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Phage therapy for intracellular MRSA infections and navigating transduction risks

Aasima Hassan *, Zainab Ibrar, Neha Kishwar, Kiran Chaudhary and Aasma Nasim

Institute of Microbiology, Faculty of Veterinary Science, University of Agriculture Faisalabad, 57000 Pakistan.

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Abstract

In response to escalating antibiotic resistance, Methicillin-resistant *Staphylococcus aureus* (MRSA) infections, especially chronic intracellular cases, pose a persistent challenge. Phage therapy offers a promising alternative, targeting intracellular MRSA effectively. This review explores phage therapy's mechanisms, efficacy, challenges, and future prospects, with a focus on transduction risks. The review details phage therapy's intricate mechanisms against MRSA, highlighting dynamic phage-bacterial interactions within host cells. Evidence and case studies underscore transduction risks, including genetic element transfer and antibiotic resistance acquisition. Studies demonstrating phage therapy's efficacy against intracellular MRSA stress the need for tailored strategies and innovative approaches for enhanced phage access and efficacy within cells. Challenges like phage resistance and cell penetration limitations are examined, with proposed solutions to improve intracellular phage activity. Cutting-edge technologies such as whole-genome sequencing and single-cell analysis are discussed for monitoring and controlling transduction events. Collaboration among researchers, healthcare professionals, and regulators is emphasized to establish robust guidelines and address biosecurity concerns in phage therapy applications.

Keywords: Methicillin-resistant *Staphylococcus aureus;* Phage therapy; Antibiotic resistance; Intracellular infection; Transduction

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections have become a significant global health concern due to their ability to resist multiple antibiotics, posing challenges in treatment and management [1]. MRSA is a strain of the bacterium *Staphylococcus aureus* that has developed resistance to beta-lactam antibiotics, including methicillin, making it difficult to eradicate using conventional antimicrobial agents [2]. These infections are associated with a wide range of clinical manifestations, from mild skin and soft tissue infections to severe and life-threatening conditions such as pneumonia, bloodstream infections, and surgical site infections [2]. The prevalence of MRSA infections in healthcare settings, communities, and livestock adds complexity to infection control measures and public health efforts [3].

Now a days Phage therapy to target and eliminate bacterial pathogens, has emerged as a promising alternative to traditional antibiotics in the face of rising antimicrobial resistance [4]. Bacteriophages are viruses that infect and replicate within bacterial cells, leading to their destruction and eventual clearance from the host [5]. This approach holds particular significance in combating infections caused by multidrug-resistant bacteria like MRSA, which pose significant challenges to conventional treatment methods [6,7]. As such, phage therapy represents a paradigm shift in the field of infectious diseases, offering targeted and potentially more effective solutions [8,9].

While phage therapy offers a promising avenue for combating bacterial infections, including those caused by multidrug-resistant pathogens like MRSA, it is crucial to address the potential risks associated with transduction in this therapeutic approach [10]. Transduction, the transfer of genetic material from one bacterium to another via bacteriophages, can

* Corresponding author: Aasima Hassan

lead to unintended consequences such as the spread of antibiotic resistance genes or the acquisition of virulence factors [11]. Therefore, understanding and mitigating transduction risks are essential steps in ensuring the safety and efficacy of phage therapy interventions [12].

2. Methicillin resistance *staphylococcus aureus* (MRSA)

S. aureus is a Gram positive bacterium of great clinical importance as it is part of skin normal flora along with its presence in the nasal cavity, and a pathogen worldwide, including Pakistan. This pathogen is common in nosocomial environments responsible for a variety of highly transmissible infections including endocarditis, osteoarthritis, dermal and soft tissue infections, pulmonary and aerobic vaginitis, and even death. However, about 25% of the population possess this bacterium without occurrence of any symptoms. Many antibiotics have lost their efficacy in killing *S. aureus* due to the acquisition of resistance to antimicrobials. The main resistant type is MRSA [13].The first time methicillin was introduced clinically was in the United Kingdom in 1961 and in the same year, emergence of MRSA was reported. MRSA is known as a super bug as it has evolved to become resistant to several antibiotic classes [14]. Over the years, MRSA has become a global public health concern, causing a wide range of infections, from skin and soft tissue infections to severe systemic infections such as pneumonia and bloodstream infections. Its resistance to antibiotics posed a significant challenge to healthcare providers, leading to increased morbidity and mortality rates [15].

This multi-drug resistance capability of the MRSA is associated with the presence of the *mecA* gene that encodes for a transpeptidase enzyme with reduced affinity to beta-lactams. Mutations in *mecA* leads to the development of *mecC* genes. MRSA isolates that possess *mecC* are animal and livestock associated *S. aureus,* and can transfer from animal associated MRSA to MRSA of human origins [16]. In addition, MRSA isolates can mutate in cell wall structure or acquire a *vanA* operon, both mechanisms of which confer vancomycin-resistance [17]. Hence antibiotics belonging to lipoglycopeptides are increasing used to treat multi-drug resistant *S. aureus* infections, however, these have limited efficacy when *S. aureus* invade human host cells and persist within them.

3. Epidemiology of MRSA in Pakistan

Understanding the epidemiology of MRSA in Pakistan is crucial for effective prevention and control measures. One study conducted by Munir and colleagues examined MRSA contamination in raw meat samples from cities in Pakistan, such as Lahore and Karachi. This research highlighted the potential for foodborne transmission of MRSA and the need to consider diverse sources of MRSA exposure [18]. Another investigation led by Ahmad and colleagues focused on the molecular epidemiology of MRSA strains in Pakistan. This study provided insights into the genetic diversity and characteristics of MRSA in the local context, MRSA isolates were highly resistant to various kinds of penicillin and cephalosporin (85 – 100 %). Among the important anti-Staphylococcal agents tested, 17 % of the isolates were resistant to fusidic acid and linezolid, both of which are used to treat MRSA infections, but susceptible to vancomycin. Furthermore, a multicenter study conducted by Idrees and colleagues explored the prevalence of community-associated MRSA strains in Pakistan to understand MRSA epidemiology beyond healthcare settings. The prevalence of *S. aureus* was 10.2% in the total number of specimens collected n = 1000. However, the prevalence of MRSA was 6.3%; *mec* genes were found in 96.8% isolates of MRSA, and both *mecA* and *mecC* were detected in 57.1% of isolates suggesting livestock was a possible reservoir of resistance genes. Thus, MRSA endemic in local areas require routine molecular and epidemiological investigation [14].

These studies highlight the multifaceted nature of MRSA transmission, encompassing healthcare facilities, community settings, and even food sources in Pakistan. Such insights are invaluable for developing targeted interventions and surveillance strategies to combat MRSA's impact on public health in Pakistan.

4. Intracellular infection by MRSA

Originally it was thought that *S. aureus* was an extracellular pathogen but now studies have shown that it possesses the ability of adhesion and invasion in the non-phagocytic host cells, with the help of Fibronectin binding proteins and a modified zipper like mechanism [19]. This intracellular nature of *Staphylococci* limits access of antibiotics to the pathogen and contributes significantly to chronic *Staphylococci* infections and persistence in hospital environments [20]. In one study, intracellular *S. aureus* was identified in 9/17 47% patients and in 7/17 39% using IHC. Surface biofilm can be identified with CSLM-FISH/PI (confocal scanning laser microscopy -fluorescence in situ hybridization) in the same piece of tissue; however, deeper imaging to the submucosa was impossible. IHC showed submucosal bacteria in three patients [21]. Jimi and colleagues investigated the drug-resistant mechanisms of intracellular survival of methicillin-resistant *S. aureus* MRSA. They established that the MRSA clinical strain, OJ-1/ could be ingested by a

macrophage cell line J774A when exposed to vancomycin, and while the number of phagocytosed intracellular OJ-1 gradually decreased it plateaued after day 7. Electron microscopy demonstrated that OJ-1 escaped the phagosomes and was localized in the J774A cytoplasm. When vancomycin was withdrawn, OJ-1 started to grow vigorously. These results indicate that intracellular phagocytosed biofilm-forming MRSA could survive for more than ten days by escaping the lysosomes and autophagosomes in macrophages. However, the mechanisms of escape from the lysosomes are still unknown [22]. The intracellular invasion of MRSA is not only a mechanism for immune evasion but also a means to establish chronic infections. Inside host cells, MRSA can form reservoirs of infection, remaining hidden from the immune system and standard antibiotic therapy. This phenomenon contributes to the perpetuation of MRSA outbreaks in healthcare settings, leading to the emergence of endemic strains [19]. Understanding the intracellular behavior of MRSA is crucial for developing innovative therapeutic approaches and infection control strategies. Targeting intracellular MRSA represents a promising avenue for combating chronic and antibiotic-resistant infections in healthcare environments. In this regard, bacteriophages hold promise and will be the focus of this program of research.

5. Bacteriophages

Bacteriophages, or viruses that infect bacteria, have been studied for their potential as an alternative treatment for bacterial infections. The discovery of bacteriophages dates back to the early 20th century by Félix d'Hérelle and Frederick Twort. Bacteriophages were initially investigated for their antibacterial properties, but the advent of antibiotics led to their relative obscurity in Western medicine [23,24]. Recent resurgence in interest in bacteriophages as a potential therapy against antibiotic-resistant bacteria, including MRSA, has been driven by a lack of viable alternatives and the understanding that new classes of antimicrobials will invariably be accompanied by resistance emergence without regulated usage. Researchers have explored the use of bacteriophages to target and kill MRSA strains, leveraging their specificity and ability to evolve alongside bacterial pathogens [25,26].

Phages infect bacteria either with lytic or lysogenic cycle, hence is categorized as strictly lytic or temperate phages, respectively. The genome of a phage may be single stranded (ss) or double stranded (ds) DNA or RNA, but the majority of known phages have ds DNA. During the lytic cycle, phage virions burst out of host cells causing death, while in the lysogenic cycle, the phage genome integrates itself into the host genome and exists as a prophage that replicates along with its host genome. The prophage remains dormant unless the lysogenic cell suffers from stressful conditions that cause the prophage to enter a lytic cycle to kill the bacterial host cell.

Phage infection can result in the transfer of bacterial DNA; this process is known as transduction. Three types of transduction exist – specialised, generalized and lateral. Specialised transduction transfers only genes adjacent to an integrated prophage genome. Generalised transduction transfers any bacterial genomic material e.g. antimicrobial resistance genes but usually at low frequencies. Lateral transduction was recently discovered as a third mechanism in *S. aureus*, in which the integrate phage genome initiated DNA packaging into phage capsids resulting in a very high frequency of bacterial DNA also being packaged into phage capsids, resulting in high frequency transduction [27]. Lateral transduction was also recently shown to be initiated by Staphylococcal pathogenicity islands SaPIs after phage infection [28], and discovered in *Salmonella* phage P22 [27], indicating this mechanism could be a risk in phage therapy and occur in other bacterial species and warrants more attention.

6. Phage therapy

Phage therapy refers to the use of phages specifically of a strictly lytic nature to treat bacterial infections. Use of phages has been very effective against otherwise untreatable infections caused by multidrug resistant bacteria, including *S. aureus* [9,29]. Compared to antibiotics, phages are highly specific, killing only target bacterium while leaving the surrounding microbiota unaffected. While phage-resistance does emerge, it is easy to select for phages to counter bacterial resistance [30,31]. Also use of phage cocktails can reduce phage-resistance emergence, and can even target a mixed community of pathogens utilizing more than one phage at the same time [25].

7. Mechanism of phage therapy for intracellular MRSA

Phage therapy has garnered increasing attention as a potential alternative to antibiotics for combatting challenging bacterial infections. One of the most pressing concerns in the field of infectious diseases is the treatment of deep-seated infections, particularly those caused by pathogens like *S. aureus* that can invade host cells and exist intracellularly. Strictly lytic phages have demonstrated the remarkable ability to kill intracellular *S. aureus*, offering a promising avenue for eradicating infections that are otherwise untreatable by antibiotics [32]. These bacteria can hide within host cells, rendering them inaccessible to antibiotics and the host's immune system. However, certain lytic bacteriophages possess

the capability to penetrate mammalian cells, infect intracellular *S. aureus* which tend to be in a slow-growing state, and effectively lyse the bacterial pathogens inside these cells [33].

Phage therapy encompasses a range of mechanisms that contribute to its efficacy against intracellular MRSA infections. One critical aspect is the specificity of phages for their target bacteria. Phages have evolved to recognize and bind to specific receptors on bacterial cell surfaces, ensuring that they selectively infect their target bacteria, such as MRSA strains [34]. This specificity minimizes collateral damage to beneficial bacteria in the host microbiota, a key advantage over broad-spectrum antibiotics.

Once attached to MRSA cells, phages can employ various strategies to penetrate and disrupt the bacterial cell envelope. Some phages produce enzymes called depolymerases that degrade components of the bacterial cell wall, such as peptidoglycan [35]. This enzymatic activity weakens the cell wall, facilitating the entry of phage genetic material into the bacterial cell. Moreover, certain phages produce endolysins, which are enzymes that target and degrade the bacterial cell membrane, leading to cell lysis and release of progeny phages [34].

Phages can also exploit bacterial cellular processes to enhance their infectivity and replication within host cells. For instance, some phages produce proteins that mimic host cell surface receptors, allowing them to bind to and enter host cells via receptor-mediated endocytosis [35]. Once inside the host cell, phages utilize the cell's machinery for their replication, leading to the production of numerous phage progeny. This intracellular replication cycle amplifies the phage population, increasing their ability to target and eliminate MRSA populations within host tissues.

Another mechanism by which phages combat intracellular MRSA infections is through the production of antimicrobial peptides (AMPs) or secondary metabolites. Certain phages encode genes for AMPs that can disrupt bacterial cell membranes or interfere with essential cellular processes, contributing to bacterial growth inhibition or cell death [34]. Additionally, some phages produce secondary metabolites that have antibacterial properties, further enhancing their therapeutic efficacy against MRSA.

Overall, the multifaceted mechanisms of phage therapy against intracellular MRSA infections highlight its potential as a targeted and effective treatment option. By leveraging phage-specificity, enzymatic activities, cellular mimicry, intracellular replication, and secondary metabolites, phage therapy offers a comprehensive approach to combating antibiotic-resistant MRSA strains within host cells.

8. Efficacy and challenges of phage therapy in intracellular environments

The efficacy of phage therapy against intracellular MRSA infections is a topic of significant interest and ongoing research. Several studies have demonstrated the potential of phages to target and eliminate MRSA within host cells, highlighting their specificity and therapeutic benefits [35–37]. However, phage therapy in intracellular environments presents unique challenges, including access to intracellular MRSA populations, the development of phage resistance, and optimizing phage efficacy within host cells.

Phage therapy has shown promising results in various studies demonstrating its efficacy against intracellular MRSA. A research has illustrated the ability of phages to penetrate host cells and target MRSA populations residing within them [35–37]. In another study revealed that 12 natural anti- *Pseudomonas aeruginosa* bacteriophage (PP1131) cocktail effective in the treatment of burn patients infected by multidrug-resistant *P. aeruginosa* [38]. The *E. coli* T4 phage was shown to undergo transcytosis from eukaryotic apical-to-basal cell layers to the circulatory system, with a small percentage remaining within these cells and remaining active for up to 18h [39,40]. It is unclear whether all phages are taken up similarly. The mechanism of *S. aureus* phage entry into mammalian cells is under intense investigation. One study revealed that phage vB_SauM_JS25, effectively penetrated and eliminated intracellular *S. aureus* within bovine mammary epithelial cells [41]. These studies often utilize in vitro and in vivo models to assess phage infectivity, replication dynamics, and antibacterial effects within intracellular MRSA environments. Furthermore, phage therapy has been evaluated in clinical settings, demonstrating its potential as an alternative or adjunct therapy for intracellular MRSA infections [34].

Despite the promising efficacy of phage therapy, several challenges exist in targeting intracellular MRSA populations. One major challenge is the limited access of phages to intracellular MRSA within host cells. The complex cellular barriers, such as cell membranes and intracellular compartments, can hinder phage entry and interaction with bacterial targets [35–37]. However, a study found that phages were only able to enter osteoblasts in the presence of *S. aureus* [42]. A third report found *S. aureus* phage 191219 was internalized by an osteoblast cell line in the absence of *S. aureus*

[43]. A better understanding of *S. aureus* phage uptake by mammalian cells is needed for the development of phage therapy tailored for intracellular killing.

Moreover, a notable challenge in phage therapy is the risk of phage transduction. Phage transduction involves the transfer of bacterial DNA by phages, which can lead to horizontal gene transfer and the spread of antibiotic resistance genes among bacterial populations [36,44]. This phenomenon highlights the importance of carefully selecting phages for therapy to minimize the risk of transduction and unintended consequences.

To address the challenges associated with phage therapy in intracellular MRSA infections, various strategies have been proposed to enhance phage efficacy within host cells. These strategies include the modification of phage particles to improve intracellular penetration and targeting, such as engineering phage proteins or adding cell-penetrating peptides (CPPs) to facilitate host cell entry [35–37]. Furthermore, combination therapies involving phages and conventional antibiotics or immune-modulating agents are being explored to enhance bacterial clearance and reduce the risk of resistance development [34,44].

9. Risk of phage transduction in phage therapy

Phage therapy, while promising in its potential to combat antibiotic-resistant bacterial infections, is not without its own set of challenges and concerns. Transduction plays a pivotal role in the dynamics of phage therapy; especially one significant concern is the role of phages in mediating the transfer of bacterial DNA such as virulence or antimicrobial resistance genes, that can increase the fitness or virulence of bacteria. Transduction refers to the process through which bacteriophages transfer bacterial DNA between bacterial cells during the infection cycle. This transfer can occur inadvertently as phages replicate within host cells, leading to the incorporation of bacterial DNA fragments into newly formed phage particles [45] The significance of transduction lies in its potential to facilitate horizontal gene transfer among bacterial populations, including the dissemination of antibiotic resistance genes [46]. One of the primary types of transduction is generalized transduction, which involves the random packaging of bacterial DNA fragments into phage particles during the lytic cycle [47]. During the lytic cycle, a phage may inadvertently package bacterial DNA fragments instead of its own DNA. When these transducing phage particles infect other bacterial cells, they can transfer a wide range of bacterial genes, including those encoding antibiotic resistance [47,48]. This type of transduction contributes significantly to the horizontal transfer of genetic material within bacterial populations. Another type, specialized transduction, operates through a more specific mechanism and occurs in temperate phages, resulting in the targeted transfer of specific bacterial genes [49]. This process occurs when a prophage excises from the bacterial genome during the transition from lysogeny to the lytic cycle. Adjacent bacterial genes may be mistakenly packaged along with phage DNA, leading to the transfer of these specific genes to recipient cells [49]. Specialized transduction can influence the expression of traits such as virulence factors or metabolic pathways in recipient bacteria. Additionally, Lateral transduction represents a unique form of transduction where genetic material is transferred between cells of different bacterial species. This process occurs when a transducing phage infects a donor bacterial cell, incorporates bacterial DNA fragments into its capsid, and then infects a recipient cell of a different bacterial species, transferring the genetic material between species [50]. Lateral transduction can contribute to genetic diversity and horizontal gene transfer across bacterial communities. Although transduction is mostly associated with temperate phages, strictly lytic phages in theory can mediate generalized and lateral transduction via SaPIs [51].

Understanding the mechanisms and significance of transduction in phage therapy is essential for several reasons. Firstly, transduction can contribute to the genetic diversity of bacterial populations by introducing novel genetic elements acquired from other bacteria. This genetic diversity, driven by transduction events, can influence bacterial adaptation and survival strategies, including the acquisition of antibiotic resistance traits [46]. Secondly, the transfer of antibiotic resistance genes through transduction poses challenges for antibiotic treatment efficacy, as it can contribute to the spread of resistant bacterial strains within clinical settings and environmental niches [52,53].

One of the key factors influencing the efficiency of transduction is the specificity of the phage's packaging machinery. Some phages exhibit high specificity and only package their own DNA, while others, particularly temperate phages, are more promiscuous and can package bacterial DNA along with phage DNA [54]. This promiscuity can lead to the transfer of various genetic elements, including antibiotic resistance genes, among bacterial populations. Several case studies highlight the significance of transduction in phage therapy and its potential impact on bacterial evolution. For instance, in a study by [55], transduction-mediated horizontal transfer of antibiotic resistance genes was observed between *E. coli* strains during phage therapy. The transducing phage, named T4-like phage, facilitated the transfer of resistance genes, including those encoding beta-lactamases, among bacterial populations [55]. Research by [56] investigated the transduction-mediated exchange of virulence factors in *P. aeruginosa* PAO1. The study identified a phage, designated PP7 and E79, capable of transferring genes associated with virulence and biofilm formation between *P. aeruginosa*

strains [56]. A recent study by [57] explored lateral transduction events in environmental bacterial communities. They reported the lateral transfer of genetic elements, including plasmids and mobile genetic elements, between different species of Enterobacteriaceae mediated by transducing phages present in wastewater samples [57]. Another study [58] investigated transduction risks in *Acinetobacter baumannii* multidrug resistant strains. They identified a prophage, capable of transferring metallo-β-lactamase (MBL) resistance genes region, such as those conferring carbapenem resistance, among *A. baumannii* isolates via transduction [58]. A study by [59] focused on transduction-mediated transfer of multidrug resistance genes in *Klebsiella pneumoniae*. The transducing phage, KP1, was found to facilitate the transfer of genes conferring resistance to multiple antibiotics, including carbapenems and cephalosporins, among *K. pneumoniae* strains [59]. Recent work by [60] investigated phage therapy for *S. aureus* infections and highlighted the potential risks of transduction-mediated transfer of virulence genes and antibiotic resistance determinants among *S. aureus* strains during treatment [60]. Another study by [61] shown that bacteriophage φ81 was packaged the staphylococcal cassette chromosome SCC*mec*, staphylococcal pathogenicity island SaPI1, genomic islands vSaα and vSaβ, and plasmids with various frequency during transduction [61]. [62] studied genetic exchange dynamics in *Salmonella Typhimurium* LT2 populations by Carbadox induction of phage-mediated gene transfer and observed transduction-mediated transfer of genetic elements, including plasmids carrying antibiotic resistance genes, in *S. Typhimurium* LT2 [62]. Furthermore, a research by [63] investigated transduction risks within *Enterococcus faecalis* and *Enterococcus gallinarum*. They identified that environmentally isolated bacteriophage, capable of transferring genes associated with antibiotic resistance among *E. faecalis* and *E. gallinarum* strains [63]. These case studies demonstrate the diverse scenarios and risks associated with transduction-mediated horizontal gene transfer in various bacterial species, highlighting the importance of understanding and mitigating transduction risks in microbial ecology, clinical settings, and phage therapy applications. Consequently, the use of phages for therapeutic purposes in hospital or agriculture settings carries the risk of inadvertently driving increased fitness in bacteria that survive phage killing, further exacerbating the global challenge of untreatable bacterial infections.

It underscores the need for careful consideration of the selection and use of phages in therapeutic interventions. Strategies to mitigate this risk may include determining whether strictly lytic phages do facilitate transduction under therapeutic conditions, strict screening of phages used in therapy to ensure they do not carry resistance genes, or focusing on the development of strictly lytic phage preparations that are less likely to facilitate gene transfer [10].

10. Future directions

Future directions in phage therapy for intracellular MRSA infections involve the development of novel phage cocktails targeting specific MRSA strains. By utilizing phages with a broad host range and lytic activity against intracellular MRSA, researchers aim to enhance the efficacy of phage therapy in eradicating intracellular bacterial reservoirs [25,64]. Furthermore, the integration of phage therapy with other antimicrobial agents, such as antibiotics or antimicrobial peptides, may offer synergistic effects and overcome resistance mechanisms [65,66]. Emerging technologies, such as whole-genome sequencing and single-cell analysis, provide opportunities to monitor transduction events in real-time. These technologies enable researchers to track genetic exchanges, identify transducing phages, and characterize transferred genetic elements, enhancing our understanding of transduction risks [67,68]. Additionally, bioinformatics tools and computational models can predict transduction probabilities and assess the impact of transduction on bacterial populations [69].

Future research focuses on developing control strategies to mitigate transduction risks in phage therapy and bacterial populations. This includes the engineering of phages with reduced transduction capabilities or specific targeting mechanisms to minimize horizontal gene transfer [70]. Moreover, biocontainment strategies, such as using genetically modified phages with limited host range, offer potential solutions to prevent unintended transduction events [71]. The implementation of precision medicine approaches in phage therapy involves personalized treatment strategies based on bacterial genomics and host factors. By analyzing bacterial genomes for transduction-prone regions or mobile genetic elements, clinicians can tailor phage therapy regimens to minimize transduction risks and optimize treatment outcomes [4,65,72]. Furthermore, integrating patient immune responses and microbiome dynamics into treatment protocols enhances therapeutic efficacy and reduces adverse effects.

As phage therapy and transduction monitoring technologies advance, biosecurity measures and ethical considerations become paramount. Collaborative efforts between researchers, healthcare professionals, and regulatory bodies are essential to establish guidelines for safe and responsible phage therapy practices [73]. This includes assessing the ecological impact of phage release, ensuring patient confidentiality and informed consent, and addressing potential concerns related to genetic modification of phages. Collaborative research initiatives and international partnerships play a crucial role in advancing phage therapy and transduction research. Sharing data, resources, and expertise across interdisciplinary teams fosters innovation and accelerates the development of effective strategies to combat

intracellular MRSA infections and transduction-mediated gene transfer [36]. Furthermore, collaborative efforts facilitate the standardization of protocols, quality control measures, and regulatory frameworks for phage-based therapies. Key research priorities in the field of phage therapy and transduction include elucidating the mechanisms underlying transduction dynamics, characterizing transducing phages and their host specificity, and assessing long-term ecological impacts of phage-mediated gene transfer [74]. Additionally, studying the interactions between phages, bacterial biofilms, and host immune responses provides insights into overcoming biofilm-associated infections and enhancing phage efficacy in complex microbial environments. Finally, raising public awareness and education about phage therapy, transduction risks, and antimicrobial stewardship is essential. Educational campaigns, scientific outreach programs, and patient advocacy groups play a vital role in disseminating accurate information, dispelling myths, and fostering informed decision-making regarding phage-based treatments and microbial ecology [47].

11. Conclusion

In conclusion, the evolving field of phage therapy for intracellular MRSA infections presents both promising opportunities and significant challenges [55]. The efficacy of phage therapy in targeting intracellular bacterial reservoirs offers a potential solution to combating MRSA infections, particularly those resistant to conventional antibiotics [40]. However, the risks associated with transduction, including the horizontal transfer of genetic elements and the potential for enhanced virulence or antibiotic resistance, necessitate careful consideration and proactive strategies.

Future advancements in phage therapy hold great promise, with potential innovations in personalized treatment regimens, synergistic approaches with other antimicrobial agents, and precision medicine strategies based on bacterial genomics and host factors. Emerging technologies for transduction monitoring and control, such as whole-genome sequencing, single-cell analysis, and bioinformatics tools, offer valuable insights into understanding transduction dynamics and assessing its impact on bacterial populations. Collaborative efforts among researchers, healthcare professionals, regulatory bodies, and patient advocacy groups are crucial in establishing guidelines, standardizing protocols, and addressing biosecurity concerns and ethical considerations associated with phage therapy [74]. Public awareness initiatives and scientific outreach programs play a vital role in disseminating accurate information, fostering informed decision-making, and promoting responsible use of phage-based therapies.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they do not have any conflicts of interest.

Declaration

We hereby declare that the manuscript titled “Phage Therapy for Intracellular MRSA Infections and Navigating Transduction Risks" is our original work and has not been published elsewhere nor is it currently under consideration for publication in any other journal.

Authors contribution

All authors have contributed significantly to the research and preparation of this manuscript and have reviewed and approved its submission to the World Journal of Biology, Pharmacy and Health Sciences.

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