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REVIEW

Management of Diabetic Foot Infections Using Phage Therapy

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Abstract: Diabetic foot infections (DFIs) represent a major and increasing complication of diabetes mellitus, often leading to hospitalization, osteomyelitis, and lower limb amputation. The rising prevalence of multidrug-resistant pathogens in DFIs has limited the effectiveness of conventional antibiotic therapy, emphasizing the need for alternative or adjunctive approaches. Bacteriophage therapy has emerged as a promising strategy due to its specificity to target bacteria, ability to penetrate and disrupt biofilms, and activity against multidrug-resistant organisms, while generally demonstrating a favorable safety profile with minimal effects on host tissues. This review critically evaluates current evidence for phage therapy in DFIs, which is dominated by in vitro studies, animal models, and a limited number of compassionate use and small clinical series. Reported outcomes show effectiveness against key pathogens including *Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter baumannii, Escherichia coli*, and *Enterococcus* species, with preliminary evidence of reduced bacterial burden and improved wound healing in select patients. Despite these encouraging findings, clinical translation is challenged by narrow phage host ranges, the need for rapid phage-pathogen matching, standardization of production, regulatory hurdles, and incomplete understanding of pharmacokinetics and host immune interactions. Therefore, while phage therapy represents a potentially safe and effective adjunct to conventional DFI management, further well-designed preclinical studies and randomized clinical trials, alongside optimized delivery systems and regulatory frameworks, are required to fully establish its clinical utility.

Keywords: diabetic foot infections, phage therapy, antibiotics

Introduction

Diabetes mellitus (DM) is an increasingly prevalent chronic condition, affecting millions globally.[1] As of 2019, approximately 436 million people were living with DM, and this number is projected to rise to 578 million by 2030.[2] This rapid increase in DM prevalence is paralleled by a surge in complications and hospitalizations, placing an immense burden on healthcare systems worldwide.[3] Among these complications, diabetic foot infections (DFIs) have emerged as one of the most serious, accounting for a significant portion of diabetes-related hospitalizations.[4] Individuals with DM face a hospitalization risk for DFIs that is 50 times higher than those without the condition.[5]

Chronic wounds in people with diabetes encompass a heterogeneous spectrum of pathological entities. Diabetic foot ulcers represent open lesions of the skin and underlying tissue that typically arise from neuropathy, ischemia, or mechanical trauma, whereas diabetic foot infections refer specifically to the microbial invasion of these ulcers or adjacent tissues, often characterized by local and systemic inflammatory responses.[6] This distinction is clinically relevant, as not all diabetic foot ulcers are infected, yet progression to infection markedly increases morbidity, treatment complexity, and the risk of limb loss.[7]

The clinical management of DFIs is particularly challenging due to the high rate of infectious complications.[8] Around 60% of diabetic foot ulcers (DFUs) progress to infection, with osteomyelitis being one of the most common and severe outcomes.[9] Osteomyelitis is not only difficult to treat but is also associated with alarmingly high rates of amputation,

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occurring in 10–15% of patients with moderate infections and in 50–60% of those with severe infections.[10] The conventional treatment approach typically involves prolonged antibiotic regimens or, in severe cases, amputation.[11] However, these strategies come with significant limitations. Extended antibiotic use can promote antimicrobial resistance, severely limiting future treatment options and exacerbating a growing global health crisis.[11,12] Amputation, on the other hand, carries profound psychological and physical consequences, including significant anxiety and reduced quality of life.[13,14] The growing prevalence of multidrug resistant organisms in this setting further constrains therapeutic options and is now recognized as a major driver of treatment failure and recurrence.[15]

Given these challenges, there is an urgent need for innovative therapies that can more effectively manage DFIs while mitigating the risks associated with current treatment modalities. Bacteriophages (phages), naturally occurring viruses that specifically target and kill bacteria, represent a promising alternative. First used therapeutically in 1919, phage therapy lost prominence with the advent of antibiotics, which were initially easier to produce and administer and less prone to resistance.[16] However, the escalating crisis of antibiotic resistance has reignited global interest in phage therapy.[17,18]

Phage therapy has shown considerable promise in treating a wide range of infections, including chronic wounds, with minimal adverse effects.[19,20] Notably, phages are capable of penetrating and degrading biofilms, which are often implicated in the chronicity and antibiotic resistance of DFIs.[21,22] This unique ability to overcome biofilm-related treatment failures positions phage therapy as a potentially transformative approach in the management of DFIs.[23] Preliminary clinical observations have suggested reductions in bacterial burden and improved wound healing in select patients; however, robust randomized controlled trials remain scarce, and the overall quality of clinical evidence is still limited.[24]

This review employs a narrative synthesis methodology, incorporating findings from recent preclinical and clinical studies to provide a comprehensive overview of the application of phage therapy in DFIs. By synthesizing current evidence systematically, this approach allows the reader to understand the efficacy, limitations, and potential clinical implications of phage therapy in managing these complex infections. The purpose of this review is to critically evaluate the current evidence on the application of phage therapy in managing DFIs. By exploring its potential benefits, limitations, and clinical implications, this review aims to underscore the importance of integrating phage therapy into the treatment arsenal for DFIs, potentially offering a more effective and sustainable solution to this growing global health challenge.

Microbial Composition in Diabetic Foot Infections

DFIs are typically polymicrobial, involving a complex community of aerobic and anaerobic bacteria. The most commonly isolated pathogens include *Staphylococcus aureus* and *Pseudomonas aeruginosa*, along with other Gram-positive and Gram-negative bacteria.[5,25,26]

Staphylococcus aureus

S. aureus is a Gram-positive bacterium known for causing a wide range of infections, including severe wound infections, skin and soft tissue infections, and osteomyelitis, due to its evolving strains.[27] *S. aureus* frequently colonizes the skin and mucosal surfaces, particularly in children, as well as in individuals with HIV or diabetes, who are more susceptible to colonization by this pathogen.[28–30] Hospital-acquired methicillin-resistant *S. aureus* (MRSA) strains are prevalent in clinical settings and typically infect immunocompromised patients, whereas community-associated MRSA strains can cause infections in otherwise healthy children and adults.[31–33]

Diabetic patients are at a higher risk of MRSA colonization and infection, which can significantly impact their clinical outcomes. A meta-analysis by Stacey et al revealed that the prevalence of MRSA colonization among diabetic patients is notably higher than in non-diabetics, with a pooled colonization rate of 9.2% among 11,577 diabetic patients. Furthermore, MRSA prevalence in DFIs was reported to be 16.78% among 10,994 cases, underscoring the importance of targeted screening and alternative therapeutic strategies.[34] Similarly, a systematic review by Zhou et al analyzed MRSA prevalence in DFUs across 20 countries, reporting an overall prevalence of 17%, with notable regional differences: 61% in South America, 20% in North America, 19% in Europe, 13% in Africa, and 11% in other regions.[35]

Although vancomycin-resistant *S. aureus* (VRSA) remains rare, its emergence poses an additional therapeutic challenge, emphasizing the need for continuous surveillance.[36,37]

S. aureus is the most common DFI isolate, often delaying wound healing and increasing amputation risk.[38,39] In patients with DFIs, MRSA infections are particularly concerning. Qi et al reported that among hospitalized patients with MRSA infections, 46.9% developed osteomyelitis and 40.8% underwent amputation or experienced disability, significantly higher than in patients infected with other pathogens.[40] Saltoglu et al observed that MRSA accounted for 19.4% of isolates, and inappropriate initial therapy was associated with reinfection and adverse outcomes.[41] Gramberg et al reported a hazard ratio (HR) for amputation of 0.7 (95% CI: 0.39–1.1) and HR for mortality of 0.89 (95% CI: 0.49–1.6) for *S. aureus* infections, indicating a moderate but clinically significant impact on patient outcomes.[42] Methicillin-resistant *S. epidermidis* (MRSE) and MRSA from DFUs also exhibit high multidrug resistance (MDR).[43]

Pseudomonas aeruginosa

P. aeruginosa is a Gram-negative bacterium that plays a significant role in the pathogenesis of DFUs.[44] Saltoglu et al found that 18.2% of *P. aeruginosa* isolates were MDR, and Gramberg et al reported that Gram-negative infections, including *P. aeruginosa*, were associated with a HR for amputation of 1.3 (95% CI: 0.78–2.1) and HR for mortality of 2.6 (95% CI: 1.4–4.8), highlighting their contribution to severe clinical outcomes and higher morbidity.[41]

Garousi et al conducted a global analysis of *P. aeruginosa* in DFU infections. Their systematic review identified a global prevalence of 16.6% for *P. aeruginosa* in DFUs, with the rates varying by region: 18.5% in Asia, 16.3% in Africa, and 11.1% in Western countries.[45] However, a recent systematic review and meta-analysis by Makeri et al focused on the prevalence of *P. aeruginosa* and *S. aureus* in DFUs across Africa, revealing that *S. aureus* (19.9%) is more frequently isolated than *P. aeruginosa* (11.8%). Despite this, *P. aeruginosa* isolates demonstrated a concerning MDR rate of 41.8%, emphasizing the need for antimicrobial stewardship and alternative therapeutic approaches.[46]

In patients with DM, the presence of *P. aeruginosa* in DFUs is associated with prolonged wound healing, increased risk of complications, and higher rates of morbidity.[47] Despite its importance, *P. aeruginosa* is often overtreated empirically. Veve et al found it in only 9% of DFU cultures, suggesting that antipseudomonal coverage should be reserved for patients with specific risk factors, such as prior treatment failure or immunocompromise.[48] Intrinsic resistance mechanisms of *P. aeruginosa* include low outer membrane permeability and efflux pumps, conferring resistance to many beta-lactams (except antipseudomonal penicillins, ceftazidime, cefepime, and carbapenems excluding ertapenem), aminoglycosides, and fluoroquinolones.[49]

Klebsiella pneumoniae

K. pneumoniae is a Gram-negative bacterium that has become an increasingly important pathogen in DFIs.[50] Although it is typically a part of the normal microbiota in the human gastrointestinal tract, it can transform into a highly pathogenic opportunistic organism, particularly in patients with diabetes due to impaired immunity, poor tissue perfusion, and delayed wound healing.[51,52]

In the study by Sultana et al, *K. pneumoniae* was identified as a prevalent Gram-negative bacterium in DFUs, though the specific prevalence rate within their study is not directly provided. The study, which included data from 73 studies across 12 Asian countries, highlighted that *K. pneumoniae* is part of the 77% of DFU infections attributed to Gram-negative bacteria.[53]

Recent evidence further indicates that *K. pneumoniae* infections in DFIs are associated with more severe disease outcomes compared to other Gram-negative pathogens. These infections have been linked to prolonged wound healing, higher incidence of osteomyelitis, and increased rates of lower-limb amputation in affected patients.[54] For example, in a study of 122 DFU patients, *K. pneumoniae* isolates demonstrated high resistance to commonly used antibiotics, including carbapenems, which limited therapeutic options and was associated with more complicated clinical courses.

A major challenge in treating *K. pneumoniae* infections in DFUs is the emergence of MDR strains. According to the study by Yang et al the prevalence of MDR *K. pneumoniae* in DFUs was found to be 3.50% (95% CI: 2.31–4.91%).[15] Many strains of *K. pneumoniae* have developed resistance to multiple antibiotics, including those commonly used to treat DFIs. This resistance is often due to the production of extended-spectrum beta-lactamases (ESBLs) and carbapenemases, enzymes that break down a wide range of antibiotics, rendering them ineffective.[55] The presence of these resistant strains significantly limits treatment options and increases the likelihood of complications such as osteomyelitis (bone infection)

and, in severe cases, the need for amputation.[56] Additionally, extensively drug-resistant (XDR) *K. pneumoniae* strains have been increasingly reported in chronic wounds, displaying near-total resistance to ampicillin, amoxicillin, and nitrofurantoin, with only relative susceptibility to amikacin, highlighting the clinical threat posed by these pathogen.[57,58]

The pathogenicity of *K. pneumoniae* in DFIs is driven by several virulence factors. These include adhesins, which facilitate bacterial attachment to host tissues; capsules, which protect bacteria from phagocytosis; and siderophores, which enable iron acquisition essential for bacterial proliferation.[59] Moreover, robust biofilm formation by *K. pneumoniae* contributes to persistent infection, resistance to host defenses and antibiotics, and the chronicity of DFIs. These factors collectively explain why highly pathogenic *K. pneumoniae* infections often result in more severe clinical outcomes, delayed wound healing, and increased risk of amputation.[60]

Acinetobacter baumannii

A. baumannii is a Gram-negative bacterium that has gained notoriety as a highly resilient and opportunistic pathogen, particularly in healthcare settings.[61] It is increasingly implicated in DFIs, where it poses significant challenges due to its ability to survive in harsh conditions and its resistance to multiple antibiotics.[33,62] *A. baumannii* is known as one of the microorganisms associated with a higher incidence of amputation.[63] In diabetic patients, *A. baumannii* can exploit the compromised immune system, poor circulation, and delayed wound healing that are characteristic of diabetes.[64] These factors create a favorable environment for the bacterium to colonize and cause infection in DFUs.[65] A significant concern with *A. baumannii* infections in DFIs is the notorious resistance of the bacterium to antibiotics. Many strains of *A. baumannii* are MDR, often displaying resistance to a wide range of antibiotics, including carbapenems, which are typically used as a last resort in treating severe bacterial infections.[66] This resistance is largely due to the bacterium's ability to acquire and express various resistance genes, often through mobile genetic elements such as plasmids, transposons, and integrons.[67] The emergence of these MDR strains severely limits the available treatment options, increasing the risk of complications such as osteomyelitis, sepsis, and, in extreme cases, the need for amputation.[68]

Escherichia coli

E. coli, a Gram-negative bacterium commonly found in the gastrointestinal tract, is emerging as a significant pathogen in DFIs.[69,70] In studies by Idrees et al and Jain et al, *E. coli* was found in 41.6% of 180 samples and 20% of 150 diabetic patients with foot ulcers, respectively.[71,72] Traditionally associated with urinary tract infections and gastrointestinal illnesses, *E. coli* is now increasingly recognized for its role in DFIs, particularly in polymicrobial infections, where it can worsen wound severity and complicate treatment.[73] In DFUs, *E. coli* often colonizes wounds alongside other Gram-negative and Gram-positive bacteria.[74]

A major determinant of therapeutic failure in *E. coli* associated DFIs is the production of extended spectrum beta lactamases, which represents the principal resistance mechanism in this species.[75] Saltoglu et al reported that 38.5% of *E. coli* isolates were ESBL producers, and reinfections were more common in patients with inadequate initial therapy.[41] Zambelli et al found that *E. coli* accounted for 8.3% of isolates and was associated with polymicrobial infections, which increase the risk of complications, treatment failure, and chronicity.[76]

The compromised immune system in diabetic patients, coupled with poor circulation and delayed wound healing, creates an environment that fosters the growth and persistence of *E. coli* and other pathogens.[77] This bacterium is especially problematic in chronic and deep infections, where it contributes to the complexity and chronicity of the infection.[78]

Enterococcus spp

Enterococcus spp., particularly *E. faecalis* and *E. faecium*, are significant pathogens in DFIs. Perzon et al focused on the prevalence and impact of Enterococcal infections in DFUs. Their study, conducted at the Hadassah Medical Center, found that enterococci were present in 35% of DFUs. These infections were predominantly polymicrobial and were associated with higher rates of amputation and longer hospital stays compared to non-Enterococcal infections.[79] Gramberg et al reported that *Enterococcus* infections were associated with HR for amputation of 0.73 (95% CI: 0.38–1.4) and HR for mortality of 0.73 (95% CI: 0.38–1.4), indicating moderate influence on severe outcomes compared to Gram-negative pathogens.[42]

In DFIs, *Enterococcus* spp. are often found in polymicrobial infections, coexisting with other pathogens such as *S. aureus, P. aeruginosa*, and various anaerobes.[80,81] The presence of *Enterococcus* spp. complicates treatment, as these bacteria frequently exhibit resistance to multiple antibiotics, including vancomycin, a major concern in clinical settings.[38] Saltoglu et al additionally found vancomycin-resistant *Enterococcus* in 7% of isolates, complicating treatment and prolonging hospital stay.[41]

Biological Phages

Phages, or bacteriophages, are the most abundant biological entities on Earth.[82] They are ubiquitous, found in soil, seawater, and on various surfaces, including extreme environments with very high or low temperatures. Additionally, they are present in hospitals, wastewater, and wherever bacteria are found, including animal and human tissues.[83] Thousands of phages have been described and classified based on their morphological characteristics, nucleic acid content, typical habitats, and the bacterial species they infect.[84]

Phages are commonly classified according to their tail structures and biological cycles.[85] This classification divides phages into two main groups: lytic (virulent) and lysogenic (temperate) phages. In the lytic cycle, phages attach to and invade bacterial cells, but they can only bind to specific bacterial receptors that match their tail structures (Figure 1). Due

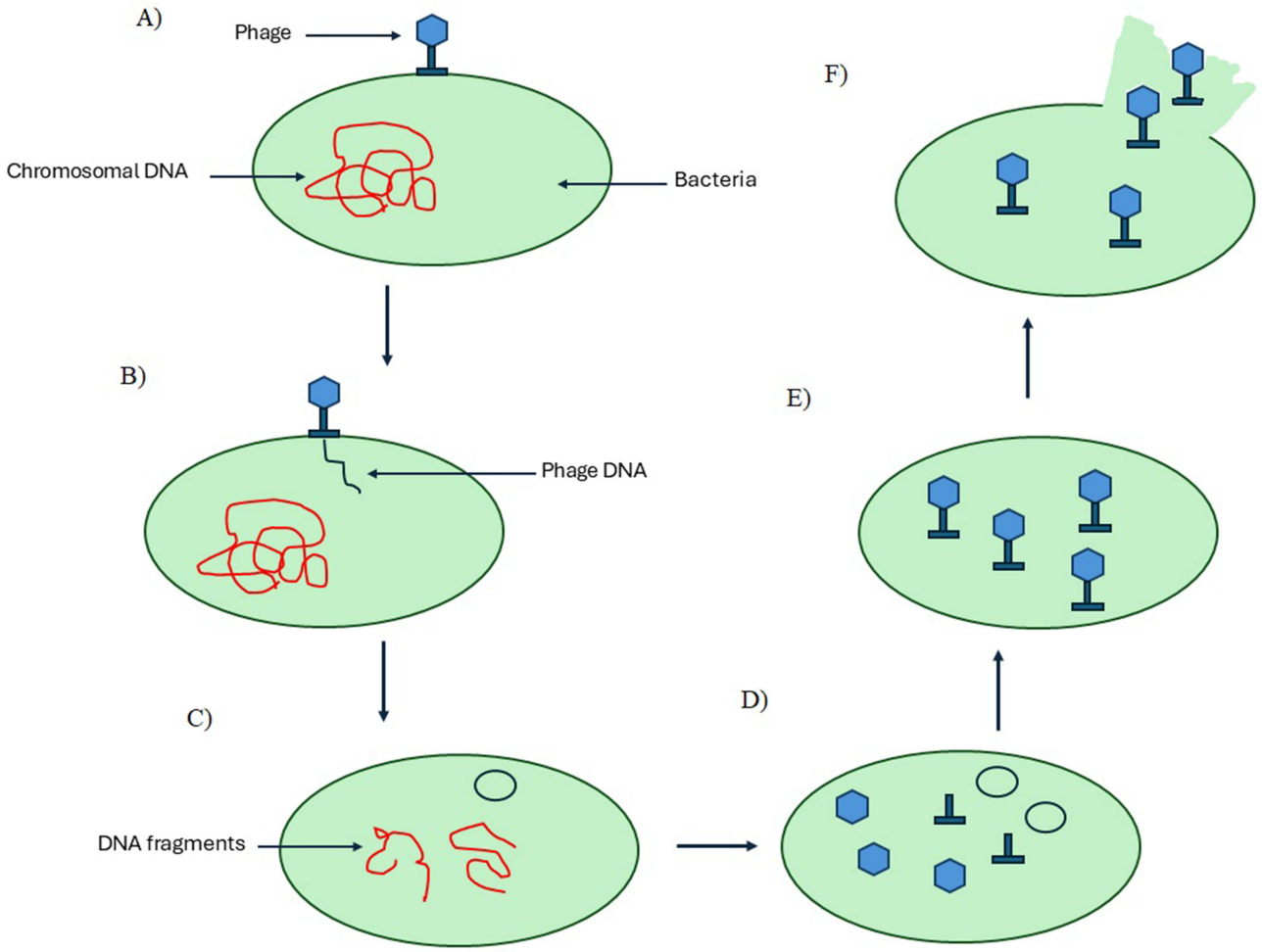

Figure 1 Mechanism of phage therapy. (**A**) The bacteriophage first attaches firmly to the surface of the bacterial host, recognizing specific receptors on the bacterial cell wall, which ensures host specificity. (**B**) Next, the bacteriophage injects its viral genome into the bacterial cell, transferring the genetic instructions necessary for viral replication directly into the host cytoplasm. (**C**) Once inside, the bacteriophage genome triggers the degradation of the bacterial host's DNA, effectively shutting down the host's normal cellular functions and redirecting resources toward viral production. (**D**) The host machinery is then hijacked to synthesize viral components, including structural proteins and nucleic acids, allowing the replication of new phage particles. (**E**) These newly produced components self-assemble into complete, mature bacteriophages, ready for release. (**F**) Finally, the bacterial cell undergoes lysis, breaking open its membrane and releasing the newly formed bacteriophages into the environment to infect additional bacterial cells, continuing the cycle.

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to the high rate of mutations in both phages and bacterial receptors, often mediated by the phages themselves, each phage can infect a limited number of bacterial strains or sometimes only a single strain.[86] This specificity explains the precise targeting of phages. Once inside the bacterial cell, the phage hijacks the bacterial machinery to produce its own genome and proteins. The phage then assembles and packages new virions before lysing the host cell to release these new phages, which can infect other bacterial cells.[86] The burst size, or the number of new phages produced, can vary depending on the characteristics of the phage, the pathogens it targets, and the environmental conditions.[87]

In contrast, the lysogenic cycle involves the integration of the phage's genetic material into the host's genome. During cell division, the viral DNA is replicated along with the bacterial DNA and passed to daughter cells. The phage remains dormant within the bacterial genome and only rarely exits this state to enter the lytic cycle.[88] Due to their ability to precisely target and kill bacteria, only lytic phages are used for therapeutic purposes.

Advantages of Phages Therapy

Phages offer several theoretical and practical advantages over traditional antibiotics in treating bacterial infections. One notable benefit is that, theoretically, no bacterium is immune to all phages. While antibiotics often have broad spectra of activity, no single antibiotic can eradicate every bacterial species. The most compelling attribute of phages is their specificity; they target only the bacteria they are designed to recognize and infect.[89]

Phages have a narrow spectrum of activity, which helps avoid one of the major drawbacks of antibiotics: disruption of the entire microbiome. Antibiotics can kill not only harmful bacteria but also beneficial ones, leading to secondary infections and the emergence of resistant strains.[90] Studies have shown that phages can be used without adversely affecting the microbiota. For instance, research with mice demonstrated that oral administration of T4-like phages targeting *E. coli* associated with diarrhea did not harm non-pathogenic *E. coli* strains.[91] Similarly, a study by Sarker et al found that administering an oral cocktail of nine T4-like *E. coli* phages to healthy adults for two days did not alter gut microbiota composition, despite the presence of phages in feces.[92]

Compared to antibiotics, phages offer several additional benefits. They are generally considered safer and better tolerated because they replicate only within target bacteria and do not infect mammalian cells. This safety profile is supported by historical use in Eastern Europe and recent studies in animals and humans, which have not reported significant adverse effects following phages therapy.[93] Furthermore, phages may require fewer doses and can remain in the body for longer periods, reducing the need for frequent administration, unlike antibiotics that often require multiple doses over several days.[94,95] Phages are also effective at targeting infections in areas difficult for antibiotics to reach, such as certain body organs or systems. For example, the lytic phage EC200 (PP), effective against the fatal neonatal meningitis strain of *E. coli*, successfully treated infected pups in a meningitis model even with low phage titers in the central nervous system.[96]

Advancements in cost-effective DNA sequencing and synthesis technologies have enabled the engineering of phages to address some limitations of antibiotics. For instance, phages can be engineered to disrupt biofilms, which are resistant to standard antibiotic treatments even when the bacteria are susceptible to the drugs.[97] An in vitro study demonstrated that a biofilm-degrading enzyme incorporated into a phages reduced bacterial biofilm cell counts by approximately 99.9%.[98] Additionally, genetic modifications in phages can combat bacterial resistance to antibiotics. For example, Edgar et al introduced genes into lysogenic phages that conferred sensitivity to streptomycin and nalidixic acid in resistant strains, significantly reducing their minimal inhibitory concentrations.[99]

Finally, phages may be a more cost-effective alternative to antibiotics, especially for treating MDR pathogens. A study by Miedzybrodzki et al found that phage therapy significantly reduced healthcare costs for patients with MRSA infections.[100]

Phage Therapy for Diabetic Foot Infections

DFIs represent a significant challenge in clinical management due to the persistent presence of MDR bacterial pathogens. With the growing limitations of antibiotics, phage therapy has emerged as a promising alternative for treating chronic wounds associated with diabetes. Recent studies have demonstrated the efficacy of bacteriophages in targeting key bacterial pathogens, reducing biofilm formation, and accelerating wound healing (Table 1).

Table 1 Phage Therapy and Their Therapeutic Outcomes Against Bacterial Pathogens in Diabetic Foot Infections (DFIs)

Bacterial Pathogen	Phage(s)/Formulation	Model/Number Treated	Outcome	Reference
Staphylococcus aureus	GRCS	Mouse mo n=20	Significant protection against bacteremia	[101]
	Ø SH-56	Rat wound mo n=18	Infection reduction; improved wound healing time	[102]
	AB-SA01	Mouse diabetic wound mo in vivo + in vitro assays	Significant bacterial load reduction; wound size reduction comparable or superior to vancomycin; effective against MDR strains	[103]
	ROSA-like phage	In vitro	Reduced bacterial virulence; enhanced biofilm formation in colonizing strains	[104]
	PseuPha1 & *RuSa1* (PVA-EU nanofiber)	Diabetic mice; n=12 wounds	Sustained phage release; significantly faster wound closure ($p<0.0001$)	[105]
Pseudomonas aeruginosa	AB-PA01	In vitro	Biofilm reduction by ~70%; increased bacterial susceptibility	[103]
	ϕPAE1 and *ϕPAE2*	In vitro; 50 clinical isolates tested	*ϕPAE1* infected 74%; *ϕPAE2* infected 58%; broad host range; stable across pH and temperature ranges	[106]
	phPS127 (*Siphoviridae*)	Rat skin infection mo in vivo + in vitro	Significant lytic activity; decreased bacterial density; biofilm eradication; promoted wound healing; reduced TNF-α and caspase-3 expression	[102]
Klebsiella pneumoniae	*Drexlerviridae* phage	In vitro	Effective against MDR strains; bactericidal activity comparable to gentamicin	[107]
	ZCKP1 (*Myoviridae*)	In vitro	Strong lytic activity; biofilm biomass reduction >50%	[108]
Acinetobacter baumannii	*Myoviridae* phage	Mouse wound mo n=10	Reduced infection; enhanced wound healing	[109]
	Abp95 (*Myoviridae*)	In vitro	Broad host range; rapid bacterial clearance	[110]
	Pϕ-Bw-Ab (*Siphoviridae*)	In vitro	Effective against XDR A. baumannii; strong antibacterial action	[111]
	Phage cocktail + endolysin	In vitro	Decreased bacterial resistance; synergistic antibacterial effect	[112]
Escherichia coli, Salmonella enterica, P. aeruginosa	Phage cocktail (hydrogel dressing)	Rat wound mo n=15	Significant bacterial load reduction; enhanced wound healing	[113]
Enterococcus faecalis	Phage therapy	Insulin-dependent diabetic mice mo	More effective than vancomycin alone and combined therapy; enhanced bacterial clearance	[114]
Enterococcus faecium	EF-M80 (Hydrogel-encapsulated)	Mouse wound mo n=12	Broad host range; biofilm degradation; accelerated wound healing; favorable histological outcomes	[115]

Abbreviations: MDR, multidrug resistance; XDR, extensively drug resistant.

Advances in Preclinical and Animal Studies

Preclinical investigations have consistently demonstrated the therapeutic potential of phage therapy in DFIs. For instance, Sunagar et al evaluated the efficacy of phage GRCS in diabetic and non-diabetic mice with *S. aureus* bacteremia.

A single phage administration achieved survival rates of 90% in diabetic mice and 100% in non-diabetic mice, compared to 0% in untreated controls, alongside substantial reductions in bacterial load.[101]

In a diabetic rat excision wound model, Kumar et al tested the broad-host-range phage Ø SH-56 against MRSA. Phage treatment significantly decreased infection levels, shortened the period of epithelization, and improved wound contraction compared to Clindamycin-treated and control groups.[102] While Sunagar et al reported nearly complete survival, Kumar et al demonstrated substantial but comparatively lower reductions in bacterial burden, highlighting variability in efficacy across phages, bacterial strains, and animal models.

Further innovative delivery systems have been explored to enhance phage therapy outcomes. Suchithra et al incorporated two phages, *PseuPha1* and *RuSa1*, targeting *P. aeruginosa* and *S. aureus*, into a polyvinyl alcohol–eudragit (*PVA-EU†*) nanofiber matrix. This formulation enabled sustained antibacterial release, effectively reduced bacterial abundance, and promoted rapid wound closure in diabetic mice.[105] Similarly, Shiue et al developed a 3D-printed porous hydrogel dressing containing a cocktail of phages against *Salmonella enterica, E. coli*, and *P. aeruginosa*. Application of this dressing in diabetic mice led to significant bacterial reduction (37–79%) and improved wound healing ratios after 14 days compared to controls.[113]

Phage therapy has also shown promise against MDR *K. pneumoniae*. Kelishomi et al identified a lytic phage from the *Drexlerviridae* family that effectively cleared infections in mice, exhibiting comparable efficacy to gentamicin, with treated mice maintaining better overall health.[107] Additionally, Taha et al characterized *ZCKP1*, a *Myoviridae* phage with a 150.9 kb dsDNA genome, which showed significant in vitro and in vivo bactericidal activity, reducing bacterial counts and biofilm biomass by over 50%.[108]

For *A. baumannii*, Shivaswamy et al investigated the therapeutic efficacy of a *Myoviridae* phage isolated from hospital sewage. Using an uncontrolled diabetic rat wound infection model, they compared five groups: non-infected controls, infected untreated rats, infected rats treated with the phage, infected rats treated with colistin, and non-infected rats treated with phage alone. Phage treatment led to a significant reduction in bacterial infection, faster wound epithelization, and improved wound contraction compared to both the antibiotic-treated and control groups.[109] Huang et al similarly described *Abp95*, a broad-host-range *Myoviridae* phage that facilitated rapid wound recovery in diabetic mouse models.[110] Additionally, Torabi et al evaluated the *Siphoviridae* phage *Pϕ-Bw-Ab* against extensively drug-resistant *A. baumannii*, demonstrating potent antibacterial activity under optimal temperature and pH conditions.[111] While preclinical studies provide strong evidence for phage efficacy, they cannot fully replicate human immune responses, comorbidities, or wound microenvironments. Therefore, these findings should be considered indicative rather than definitive.

Clinical Insights into Phage Therapy for DFIs

The translation of phage therapy into clinical practice has shown promising potential for managing DFIs, particularly in the context of rising antibiotic resistance. Young et al reported a prospective case series involving ten patients with chronic DFIs treated with a personalized anti-staphylococcal phage cocktail, resulting in significant clinical improvement or complete resolution in nine out of ten cases, underscoring the feasibility of compassionate phage use for persistent infections.[116] Similarly, Mendes et al conducted a clinical study evaluating topically applied phage cocktails for treating *S. aureus* and *P. aeruginosa* infections in diabetic patients. The treatment yielded notable reductions in bacterial counts and visible wound healing improvements, indicating that phage therapy, when combined with standard debridement, could be an effective adjunct in chronic wound care.[117]

Beyond these clinical insights, extensive preclinical studies strengthen the translational foundation. For instance, Kifelew et al investigated the efficacy of *AB-SA01*, a *cGMP-grade* phage cocktail comprising three *Myoviridae* phages, which has already undergone two Phase I clinical trials for MDR *S. aureus* infections. In a diabetic mouse model, *AB-SA01* treatment significantly reduced bacterial burden and wound size compared with saline controls, performing comparably or better than vancomycin. Importantly, no adverse events related to phage application were observed, and post-mortem examination revealed no systemic pathology, supporting its safety and clinical readiness for DFUs.[103] Likewise, Kamer et al characterized phage *phPS127*, a *Siphoviridae* family member, targeting *P. aeruginosa*, a key opportunistic pathogen in DFIs. Detailed in vitro and in vivo analyses confirmed that *phPS127* efficiently reduced bacterial load, disrupted biofilms, lowered pro-inflammatory cytokines (TNF-α), and decreased apoptosis markers

(caspase-3), culminating in significant wound healing acceleration in a rat skin infection model.[118] Clinical translation requires standardized phage production, rigorous quality control, and compliance with regulatory frameworks. Variability in phage preparations and dosing strategies currently limits broader clinical adoption.

Some evidence also suggests that phages may modulate bacterial pathogenicity. For example, the ROSA-like prophage identified by Messad et al reduced bacterial virulence but enhanced biofilm formation, indicating that phage effects can be complex and context-dependent.[104]

Focusing on *P. aeruginosa*, which remains a major concern for antibiotic resistance, Mohamed et al isolated two potent phages, *ϕPAE1* and *ϕPAE2*, from sewage samples. Both phages showed broad host ranges, infecting over half of clinical isolates, and remained active under diverse temperature and pH conditions. Their stability and host specificity, alongside resistance to common organic solvents and prolonged storage resilience, highlight their promise as robust anti-Pseudomonas agents for chronic wounds.[106]

Phage therapy is also being explored for resistant Gram-positive pathogens beyond *S. aureus*. Oli et al demonstrated that phage treatment outperformed vancomycin alone in controlling vancomycin-resistant *E. faecalis* (VREF) infections in an insulin-dependent diabetic mice model. This suggests a potential role for phages as an alternative or supplement to last-line antibiotics in immunocompromised patients.[114] Extending this, Khazani Asforooshani et al characterized the *E. faecium* phage *EF-M80*, which showed a broad host range, biofilm degradation capacity, and genomic stability. When formulated in a hydrogel, EF-M80 significantly improved wound healing markers, including enhanced collagen deposition, neovascularization, and tissue regeneration, further supporting the promise of advanced delivery platforms for phage therapy.[115]

Synergistic Effects of Phage Therapy in Combination with Other Compounds

Phage-antibiotic synergy, observed between phages and antibiotics, has generated significant interest due to its potential to enhance bacterial eradication.[119,120] Initially, this term described the phenomenon where sublethal concentrations of antibiotics stimulated phage replication, leading to an improved antimicrobial effect. Today, it broadly refers to any scenario where combined use of phages and antibiotics results in synergistic antimicrobial effects.[89]

Current understanding indicates that this synergy arises through several complementary biological processes. Antibiotics may alter bacterial cell morphology, metabolism, or division rates, thereby increasing phage adsorption, intracellular replication, and burst size.[121] Conversely, phage infection can resensitize bacteria to antibiotics by selecting for resistance mutations that impair efflux pumps, membrane integrity, or virulence determinants, creating evolutionary trade-offs that restore antimicrobial susceptibility.[122] In addition, phage-mediated lysis disrupts bacterial biofilm architecture and releases extracellular polymeric substances, enhancing antibiotic penetration into previously protected microbial communities.[123]

This synergy is particularly important in the treatment of DFUs, where antibiotic resistance is common (Table 2). Several studies have highlighted the potential of phage-antibiotic synergy in treating infections. For instance, Liu et al focused on *P. aeruginosa* infections in DFUs, demonstrating that phage APTC-PA18, when combined with ciprofloxacin, exhibited synergistic effects against both planktonic and biofilm forms of the bacteria.[124] Mubeen et al reported that combining phages with antibiotics like meropenem significantly enhanced bacterial killing against *P. aeruginosa* compared to either treatment alone.[125] Mubeen et al reported that combining phages with antibiotics like meropenem significantly enhanced bacterial killing against *P. aeruginosa* compared to either treatment alone.[126] Oliveira et al explored phage therapy in combination with honey against *E. coli*, showing that combining *E. coli*-specific phages with honey significantly enhanced biofilm disruption, resulting in severe membrane disruption, collapse of bacterial cells, and prevention of biofilm formation.[127]

In animal model studies that reflect clinical relevance, Chhibber et al investigated diabetic mice induced with acute hindpaw infections using *S. aureus* ATCC 43300. The researchers found that a single administration of phage MR-10 was as effective as linezolid alone in resolving the infection. However, combination therapy of MR-10 with linezolid proved significantly more effective in reducing bacterial load, lesion scores, and foot myeloperoxidase activity, as well as in

Table 2 Synergistic Effects of Phage Therapy in Combination with Other Compounds for Treating Diabetic Infections

Target Bacteria	Phage Used	Combined Compound	Observations	Reference
P. aeruginosa (DFUs)	*APTC-PA18*	Ciprofloxacin	Synergistic effects against planktonic and biofilm forms, promising for DFUs.	[124]
P. aeruginosa (diabetic patients)	Not specified	Meropenem	Combination significantly enhanced bacterial killing compared to either treatment alone.	[125]
S. aureus (diabetic mice with acute hindpaw infections)	*MR-10*	Linezolid	Combination therapy reduced bacterial load, lesion scores, and myeloperoxidase activity while promoting tissue healing.	[128]
MDR *P. aeruginosa*	*F1Pa*	Beta-lactam antibiotics	Synergistic reduction in mature biofilm viability and biofilm formation in an in vitro wound model.	[126]
E. coli (chronic wounds, including DFUs)	*E. coli*-specific phages	Honey	Enhanced biofilm disruption, severe membrane damage, and bacterial cell collapse.	[127]

Abbreviations: DFUs, diabetic foot ulcers; MDR, multidrug resistance.

promoting faster tissue healing. Importantly, this combined approach also reduced the likelihood of resistant mutant emergence.[128] Although current clinical data on phage-antibiotic synergy in diabetic foot infections remain limited, these findings from animal models provide strong translational potential for combined therapy to overcome resistant bacterial strains, improve treatment outcomes, and reduce the need for high-dose antibiotics that may cause adverse effects.[129]

Limitations of Phage Therapy

DFUs are often complicated by infections caused by multiple bacterial species.[69] One of the primary limitations of phage therapy in this context is the narrow spectrum of bacteriophage activity due to their high specificity, which restricts their effectiveness against diverse bacterial populations commonly found in DFUs.[130] Additionally, lysogenic bacteriophages, which can integrate into bacterial genomes, may further complicate treatment by inhibiting other phages' lytic activities and possibly transferring harmful genes, such as those for antibiotic resistance, to the bacteria involved in the infection.[131]

An important consideration in translating phage therapy to clinical practice is the mode of administration. Topical application remains the most practical approach for diabetic foot infections, as it delivers high concentrations of phages directly to the wound site with minimal systemic exposure and is easy to integrate into routine wound care. However, a major limitation is that phages can be rapidly cleared from the wound surface due to exudate, and their penetration into deeper infected tissues is limited.[132] Recent studies have explored encapsulating phages in hydrogels to address these issues, showing that such formulations can prolong phage residence time, maintain activity, and enhance wound healing outcomes in animal models.[133] For deeper infections, such as osteomyelitis, systemic administration may be required, though this approach carries risks of immune neutralisation and rapid clearance from circulation. Alternatively, intralesional or subcutaneous injections could provide higher local tissue concentrations while avoiding systemic exposure.

The lack of standardized policies and regulatory frameworks for phage therapy presents another significant challenge in treating DFUs. Without clear standards for phage isolation, purification, and clinical application, there is considerable variability in the efficacy of phage preparations, which can lead to inconsistent treatment outcomes.[134,135] This variability is particularly problematic for managing complex infections like those seen in DFUs.[135]

An additional major limitation of phage therapy in DFIs is the capacity of bacteria to develop resistance to bacteriophages through multiple molecular and phenotypic mechanisms. These include modification or loss of bacterial surface receptors required for phage adsorption, activation of intracellular defense systems such as restriction–modification and CRISPR–Cas immunity, abortive infection pathways that terminate phage replication, and superinfection exclusion systems encoded by prophages.[136–139] Moreover, bacteria residing within biofilms, which are common in chronic diabetic wounds, can exhibit increased tolerance to phages due to reduced metabolic activity, physical shielding

by extracellular polymeric substances, and spatial heterogeneity, thereby limiting phage penetration and efficacy.[140] Phase variation and phenotypic heterogeneity further contribute to transient phage insensitivity, enabling bacterial persistence under therapeutic pressure and increasing the risk of treatment failure or relapse.[141] Additionally, the pharmacokinetic properties of phages, including their absorption, distribution, metabolism, and excretion, are not well understood, making it difficult to determine the appropriate dosages and administration methods for effective treatment.[142,143] This challenge is compounded by the body's ability to degrade phages, which makes it difficult to maintain therapeutic concentrations at the infection site.[144,145]

Finally, interactions between bacteriophages and the human body during treatment can have adverse effects, such as the release of bacterial toxins during lysis, which may exacerbate infections or lead to septic conditions in DFUs patients.[146,147] There is also a risk of immune reactions to phage proteins, although such occurrences are generally rare.[148] Despite the potential benefits of phage therapy, the lack of data from double-blind randomized controlled trials limits its current application in treating DFIs.[149]

Conclusion

The escalating prevalence of DFIs and the global rise in antimicrobial resistance underscore the urgent need for innovative and effective therapeutic strategies. Phage therapy, owing to its host specificity, ability to penetrate and disrupt biofilms, and activity against MDR pathogens, represents a promising adjunct or alternative to conventional antibiotic treatment. The studies reviewed in this article highlight encouraging in vitro, animal, and early clinical evidence supporting the efficacy of phages alone or in combination with antibiotics in targeting key DFI pathogens. However, despite these promising findings, the translation of phage therapy into routine clinical practice has been hindered by a limited number of large-scale randomized controlled trials (RCTs). Several factors appear to underlie this stagnation, including regulatory uncertainty regarding phage classification and approval pathways, difficulties in standardizing phage production under good manufacturing practice conditions, and the personalized nature of phage therapy that requires rapid pathogen phage matching, which is difficult to accommodate within conventional trial designs. Additional obstacles include restricted commercial incentives, intellectual property constraints, incomplete understanding of phage pharmacokinetics and host immune responses, and concerns regarding the emergence of phage-resistant bacterial variants during treatment. The polymicrobial character of many DFIs, challenges in recruiting patients with microbiologically confirmed infections, and ethical concerns related to placebo-controlled designs in limb-threatening disease further complicate the execution of rigorous RCTs, helping to explain why current clinical evidence is largely derived from compassionate-use cases, small observational cohorts, and early-phase studies rather than definitive trials. Future research efforts should therefore prioritize the development of adaptive and pragmatic clinical trial designs tailored to personalized antimicrobial strategies, alongside harmonized regulatory frameworks and standardized manufacturing pipelines. Optimization of phage selection, dosing strategies, formulation technologies, and delivery platforms remains essential to ensure reproducible and clinically meaningful outcomes. In addition, although phage bioengineering has demonstrated potential in enhancing bactericidal activity, broadening host range, and mitigating resistance in other infectious contexts, its application in DFIs remains largely unexplored and warrants focused investigation. Clinically, phage therapy may be considered in patients with DFIs who present with chronic, non-healing wounds, infections caused by multidrug-resistant pathogens, or infections complicated by biofilm formation, particularly when conventional antibiotic therapy has failed. Early integration of phages into the treatment plan may enhance bacterial clearance, reduce the risk of amputation, and improve wound healing outcomes. As the global health community continues to confront the mounting burden of antibiotic resistance, the thoughtful integration of phage therapy, potentially including engineered phages, into multidisciplinary DFI management strategies may ultimately represent a significant advance in limb salvage, infection control, and patient outcomes.

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Author Contributions

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