Emerging Therapeutic Treatments for Multidrug-Resistant Bacteria: A Review

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Abstract. The rapid rise of multidrug-resistant (MDR) bacteria poses a severe global health threat, rendering many conventional antibiotics ineffective and contributing to increased morbidity, mortality, and healthcare costs. In response to this escalating crisis, novel antimicrobial strategies are being explored, including bacteriophage therapy, CRISPR-Cas systems, and nanoparticle-based therapeutics. This review examines these innovative approaches' mechanisms, clinical progress, and limitations in combating MDR pathogens, particularly the WHO-prioritized ESKAPE group. Bacteriophages offer strain-specific bacterial killing with minimal off-target effects, but regulatory uncertainty, immune responses, and narrow host ranges hinder their use. CRISPR-Cas systems provide precise gene-editing capabilities to eliminate resistance genes or target specific bacterial strains, though concerns about off-target effects, delivery systems, and biosafety remain unresolved. Nanoparticles, including silver and gold NPs, and nano-drug delivery systems exhibit broad-spectrum antimicrobial properties and targeted delivery potential but raise cytotoxicity, standardization, and long-term safety issues. Despite their promise, each strategy faces critical challenges that must be addressed before clinical translation is viable. Integrating these therapies, alongside continued research, ethical oversight, and global collaboration, may offer a sustainable and adaptable solution to the growing burden of antimicrobial resistance.

Keywords: Phage Therapy; CRISPR/CAS; Nanoparticles; Multidrug-resistant Bacteria; Nano-Drug Delivery Systems (nano-DDS).

1. Introduction

The rapid increase and spread of multidrug-resistant (MDR) bacteria pose a significant threat to public health, clinical medicine, and global healthcare systems. The WHO has expressed grave concern regarding the continued increase in the development of antimicrobial resistance (AMR) among bacteria, with 1.27 million deaths directly associated with drug-resistant bacteria in 2019, with estimates that as many as 10 million people could die annually from AMR by 2050 if current trends persist [1,2]. This escalating threat has prompted the WHO to declare AMR one of the top 10 global public health threats, triggering initiatives worldwide to develop novel, more effective treatments and targeting strategies.

Bacteria have developed various mechanisms that enable them to become resistant to antimicrobials. These include enzyme deactivation, drug modification, decreased cell permeability, efflux pumps, and alterations at the target site [3]. These mechanisms are amplified through the overuse and misuse of antibiotics in clinical settings, with many species exhibiting resistance to multiple classes of antibiotics. Most major antibiotic classes still in use were discovered between the 1940s and 1960s, with few new antibiotics developed since then. Some strains have become resistant to almost all commonly available agents.

An example is methicillin-resistant Staphylococcus aureus (MRSA), which is resistant to many antibiotics outside methicillin, including macrolides, tetracyclines, aminoglycosides, lincosamides, and others. These strains demonstrate disinfectant resistance, allowing methicillin-resistant Staphylococcus aureus (MRSA) to play a significant role in hospital-acquired infections [4]. WHO classified it as a “critical priority” due to its high mortality rates, limited treatment options, and frequent outbreaks in hospital settings.

Many countries saw an increase in hospitalizations and deaths related to MDR bacteria in recent years. In the EU, approximately 33110 deaths were associated with ABR bacteria, with the burden in

hospitals still growing [5]. Similarly, Lim and his colleagues estimated the burden of multidrug-resistant pathogens in Thailand in 2010, with 43% of deaths caused by MDR bacteria with hospital-acquired infections [6]. In response, there has been a growing interest in developing non-traditional antimicrobial agents and innovative delivery systems in recent years. Promising approaches include phage therapy, nanoparticles (NP), and CRISPR-Cas9 editing. These methods show promising results in combating MDR bacteria; however, safety concerns and regulations remain undetermined. This review will summarize the latest techniques for combating MDR bacteria, assess their practical applications in vivo and clinical settings, and discuss prospects and limitations.

2. Phage Therapy

Phage therapy was first utilized in the 1930s. The discovery of antibiotics as a convenient and inexpensive method to combat bacteria quickly overshadowed phage therapy, leading to a decline in interest in the field [7]. However, in recent years, phage therapy has seen a surge in interest and development following the increasing concern and burden in the healthcare system caused by major MDR bacteria, known as the ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species), as well as the decline in the development and effectiveness of new antibiotics. Phage therapy is effective against Methicillin-resistant *Staphylococcus aureus* (MRSA), with results demonstrating good lytic activity against MRSA in vitro and a decrease in bacterial count in vivo in rabbits [8]. Research has shown the effectiveness of phage therapy, with a study demonstrating that bacteriophages are effective against vancomycin-resistant *Enterococcus faecium*. Clinical trials on patients have also been conducted with largely successful results. It has effectively treated typhoid fever and demonstrated efficacy in treating colistin-only-sensitive Pseudomonas aeruginosa septicemia in a patient with acute kidney injury [9,10]. In a 2022 case report, a patient with disseminated cutaneous *Mycobacterium chelonae* was treated with phage therapy after 10 different antibiotics failed to control the infection [11]. The patient's symptoms lessened within the next few weeks following the treatment. Although the patient developed IgG antibodies, this did not negate the overall clinical improvement observed in the patient [12]. Phage therapy offers numerous advantages, making it a favorable alternative to traditional antibiotics. Firstly, bacteriophages are extremely specific, targeting only their host, thereby minimizing the risk of secondary infections. Additionally, phages replicate only at the site of infection, thereby limiting damage to other parts of the body. This differs from traditional antibiotics, which can cause adverse effects throughout the body [13].

Although bacteria can become resistant to bacteriophages, it is not as worrisome as drug resistance. It is believed that phages co-adapt with bacteria, thereby overcoming the phage resistance exhibited by bacteria over time in recurring or chronic infections [14]. However, since multiple strains are usually present during an infection, a phage cocktail composed of multiple phage species has been proposed to combat this weakness. In vitro, phage cocktails effectively decrease mixed-species bacteria count, indicating the potential for phages to mitigate MDR infections [15,16]. It has also been suggested that phage therapy be used with traditional antibiotics to expand its antibacterial spectrum. While there are no FDA-approved phage therapies yet, some clinical trials are in phase 3, with the United States leading the phage-related industry-sponsored trials [17].

3. Nanotheraperutics

Nanotherapeutics, such as nanoparticles (NPs) and nanotechnology-based drug delivery systems (nano-DDS), have also been proposed as an alternative to combat MDR bacteria in recent years. Inorganic nanoparticles, such as gold and silver, have been studied as antimicrobial agents due to their unique antimicrobial properties and high compatibility within living organisms. Studies have shown that silver and gold nanoparticles exhibit antimicrobial properties, reducing bacterial counts

and causing cell death by puncturing holes in the bacterial walls [18, 19]. NPs achieve this by interacting with the bacterial cell wall through electrostatic attraction, hydrophobic interactions, receptor–ligand interactions and van der Waals forces. Apart from puncturing bacterial cell walls, NPs can bind to intracellular components, such as DNA, ribosomes, and enzymes, once they enter the bacteria, disrupting essential cellular functions [20]. In addition to NPs, nano-DDS have been proposed as an effective method for transporting antimicrobials directly to the site of infection. Nanoparticle drug delivery systems (nano-DDS) can improve and modify various pharmaceuticals' efficacy beyond traditional formulations' limitations. Specifically, nano-DDS can encapsulate medications, safeguarding them against degradation, directing them to targeted sites within the body, and facilitating their release in a controlled manner in response to specific stimuli [21]. Using nano-DDS with other antimicrobial methods could provide more effective results against MDR bacteria. For example, Lipid-based nanovesicles have been proposed to be used together with phages to enhance their effectiveness, as phages can accumulate in specific organs and have a hard time penetrating the depth of infection sites due to the presence of dead tissue debris, necrotic cells, immune cells, etc. [22,23]. However, there are several limitations to NPs and nano-DDS. Some of these include the interactions and toxicity of nanoantibiotics within the human body, appropriate routes of administration, exposure through other routes, and their long-term effects [24].

4. CRISPR-Cas System

The CRISPR-Cas (Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated proteins) system, initially discovered in *Escherichia coli* K-12, is a bacterial adaptive immune mechanism. Besides serving as a primitive immune system, CRISPR-Cas regulates bacterial and archaeal genes, virulence, and stress physiology. Two main types of CRISPR-Cas systems are studied: Type I and Type II. Type I CRISPR systems are the most prevalent in natural environments and rely on a multi-protein effector complex known as the CRISPR-associated complex for antiviral defense (CASCADE). This system utilizes the Cas3 exonuclease to process invasive DNA.

In contrast, Type II CRISPR systems utilize endonuclease Cas9 to introduce double-stranded breaks in target DNA [25]. Unlike traditional antibiotics that broadly inhibit essential bacterial processes, CRISPR-Cas are extremely precise, enabling the selective killing of resistant strains. Two main approaches utilize CRISPR-Cas systems to combat MDR bacteria: pathogen-focused and gene-focused approaches. Targeting specific sequences within the bacterium's genome, which results in cell death and strain killing, is a pathogen-focused approach. Whilst a gene-focused approach involves targeting plasmids that carry resistant genes, removing those plasmids, and making the bacterium sensitive to antibiotics again. A study using the genome of Escherichia coli has demonstrated that repurposing the type I CRISPR-Cas system can selectively eliminate specific bacterial strains based solely on DNA sequence recognition, achieving a 99.9% rate of bacterial removal *in vitro* [26]. Research has also suggested using the CRISPR-Cas system to treat ESKAPE pathogens such as Carbapenem-resistant A. baumannii, highlighting its potential use to combat the increasingly resistant strains [27]. Although this system is a potent tool against MDR bacteria, delivery of the system into target bacteria still poses an issue. Due to their accuracy, using phages as carriers has been proposed as an effective way to deliver the CRISPR-Cas system into the target bacterium [28]. It has already been shown that phages can carry antimicrobial proteins and genetics into targeted bacteria [29]. However, phages often target a few strains of bacteria, making treating multi-strain infections using CRISPR-Cas systems challenging. Furthermore, the effects of off-targeting, immune responses to Cas proteins, and the lack of a scalable delivery system remain significant concerns [30].

5. Limitations and Future Prospects

The overuse and misuse of antimicrobials have led to an exponential growth of AMR bacteria, eventually resulting in the rise of MDR and ESKAPE pathogens. Although these treatments discussed for MDR bacteria provide innovative insights into alternatives to treat MDR bacteria, many limitations and hurdles still need to be addressed.

Bacteriophage and phage therapy lack regulatory frameworks for phage production, storage, and administration, which poses a significant obstacle to widespread adoption. There is also a lack of randomized controlled trials and trials that test for standardized doses, clinical failure, and standardized data collection [31]. Phages are also highly specific, requiring precise pathogen identification and customized phage cocktails, which takes time and makes mass production and rapid deployment difficult. Concerns about endotoxin and immune responses from long-term administrations also pose an issue, with a lack of understanding of how phages interact with the immune system once injected and how they could affect treatment [32]. To overcome these challenges, systematic studies and clinical trials should be conducted to study its effects in vitro and assess potential effects when administered with other drugs. In addition, combining phage therapy with traditional antibiotics may significantly decrease the likelihood of bacteria developing resistance [32].

CRISPR-Cas technology faces the risk of off-target mutations, resulting in harmful effects observed in large genome sequences, such as human cells [33]. In clinical settings, complex bacterial populations increase the chance of off-targeting. It also lacks delivery methods to transport CRISPR to its desired location. The use of phages as delivery systems has been considered; the narrow range of targets that phages have poses an issue in clinical settings, where they face complex microbial communities [34]. Moreover, ethical and biosafety concerns surrounding gene-editing tools in microbial populations may limit regulatory approval and public acceptance. To overcome these challenges, more standardized trials should be done to assess its safety *in vitro* and develop clear guidelines to regulate its use. Developing suitable delivery vectors would expand the range of targets that CRISPR can access.

Nanoparticles and nano-DDS face limitations in clinical translation. Key concerns include cytotoxicity to human cells, lack of target specificity, and the potential for inducing bacterial resistance with prolonged or sub-lethal exposure. Furthermore, variability in nanoparticle synthesis methods can lead to inconsistent size, shape, and surface charge, significantly influencing antimicrobial efficacy and safety [36]. To overcome these barriers, future research should focus on surface functionalization techniques, such as coating nanoparticles with biocompatible polymers or ligands that target bacterial cell components, to enhance specificity and reduce off-target effects. Hybrid nanosystems, such as NP-antibiotic conjugates, offer additional promise by combining multiple antimicrobial modalities while minimizing toxicity [37]. Standardization of synthesis protocols and comprehensive in vivo studies are also crucial to evaluate pharmacokinetics, toxicity, and efficacy.

While novel therapeutic strategies such as bacteriophage therapy, CRISPR-Cas systems, and nanoparticle-based antimicrobials offer significant promise in addressing the escalating threat of multidrug-resistant (MDR) bacteria, each approach is currently limited by technical, clinical, and regulatory challenges.

6. Conclusion

The global rise of multidrug-resistant (MDR) bacteria presents an urgent challenge, complicated by the diminishing efficacy of conventional antibiotics. This review highlights the promising but still emerging roles of bacteriophage therapy, CRISPR-Cas systems, and nanoparticle-based therapeutics as new strategies to combat MDR pathogens, including critical threats such as the ESKAPE pathogens. Each of these technologies offers distinct advantages—high specificity, novel mechanisms of action, and adaptability—but also faces significant barriers, including regulatory uncertainty, delivery limitations, immunogenicity, and safety concerns.

The future of antimicrobial innovation will depend on overcoming these limitations through coordinated efforts. Standardized clinical trials, scalable production techniques, and reliable delivery platforms will be key to unlocking these therapies' clinical potential. Furthermore, combinatorial approaches, such as combining individual therapies with antibiotics, delivering CRISPR systems and NPs via engineered vectors, or enhancing nanoparticle specificity and targeted delivery, may improve therapeutic outcomes while reducing the risk of developing resistance.

Global collaboration among scientists, clinicians, regulatory agencies, and public health agencies is essential to fully integrate these technologies in clinical practice. Only through such efforts can we move from experimental promise to practical application, ensuring a sustainable defense against the growing threat of antimicrobial resistance.

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