Resistant Bacteria in Chronic Wounds

Gaikwad Aishwarya Rajendra[1] and Dr. Naveen Singh Chouhan[2]
[1]Research Scholar, Department of Microbiology
[2]Professor, Department of Microbiology
Vikrant University, Gwalior, M.P

Abstract: *Chronic wounds represent a major healthcare challenge due to prolonged healing time, recurrent infection, and increasing prevalence of multidrug-resistant (MDR) bacterial pathogens. Conventional antibiotic therapy has become progressively ineffective against resistant organisms such as Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter baumannii, and Enterococcus faecalis. Bacteriophage therapy has emerged as a promising biological alternative for combating MDR bacterial infections in chronic wounds. Bacteriophages are viruses that specifically infect and lyse bacterial cells without affecting normal human flora. Their high specificity, self-replicating nature, biofilm penetration capability, and low toxicity make them attractive therapeutic agents.*

This paper explores the mechanisms, therapeutic applications, advantages, limitations, and future prospects of bacteriophage therapy in chronic wound management. The study further discusses bacteriophage-host interactions, phage cocktails, synergistic effects with antibiotics, and clinical evidence supporting phage therapy. Recent advancements in bioengineered phages and personalized phage therapy are also highlighted. The findings indicate that bacteriophage therapy could become an effective strategy to reduce antibiotic resistance and improve wound healing outcomes in patients suffering from chronic infections..

Keywords: Bacteriophage therapy, biofilms, phage cocktails, antimicrobial resistance, wound healing, personalized medicine.

I. INTRODUCTION

Chronic wounds are wounds that fail to proceed through the normal stages of healing within an expected period, usually three months. These wounds include diabetic foot ulcers, venous leg ulcers, pressure ulcers, and burn wounds. Chronic wounds are often colonized by polymicrobial communities that develop resistance against conventional antimicrobial therapies. The emergence of multidrug-resistant bacteria has significantly complicated wound management worldwide. Organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and carbapenem-resistant *Pseudomonas aeruginosa* are frequently associated with chronic wound infections.

Antibiotic resistance occurs due to excessive antibiotic usage, horizontal gene transfer, genetic mutations, and biofilm formation. Biofilms are structured bacterial communities enclosed within extracellular polymeric substances that protect bacteria from antibiotics and host immune responses. Biofilm-associated infections are extremely difficult to eradicate using traditional antibiotics because drug penetration becomes limited and bacterial metabolic activity decreases within biofilms.

Bacteriophage therapy has gained renewed attention as a potential solution to antibiotic resistance. Bacteriophages, commonly known as phages, are viruses that infect bacteria by attaching to specific receptors on bacterial surfaces. After penetration, phages replicate within bacterial cells and eventually cause bacterial lysis. Since their discovery by Frederick Twort and Félix d'Hérelle in the early twentieth century, bacteriophages have been explored for therapeutic

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purposes. However, the introduction of antibiotics temporarily reduced interest in phage therapy. The rise of antimicrobial resistance has once again highlighted the importance of phage-based therapeutics.

BIOLOGY AND MECHANISM OF BACTERIOPHAGES

Bacteriophages are highly abundant biological entities found in soil, water, sewage, and the human microbiome. Structurally, phages consist of nucleic acid enclosed within a protein capsid. Some possess tail fibers that facilitate attachment to bacterial hosts.

The bacteriophage life cycle generally follows two pathways:

Lytic Cycle

Lysogenic Cycle

In the lytic cycle, phages attach to bacterial receptors, inject their genetic material, synthesize viral components, assemble progeny phages, and lyse the bacterial cell. The lytic cycle is therapeutically valuable because it directly destroys pathogenic bacteria.

The lysogenic cycle involves integration of phage DNA into the bacterial chromosome, forming a prophage. Temperate phages following lysogenic cycles may transfer virulence genes and are generally avoided in therapeutic applications.

The kinetics of bacteriophage replication may be represented as:

$$\frac{dP}{dt} = \beta BP - \delta P$$

where:

P = phage population

B = bacterial population

β = phage replication rate

δ = phage decay constant

This equation demonstrates the self-amplifying nature of phages during bacterial infection.

MULTIDRUG-RESISTANT BACTERIA IN CHRONIC WOUNDS

Chronic wound environments favor bacterial persistence due to reduced oxygenation, impaired immunity, necrotic tissue, and excessive inflammation. MDR pathogens dominate these wounds and reduce treatment success.

COMMON MDR BACTERIA IN CHRONIC WOUNDS

Bacterial Species	Resistance Characteristics	Clinical Impact
Staphylococcus aureus (MRSA)	Resistant to β-lactam antibiotics	Delayed healing and systemic infection
Pseudomonas aeruginosa	Carbapenem resistance	Strong biofilm formation
Acinetobacter baumannii	Extensive drug resistance	Hospital-acquired wound infections
Enterococcus faecalis	Vancomycin resistance	Persistent wound colonization
Klebsiella pneumoniae	ESBL production	Tissue necrosis and inflammation

These pathogens exhibit high adaptability and survive harsh wound environments by producing virulence factors and forming protective biofilms.

BIOFILM FORMATION AND CHALLENGES

Biofilms play a central role in chronic wound persistence. Bacteria embedded within biofilms become 100–1000 times more resistant to antibiotics than planktonic bacteria.

Biofilm formation occurs in four stages:

Initial attachment

Microcolony formation

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Biofilm maturation
Dispersion
The biofilm growth process can be represented mathematically as:

$$N(t) = N_0 e^{rt}$$

where:
N(t) = bacterial population at time t
N_0 = initial bacterial count
r = growth rate constant
Bacteriophages can penetrate biofilms through enzymatic degradation of extracellular polymeric substances. Many phages produce depolymerases capable of breaking down biofilm matrices, thereby improving bacterial eradication.

THERAPEUTIC APPLICATIONS OF BACTERIOPHAGE THERAPY

Bacteriophage therapy involves administration of lytic phages directly to infected wounds. Phages may be applied topically, intravenously, orally, or through impregnated dressings.

MODES OF PHAGE ADMINISTRATION

Administration Method	Advantages	Limitations
Topical application	Direct wound targeting	Requires repeated dosing
Intravenous delivery	Treats systemic infection	Immune clearance possible
Phage-embedded dressings	Sustained release	Stability concerns
Hydrogels and nanofibers	Enhanced penetration	Manufacturing complexity

Topical application remains the most effective approach for chronic wounds because it delivers high phage concentrations directly to infection sites.

PHAGE COCKTAILS AND COMBINATION THERAPY

Single-phage therapy may lead to bacterial resistance development. To overcome this issue, researchers use phage cocktails containing multiple phages targeting different bacterial receptors.
Combination therapy involving bacteriophages and antibiotics has shown synergistic effects. Phages disrupt biofilms and increase antibiotic penetration, while antibiotics weaken bacterial defense mechanisms.

ADVANTAGES OF PHAGE-ANTIBIOTIC SYNERGY

Feature	Therapeutic Benefit
Enhanced bacterial killing	Faster infection clearance
Reduced antibiotic dosage	Lower toxicity
Biofilm disruption	Improved wound healing
Delayed resistance development	Long-term therapeutic efficacy

Studies indicate that phage-antibiotic combinations significantly reduce bacterial load compared with monotherapy.

CLINICAL EVIDENCE OF PHAGE THERAPY

Several experimental and clinical studies have demonstrated the effectiveness of bacteriophage therapy against chronic wound infections.

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SELECTED STUDIES ON PHAGE THERAPY

Study	Target Organism	Outcome
Fish et al. (2016)	*Pseudomonas aeruginosa*	Reduced wound bacterial load
Jault et al. (2019)	Burn wound pathogens	Improved infection control
Morozova et al. (2018)	MRSA	Enhanced healing rates
Abedon et al. (2017)	Biofilm-associated bacteria	Effective biofilm reduction

Clinical observations suggest that phage therapy can accelerate granulation tissue formation and decrease wound inflammation.

ADVANTAGES OF BACTERIOPHAGE THERAPY

Bacteriophage therapy offers several benefits over traditional antibiotics:
High specificity toward target bacteria
Minimal disruption of beneficial microbiota
Self-replication at infection sites
Effective biofilm penetration
Reduced toxicity and side effects
Potential against antibiotic-resistant bacteria
Adaptability through phage evolution
Unlike broad-spectrum antibiotics, phages selectively eliminate pathogenic bacteria while preserving healthy microbial communities.

LIMITATIONS AND CHALLENGES

Despite promising outcomes, several limitations hinder widespread clinical implementation of phage therapy.

MAJOR CHALLENGES

Challenge	Description
Narrow host range	Individual phages target limited bacterial strains
Immune response	Neutralization by host immunity
Regulatory barriers	Lack of standardized approval frameworks
Phage resistance	Bacterial mutation against phage receptors
Manufacturing issues	Difficulty in large-scale purification

Regulatory concerns remain one of the largest barriers because phage preparations require personalized customization based on bacterial susceptibility.

ADVANCES IN BIOENGINEERED PHAGES

Modern biotechnology has enabled genetic modification of bacteriophages to improve therapeutic efficiency. Engineered phages can carry antimicrobial peptides, biofilm-degrading enzymes, or CRISPR-Cas systems targeting resistance genes.
CRISPR-assisted phage therapy selectively removes antibiotic resistance determinants from bacterial populations. Bioengineered phages also enhance host specificity and prolong phage persistence within wound tissues.
Synthetic biology approaches may further improve stability, safety, and therapeutic precision of phage-based treatments.

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PERSONALIZED PHAGE THERAPY

Personalized phage therapy involves isolating bacterial strains from patients and selecting phages specifically active against those pathogens. Personalized approaches maximize therapeutic efficacy and reduce treatment failure.

The personalized treatment process includes:

Isolation of wound bacteria
Antibiotic susceptibility testing
Phage screening
Phage amplification
Clinical administration
Monitoring therapeutic response

Personalized phage banks are increasingly being developed to support rapid therapeutic interventions.

FUTURE PERSPECTIVES

The future of bacteriophage therapy depends on multidisciplinary collaboration among microbiologists, clinicians, genetic engineers, and pharmaceutical industries. Artificial intelligence may help predict phage-host interactions and optimize phage cocktail design. Nanotechnology-based phage delivery systems could improve stability and targeted delivery.

Future research should focus on:

Large-scale randomized clinical trials
Standardization of phage formulations
Long-term safety studies
Regulatory harmonization
Development of universal phage libraries

Integration of phage therapy into wound care protocols may substantially reduce global antimicrobial resistance burden.

II. CONCLUSION

Bacteriophage therapy represents a promising alternative strategy against multidrug-resistant bacterial infections in chronic wounds. Its ability to specifically target pathogenic bacteria, penetrate biofilms, and synergize with antibiotics makes it highly valuable in modern wound management. Although several regulatory, immunological, and manufacturing challenges remain unresolved, ongoing advancements in genetic engineering, synthetic biology, and personalized medicine continue to improve therapeutic potential. Clinical evidence increasingly supports the safety and efficacy of phage therapy in chronic wound treatment. Therefore, bacteriophage-based therapeutics may become an important component of future antimicrobial strategies aimed at overcoming the global crisis of antibiotic resistance.

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