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LETTERS

Combating antimicrobial resistance: A paradigm shift from general to precision medicine

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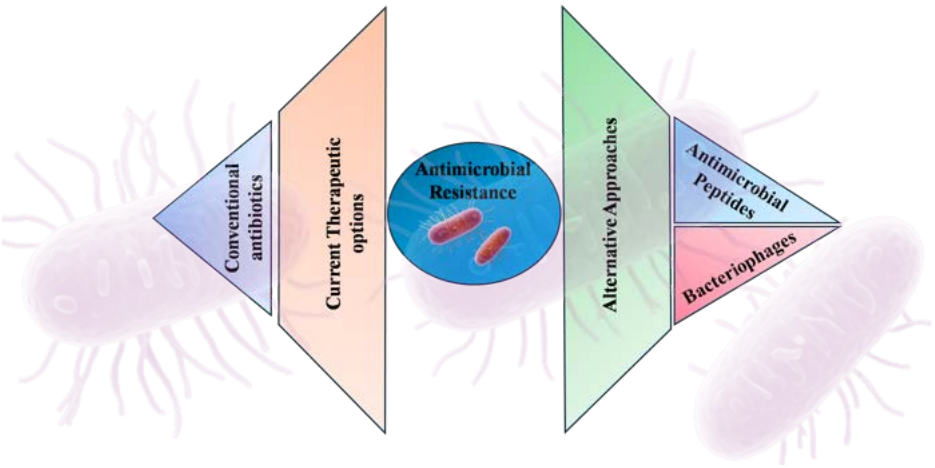
Review Article

ABSTRACT

Antimicrobial resistance (AMR) poses a significant threat to global health. It makes treating bacterial infections increasingly difficult. AMR arises from various mechanisms of antibiotic resistance including enzymatic inactivation, target alteration, efflux pumps, and decreased permeability. The limited and often ineffective treatments relying on antibiotics and their combinations result in increased morbidity and mortality. Therefore, it is essential to explore alternative methods for combating the challenge of AMR. In recent years, there has been a notable shift towards precision medicine in the battle against AMR. Precision medicine, characterized by its focus on individualized treatment tailored to patients' specific genetic makeup, offers a paradigm shift in addressing AMR challenges. By pinpointing molecular targets responsible for infection, precision medicine enables more targeted and effective therapies, minimizing the risk of antimicrobial resistance development. Precision medicine can provide an alternative option to combat AMR by focusing on targets responsible for the infection. Bacteriophages and antimicrobial peptides (AMPs) are groups of antimicrobials that can serve as novel alternatives to antibiotics for combating the global antibiotic resistance challenge. They have the potential to be used as targeted therapy. Despite challenges such as limited host range, which refers to the specific bacteria they can infect, and regulatory concerns related to their approval and usage, bacteriophages have proven effective against bacteria causing infections. Meanwhile, AMPs provide a potential treatment approach against antibiotic-resistant bacteria due to their low molecular weight and broad-spectrum antimicrobial activity. AMPs can serve as a first line of defense against microorganisms. When used alone or combined with other biomaterials to increase therapeutic action, they can serve as a first line of defense against microorganisms. This review article aims to provide a comprehensive overview of the current understanding and clinical potential of bacteriophages and AMPs as alternatives to conventional antibiotics in addressing the pressing challenge of AMR.



Keywords: Alternative treatment options, Antimicrobial peptides, Bacteriophages, Antibiotic resistance, Precision Medicine

INTRODUCTION

Antimicrobial resistance (AMR) is a serious global health issue in the 21st century and poses a threat to the effectiveness of treatments. AMR arises when microorganisms such as bacteria, viruses, fungi, and parasites evolve and become resistant to medication. It makes infections harder to treat. According to a WHO report, more than 50% of life-threatening infections caused by bacteria are becoming resistant to treatment.[1,2] According to a report published by the United Nations on AMR in April 2019, drug-resistant diseases have the potential to cause 10 million deaths annually by 2050 if effective measures are not taken to address this issue.[3] According to estimates, bacterial AMR caused 4.95 million fatalities worldwide in 2019 and was directly responsible for 1.27 million deaths. One in 5 people, who died from AMR infection was a child under 5 years of age, and

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previously infected from treatable infections.[4] Currently, AMR pathogens are causing 700,000 deaths per year, which is an alarming number that surpasses deaths from other diseases, and this situation is expected to worsen by 2050 (Figures 1 & 2).[5,6,7]

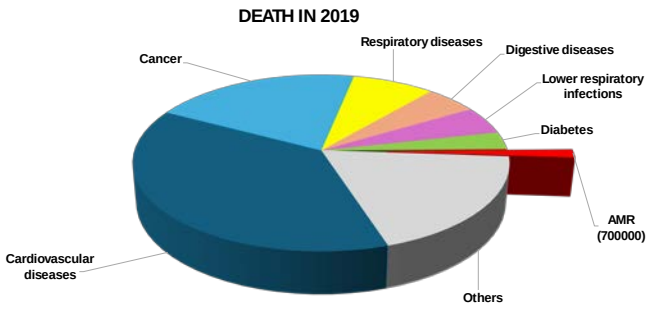

Figure 1. Recent statistics of deaths caused by major diseased conditions along with AMR.

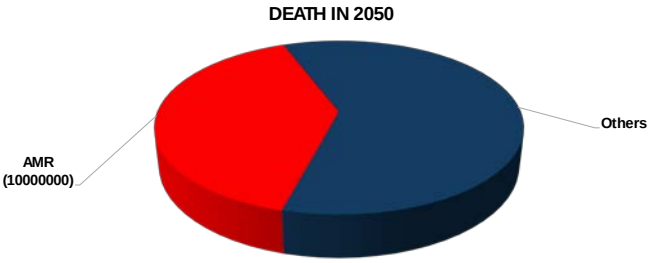

Figure 2. Expected death caused by AMR in comparison to other disease in 2050.

AMR is caused by different factors including the absence of a proper surveillance system, overuse and misuse of antimicrobials, poor infection control, lack of patient and public awareness, limitation of recent AMR data, and inadequate diagnostic capacity.[8] The antibiotic resistance has worsened due to the COVID-19 pandemic through the use and abuse of antibiotics, disruption of surveillance and preventive systems, and a decline in the research and development of novel antibiotics.[9] Some bacterial strains have evolved into superbugs, they are resistant to most or all the existing antibiotics, such as the ESKAPE group (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) of bacteria.[10,11,12,13] From the initial discovery of the first naturally occurring antibiotic, penicillin, by Alexander Fleming, resistance has been observed. Fleming warned about antibiotic resistance in his Nobel Prize lecture in 1945, saying "there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."[14,15,16,17] Till now, the pharmaceutical industry has addressed this issue by making modifications to current antibiotics and growing new ones. However, in the last forty years, only three new categories of antibiotics (lipopeptides, oxazolidinones, and streptogramins) have been brought into the market, and they all are meant for treating gram-positive bacterial infections. Additionally, bacteria have proven their capacity to rapidly escalate antibiotic resistance, diminishing the effectiveness of this technique. This surely emphasizes the need for new antibacterial agents that work in a different way from traditional antibiotics. The urgent need has triggered global efforts in the development of innovative alternatives, with bacteriophages (phages) and antimicrobial peptides (AMPs) being promising candidates. This review aims to offer a thorough comprehensive study of conventional antibiotics, bacteriophages and antimicrobial peptides, including an illustration of our current understanding of these new preventive strategies, focusing on the mechanism of action, specificity and safety, antimicrobial status, and the relative advantages and disadvantages of its possible occurrence in clinical practice settings.

FACTORS CONTRIBUTING TO THE DEVELOPMENT AND SPREAD OF AMR

AMR is influenced by various factors. Some of the important factors contributing to the development and spread of AMR are overuse and misuse of antibiotics in both humans and animals, as well as improper use of antibiotics as growth promoters in livestock, which leads to the development of antibiotic resistance. Improper prescription practices, self-medication, and failing to complete antibiotic courses also contribute to the development of AMR.[18] Poor infection control practices, such as inadequate sterilization of medical equipments and poor hand hygiene, can increase the risk of infection and the demand for antibiotics, which can lead to AMR. Due to the increase in international travel and commerce, it becomes easier for the rapid transmission of resistant bacteria across the globe, which makes AMR a worldwide health concern.[19] Overcrowding, especially in healthcare settings, inadequate sterilization of medical equipments, and poor hand hygiene can lead to the spread of resistant bacteria.[20] Inadequate access to high-quality healthcare and lack of awareness may result in the misuse of antibiotics as well as self-medication. The indiscriminate use of antibiotics in agriculture to treat livestock as well as growth promoters can lead to transferring of antibiotics to humans. Environmental contamination with antibiotics and resistant bacteria from agricultural and healthcare settings also leads to the AMR.[21]

MECHANISM OF ANTIBIOTIC RESISTANCE

Bacteria can acquire resistance to antibiotics through two main mechanisms: genetic mutations in their own genome, leading to cross-resistance to multiple drugs, or by acquiring resistance genes from other microbes through horizontal gene transfer processes like conjugation, transformation, or transduction. Once resistant, bacteria can employ various strategies to resist antibiotics, including inactivating the antibiotics, modifying antibiotic targets, altering membrane permeability, and utilizing bypass metabolic pathways (as shown in Figure 3).[22,23,24]

ACQUISITION OF RESISTANCE

Natural resistance or development

Antibiotic resistance is not only a result of human activity. Rather, it is a naturally occurring process as a result of

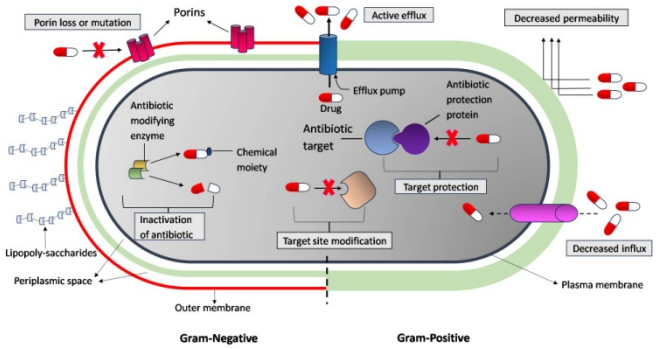

Figure 3. Different mechanisms of antibiotic resistance.

interactions between bacteria (or other diseases) and their environment.[25] Bacterial populations show genetic diversity due to genetic recombination and mutations. Certain members of the population can possess inherent traits, stemming from genetic compositions that confer resistance to particular antibiotics. The development of antibiotic-resistant bacteria through processes of evolution may be the cause of this antibiotic resistance.[26] When antibiotics are introduced into an environment (like the human body), the bacterial populations undergo selection pressure. During this process, antibiotic-susceptible bacteria are eliminated, while some bacteria become less susceptible or resistant due to their advantageous genetic mutations. This leads to an increase in the proportion of resistant bacteria over time.[27,28]

Horizontal gene-transfer and mobile genetic elements

The transmission of genetic material across distinct species is known as horizontal gene transfer (HGT) or lateral gene transfer. HGT is more common among bacteria-to-bacteria, but it can also occur between other organisms, such as bacteria which act as donors, and organisms like fungi, animals, and plants which act as recipients.[29] HGT is most frequently mediated by mobile genetic elements. Mobile genetic elements (MGEs) are the segments of DNA that can move from one location to another location within a genome or between different genomes and play an important role in displaying various physiological functions of bacterial cells.[30,31] Transformation, transduction, and conjugation are the three primary mechanisms through which HGT occurs in bacteria. Other mechanisms involved in the HGT are gene transfer agents (GTAs), nanotubes, and membrane vesicles (MVs).[32] The transformation mechanism of HGT allows bacteria to take up naked DNA from the environment, from the bacterium that has died, and release their DNA into the surrounding environment. The DNA can be inserted into the bacterial genome by homologous recombination or by non-homologous end joining.[33] Transduction is a genetic recombination process in which the bacterial genes are incorporated into the genome of bacterial viruses (bacteriophages) and carried to another bacterial cell when the bacteriophage starts a new cycle of infection. In this process, a few specific genes are transduced.[34] Conjugation is a mechanism by which bacterial cells can transfer genetic material to other bacteria through direct or bridge-like contact. The transferred genetic material is usually plasmid, a circular DNA molecule that can replicate self-reliantly from the bacterial chromosome.[35]

Modification of antibiotic targets

One of the most important strategies by which bacterial cells acquire MDR is modification of the antibiotic binding sites, which reduces the binding affinity between the drugs and the targets. Such types of target modification may include 1) enzymatic modification of the binding sites (addition of methyl group), 2) point mutation in the target encoding genes, and 3) replacement of the original target.[36] β-lactamases are the oldest known antibiotic degrading enzyme that causes hydrolysis of the β-lactam ring of the β-lactam class of antibiotics and renders them ineffective. In 1940, the first case of β-lactamase resistance was reported. The study found an enzyme produced by the strain of *Escherichia coli* can destroy penicillin used to kill bacterial cells.[37] Ambler classified the β-lactamase into four different classes based on their amino acid sequence and these are class A, B, C, and class D. Class A β-lactamase is the ESBL (extended-spectrum β-lactamases). Class B β-lactamase is the metallo-β-lactamases. Class C β-lactamases is the AmpC β-lactamases and class D β-lactamases is the OXA β-lactamases. Class A, C, and D require serine substrate for the hydrolysis of the β-lactam ring and thus it is called serine β-lactamases. Class B β-lactamases are also known as metallo-β-lactamases because they are dependent on bivalent metal ions, often zinc, to function.[38] Some most dangerous and frequent β-lactamases are ESBLs and carbapenemases.[39] N-acetyltransferase is an enzyme that can cause antibiotic modification and resistance by adding an acetyl group to aminoglycosides. These drugs bind to the ribosome of bacteria to prevent the production of proteins by the bacteria. Acetylation reduces the affinity of aminoglycosides to bind with the ribosome and reduces the ability to inhibit bacterial protein synthesis. Aac(6')-lb is one of the most common plasmid-mediated N-acetyltransferase genes found in Gram-negative bacteria such as *K. pneumonia* and *E. coli*.[40] O-phosphotransferase causes antibiotic modification by adding a phosphate group to the aminoglycoside. This causes inactivation of antibiotics and makes them ineffective against bacteria. Both Gram-negative and Gram-positive bacteria can produce the enzyme, but the function and structure are different depending on the bacteria.[41] The aph(3')-la gene encodes APH(3')-la enzyme that phosphorylates the 3'-hydroxyl group of various aminoglycosides such as kanamycin, neomycin and gentamycin. aph(6)-la gene encodes APH(6)-la enzymes that phosphorylate 6'-hydroxyl group of streptomycin and spectinomycin.[42] Enzyme rRNA methyltransferase encoded by *emr* genes (erythromycin ribosomal methylation), causes macrolide resistance by enzymatic modification of the target site through methylation. This enzyme adds one or two methyl groups to the adenine residue in position A2058 of domain V present in the 23S rRNA, a part of the large (50S) ribosomal subunit. Because of this alteration, macrolides antibiotics have a lower affinity for attaching to the ribosome and are unable to suppress protein synthesis.[43] Rifampin resistance is the best example of mutation-based resistance.[44,45]

Cell permeability

The antibiotic must penetrate the cell membrane of the bacterial cell in order to begin its antibiotic activity.[46] There are mainly two different types of mechanisms through which antibiotics penetrate the bacterial cells: passive and active diffusion.[47,48] The primary enzymes involved in the manufacture of peptidoglycan, the principal building block of bacterial cell walls, are penicillin-binding proteins (PBPs). Some bacteria can alter the structure of PBPs to reduce the binding affinity for penicillins and other antibiotics that target the bacteria cell wall. Examples of some bacteria that express altered PBPs are methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae*, and Vancomycin-resistant *Enterococcus* (VRE).[49] Vancomycin is a glycopeptide antibiotic, which inhibits the synthesis of peptidoglycan. Peptidoglycan is composed of repeating units of N-acetylglucosamine and N-acetylmuramic acid which are linked by peptide bonds. Enterococcus bacteria acquire resistance by altering the peptidoglycan synthesis pathway. This altered peptide chain has a lower binding affinity to vancomycin, making it less effective in inhibiting cell wall synthesis. It possesses ~1000-fold lower binding affinity for D-Ala-D-Lac and ~7-fold lower binding affinity for D-Ala-D-Ser.[50] Certain bacteria's outer membrane has holes that are created by proteins called porins. It is mainly found in Gram-negative bacteria but also found in some Gram-positive bacteria such as *Mycobacterium tuberculosis* and *Bacillus anthracis*. They allow the passage of small molecules such as water, ions, nutrients, and some antibiotics. Mutation can affect its structure, function, expression, and regulation. One of the most important and common mechanisms of porin mutation is an alteration of the porin gene sequence. The mutation reduces the permeability and affinity of drugs, by altering the electrostatic interaction between the drug and the porin.[51] OmpF is a larger-channel porin that allows more molecules to enter the cell, while OmpC is a smaller-channel porin that resists the molecule from entering the cells. Under high osmolarity or antibiotic stress conditions, OmpF expression is reduced and OmpC expression is increased, resulting in lower permeability.[52]

Drug efflux pump

The purpose of bacterial efflux pumps, which are a type of proteins found in bacterial plasma membranes, is to recognize and eliminate various pathogens that have entered the cytoplasm of the organism through the bacterial cell wall and excrete before they can harm the target. The first case of efflux pump was noticed in the 1980s when tetracycline was pumped out of the cytoplasm of *E. coli*.[53] Efflux pump resistance mechanisms show resistance to a wide range of antibiotic classes including fluoroquinolones,β-lactams, aminoglycosides, macrolides, and tetracyclines.[54] There are five major classes of efflux pumps: (1) the major facilitator superfamily, (2) the small multidrug resistance family (SMR), (3) the resistance-nodulation-cell-division family, (4) the ATP-binding cassette family, and (5) the multidrug and toxic compound extrusion family.[55] Further, based on their energy sources, efflux pumps are classified into two

Table 1. List of currently used antibiotics against Gram-negative AMR bacteria.

Currently used antibiotics	Gram-negative AMR bacteria	Mechanism of action	Current clinical status	Ref.
Ceftazidime/ avibactam	Carbapenem resistant Enterobacteriaceae, *P. aeruginosa, A. baumannii*	Inhibit cell wall synthesis	Resistance has been reported due to mutation.	66,67
Meropenem/ vaborbactam	Carbapenem resistant Enterobacteriaceae, *P. aeruginosa, E. coli*	Inhibits cell wall synthesis	Resistance occurred due to mutation or production of metallo-β-lactamases	66–68
Ceftolozane/ tazobactam	*E. coli, K. pneumoniae, Proteus mirabilis, P. aeruginosa*	Inhibit cell wall synthesis and β-lactamase enzyme	Resistance occurred due to the production of AmpC	66, 67, 69
Eravacycline	Carbapenem resistant Enterobacteriaceae, *A. baumannii, K. pneumoniae, Enterobacter cloacae*	Block the tRNA binding site and inhibit protein synthesis	Resistance occurs due to the efflux pump	66,67
Levofloxacin	*K.pneumoniae, P. aeruginosa, E. coli*	DNA gyrase and topoisomerase inhibition will stop DNA replication and transcription	Resistance increases due to mutation and efflux pump	66,67
Ampicillin	Enterobacteriaceae, *Haemophilus influenzae, Listeria monocytogenes*	Inhibit cell wall synthesis by binding with PBP	Resistance occurred as a result of β-lactamases synthesis	67
Cefiderocol	*A. baumannii, Stenotrophomonas maltophilia,* Carbapenem resistant Enterobacteriaceae	Prevent the production of cell walls	Metallo-β-lactamasesproduction causes resistance	70
Delafloxacin	*A. baumannii, E. coli, K. pneumoniae, Haemophilus influenzae*	Inhibit DNA gyrase and Topoisomerase IV	Efflux pump and mutations cause resistance	71
Colistin	*P. aeruginosa, A. baumannii, K. pneumoniae,* Enterobacteriaceae	Disrupts bacterial cell membrane	Resistance occurs due to the modification of LPSand also overuse and misuse	69
Nalidixic acid	*E. coli, Salmonella spp., Shigella spp.*	Inhibit DNA gyrase	Resistance occurs due to the mutation of the gyrA gene encoding DNA gyrase subunit A	67

categories, ATP-binding cassette (ABC) superfamily and proton motive force (PMF)-dependent superfamily.[56,57,58] Tetracycline resistance is the finest example of efflux-mediated antibiotic resistance. In this mechanism, the Tet efflux pump which belongs to MFS excretes out the tetracycline using proton exchange as the source of energy. Most of the efflux-pump resistance mechanism is found in Gram-negative bacteria, except Tet(K) and Tet(L) which are found predominantly in Gram-positive bacteria.[59,60] The MefA and MefE are the well-known efflux-pump encoded by *mef* genes that excrete out the antibiotics in the macrolide class. Along with other streptococci and Gram-positive bacteria, *Streptococcus pyogenes* and *Streptococcus pneumoniae* are the primary hosts of the Mef efflux pump.[61]

Current Therapeutic Options for Bacterial Infection

Single or combination of different antibiotics

Conventional antibiotic therapy is used for the treatment of bacterial infections by either taking a single or a combination of two or more antibiotics. The main problem with using a single antibiotic drug in the treatment of bacterial infection is that it can increase the risk of antibiotic resistance. But, when a combination of antibiotics is used, it can have some advantages over monotherapy. Combination antibiotic therapy increases the antibacterial spectrum and can target a wide range of bacteria, especially when infection is caused by multiple or unknown pathogens.[62,63] It can prevent or delay the development of resistance. This can preserve the efficacy of existing antibiotics and extend their clinical usefulness.[64]However, combination therapy also has some challenges and disadvantages, such as increasing risk of toxicity and adverse effects, increased cost and complexity of treatment, and lack of proper guidelines.[65] Different antibiotics are used for different types of infections and diseases (Tables 1 & 2) caused by both Gram-positive and Gram-negative MDR bacteria.

Limitations

The main problem of antibiotic therapy in microbial infection is the resistance of the drugs, shown by the microbes through different mechanisms which are given above. Some other factors that limitation of antibiotic therapy in antimicrobial resistance are the misuse and overuse of antibiotics, such as prescribing them for viral infection, lack of new antibiotics being developed, the insufficient surveillance and monitoring of resistance patterns, which create difficult situations in choosing the most effective antibiotic against each infection, and the inadequate infection prevention and control measures.[76] To overcome the limitations of conventional antibiotic therapy there is an urgent need for a paradigm shift towards precision medicine. Despite originally being quite successful, conventional antibiotic therapies are now challenged by the emergence of resistant bacterial strains. The different limitations of conventional antibiotic therapy mentioned above highlight the necessity of precision medicine, which provides a more individualized approach to care. The goal of precision medicine is to determine the most effective treatment based on the unique qualities of each patient, the characteristics of the microbes, and the dynamics of the microbial infection. Precision medicine can provide an individualized treatment plan that maximizes therapeutic results while lowering the chance of resistance development by utilizing advanced technologies such as genomics, proteomics, and bioinformatics. Thus, precision medicine has the potential to combat AMR by providing targeted and effective solutions and addressing the drawbacks of traditional antibiotic therapy.[77,78]

Alternative Treatment Options

Precision medicine

Precision medicine is a revolutionary approach that customizes medical decisions, interventions, and therapies for individual patients according to their genetic composition, distinctive traits, and expected outcomes. Precision medicine concedes that every patient has different demands when it comes to their health rather than taking a one-size-fits-all approach.[79] Precision medicine allows medical professionals to customize antibiotic treatments for each patient based on their unique immune response, genetic makeup, and the type of specific infection. By selecting the most effective antibiotic for a particular patient we can maximize the potential outcome while lowering the risk of resistance.[77] AMR genomic surveillance combines data from the environment, humans, and animals. This comprehensive method helps us to understand interrelated factors responsible for the resistance. By identifying the genetic cause of the resistance, precision medicine provides personalized therapy.[80,81]

Key components

Precision medicine in the context of AMR, encompasses several essential components that work together to customize the

Table 2. List of currently used antibiotics against gram-positive AMR bacteria.

Currently used antibiotics	Gram-positive AMR bacteria	Mechanism of action	Current clinical status	Ref.
Penicillin	Staphylococcus, Streptococcus, Enterococcus	Inhibit peptidoglycan synthesis in cell wall	Resistance is common, especially in MRSA and VRE	72
vancomycin	Staphylococcus, Streptococcus, Enterococcus, *Clostridium difficile*	Inhibit cell wall synthesis	Resistance is increasing especially in VRE and VRSA	73
Linezolid	Staphylococcus, Streptococcus, Corynebacterium	Attach to the 23S rRNA of 50S ribosomal subunit to inhibit the production of new proteins	Resistance is low but emerging especially in MRSA and VRE	74
Fosfomycin	Staphylococcus, Enterococcus, *L. monocytogenes*	Inhibit cell wall synthesis	Resistance is low but variable	75

unique requirements and features of each patient. Biomarkers play an important role in precision medicine because they help in the distinction between bacterial and viral infections, which is necessary for the proper administration of antibiotics.[82] The application of "omics"-based technologies such as proteomics, genomics, and metabolomics, helps in a better understanding of disease mechanisms and allows the development of targeted therapies.[77] Development in nano-biotechnology highlights the potential of targeted therapy, which can reduce adverse effects and improve therapeutic efficacy.[83] Personalized medicine regimes not only consider the genetic factor, lifestyle, and environmental influences but also personal preferences in the treatment decision. It highlights a more comprehensive perspective of the patients, accounting for their unique conditions and values.[84]

Limitations of precision medicine

It is difficult to incorporate vast amounts of data, particularly genetic information, into therapeutic practice. Effective precision medicine depends on ensuring the data's correctness, security, and interoperability.[85] It remains challenging to distinguish between bacterial and viral infections, which frequently leads to inappropriate antibiotic use.[77] One of the biggest challenges to incorporating precision medicine into standard clinical treatment is the lack of advanced technologies. Due to technological constraints, pathogen identification and antibiotic susceptibility testing may take longer than expected, affecting treatment choices.[86] It is also challenging to develop effective therapies for patients with multiple disease conditions, and the high cost of testing and treatment can be a barrier to implementing precision medicine.[87] One of the most significant challenges in the implementation of precision medicine is regulatory issues. As precision medicine requires personalized data that may not fit with the conventional clinical trial models, it complicates the foundation for generating evidence for the precision medicine. In the era of precision medicine, patient involvement in the regulatory process is difficult but essential.[88]

Antimicrobial peptides (AMPs) against antibiotic resistance

One of the possible alternatives for the emerging antibiotic resistance is AMPs. AMPs are short protein molecules that can inhibit or kill microorganisms, including bacteria, fungi, viruses, and parasites.[89] The average number of amino acid residues in an AMP is 33.26 with a range of 10 to 60. Nearly all AMPs are cationic, with an average net charge of 3.32. There are also several anionic AMPs, which contain acidic amino acids including glutamic acid and aspartic acid.[90] A total of 3791 AMPs have been documented to date, according to the AMP database; Data Repository of AMPs (DRAMP).[91] AMPs can act on a variety of targets, including the bacterium's intracellular and plasma membrane targets. They can also be effective against bacteria that are resistant to antibiotics.[92,93] Furthermore, AMPs also exhibit anticancer activity, but their current clinical application is mainly for the treatment of pathogenic bacteria, wound healing, and inflammation.[94]

Sources of AMPs

One of the most important AMPs is Nisin, which is produced by the bacterium *Lactococcus lactis.*[95] Because of its antibacterial properties, nisin is currently used as a food preservatives.[96] Copsin, an AMP originating from *Coprinopsis cinerea*, has antibacterial activity against a variety of Gram-positive bacteria by inhibiting cell wall synthesis, such as *Enterococcus faecalis.*[97] There are multiple families of AMPs that are derived from plants, such as thionins, defensins, and cyclotides. These AMPs protect the plant from the different pathogenic microorganisms.[98] Plant seeds, stems, roots, and leaves are abundant sources of thionins, which exhibit antibacterial properties against both Gram-positive and Gram-negative bacteria.[99,100] Another family of AMPs known as cathelicidins have different peptide lengths, amino acid sequences, and protein structures in addition to the highly conserved cathelin domain.[101] They are processed and released by leukocyte activation from neutrophils and macrophage secretory granules where they are stored in a nonfunctional state.[102] Fish is the source of the cathelicidins (codCath1 and CATHBRALE), which have antibacterial properties against a variety of Gram-positive and Gram-negative bacteria.[103] Cathelicidin-related peptides (crotalicidin) have been found in the South American rattlesnake. These peptides have the ability to eliminate 90% of *P. aeruginosa* and *E. coli* cells in 5-30 minutes and 90-120 minutes, respectively.[104]

Classification of AMPs

AMPs are classified into 4 classes based on (a) source, (b) activity, (c) structural characteristics, and (d) amino acid-rich species.[90]

a) Based on source

Antimicrobial Peptide Database3 (APD3) classifies AMPs according to their origins into four categories: microbes, insects, amphibians and mammals.[90] Defensins and cathelicidins are the two main groups of AMPs found in mammals. These are found in humans, sheep, cattle etc.[105] Human host defense peptides (HDPs) are the peptides produced in humans that protect them from microbial infection. Amphibian peptides protect amphibians from pathogens. Amphibian AMPs mostly originate from frogs, with magainin being the most well-known.[106] The most well-known AMP from insect is cecropin, which is produced by drosophila, bees, and guppy silkworms. It has anti-cancer and anti-inflammatory activity.[107] Nisin and gramicidin

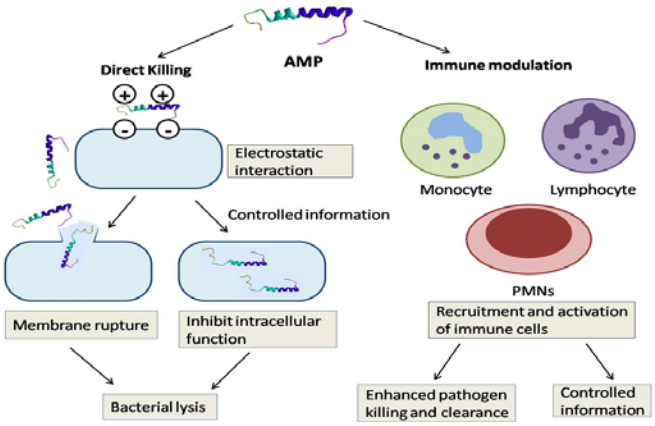

Figure 4. Mechanism of action of AMPs.

are the example of most important microorganism-derived AMPs derived from different bacteria, fungi like *L. lactis*, and *Bacillus subtilis*.[108]

b) Based on activity

The eighteen groups that comprise the action of AMPs include antiviral, antifungal, anti-human immunodeficiency virus (HIV), antibacterial, antiparasitic, and anti-tumor peptides.[109] When applied to harmful fungus like Aspergillus and *Candida albicans*, antifungal peptides have outstanding antifungal properties. *A. flavus* produces aflatoxin, a carcinogen. For instance, *A. flavus* MD3 growth can be inhibited by an antifungal peptide of the sequence FPSHTGMSVPPP.[110] Antiviral peptides have potent antiviral activity against viruses. The most important examples of this type of peptide are defensins, LL-37, and maximin3.[111,112] Numerous peptides with antiparasitic properties, such as temporins-SHd and cathelicidin, exhibit strong inhibitory effects on parasites.[113] Puroindoline A and indolicidin are examples of anticancer peptides that can combat cancer cells.[114]

c) Amino acid-rich species

As a non-polar amino acid, proline acts somewhat differently from other amino acids. Rather than destroying the bacterium by rupturing the membrane, proline enters the bacterial cytoplasm through the inner membrane transporter sbmA and results in cell death.[115] The histidine-rich AMP HV2 ruptures cell membranes and kill the bacterial cells.[116] Tryptophan and arginine rich AMPs disrupt bacterial membranes, destabilizing them and causing cell death.[117]

d) Structural characteristics

Based on their structure, AMPs are classified into four groups: (i) β-sheet and α-helical peptides, (ii) linear extension structure, (iii) β-helix and β-sheet peptides, and (iv) linear α-helical peptides.[118]

Table 3. List of currently used antibiotics against gram-positive AMR bacteria.

Compound Names	Sources	Microorganisms	Mechanism of action	Clinical Status	Ref
Nisin A	*Lactococcus lactis*	*S. aureus, S. pneumoniae, Enterococci* & *C. difficile*	It kills bacteria by forming pores in the cytoplasmic membrane disrupting and peptide-glycan synthesis	Shows resistance, especially in Gram-positive bacteria	121
Gramicidin S	*Bacillus brevis*	*S. aureus &E. coli*	It kills bacteria by forming channels in the cell membrane	Till now it has not shown sign of resistance to any bacteria	122,123
Polymyxin B	*Paenibacillus polymyxa*	*K. pneumonia & A. baumannii*	It causes cell disruption and leakage of cellular content, ultimately cell death	Some Gram-negative bacteria show resistance	124
Daptomycin	*Streptomyces roseosporus*	MRSA & VRE	It causes disruption of bacterial cell membrane	Show resistance, especially in Gram-positive bacteria	125
Teixobactin	*Eleftheria terrae*	MRSA, VISA, *S. pneumoniae, C. difficile & Bacillus anthracis*	Inhibit bacterial cell wall synthesis	Till now there is no resistance has reported	126
Melittin	*Apis mellifera* venom	MRSA, *A. baumannii*, & KPC-producing *K. pneumoniae*	It kills bacteria by disrupting bacterial cell though pore formation	It shows resistance through various mechanism	127
Magainin 2	Skin of African clawed frog, *Xenopus laevis*	*A. baumannii* & *P. aeruginosa*	Kill bacteria by disrupting bacterial cell membrane	Show resistance through various mechanism	128
Cathelicidin (LL-37)	Found in neutrophils	*S. aureus, E. coli, H. pylori, K. pneumoniae, P. aeruginosa*	Kill bacteria by disrupting the bacterial cell membrane	Show resistance in both Gram-positive and Gram-negative bacteria	129
Buforin	Asian toad *Bufo gargarizans*	*E. coli*	Kill bacteria by disrupting the bacterial cell membrane	Show resistance to many bacteria	130
β-defensin 2	Produced by various epithelial cells	*E. coli*& *Salmonella*	Kill bacteria by disrupting the bacterial cell membrane and interfering with their metabolism	Show resistance by producing some enzyme or biofilm	131
lactoferricin B	Derived from milk protein lactoferrin	*E. coli, K. pneumoniae* & *S. aureus*	Disrupt bacterial cell membrane and causes cytoplasmic leakage	Resistance occurs due to the production of proteases	132
Friulimicin B	*Actinoplanes friuliensis*	MRSA	Inhibit bacterial cell wall synthesis	Bacteria such as *S. aureus, S. pneumoniae*	133
Cecropin A	*Hyalophora cecropia*	*S. aureus*, & MRSA	Kills bacteria by forming pores in the membrane	Show resistance by various bacteria	134

Mechanism of action of AMPs

AMPs have different mechanisms of action, depending on their charge, hydrophobicity, and target (Table 3). Some common mechanisms are plasma membrane disruption, where the AMPs can interact with the negatively charged particles of the cell membrane such as lipopolysaccharides, and phospholipids (Figure 4). It causes the formation of pores, channels, or micelles which results in the leakage of cytoplasmic components or influx of external compounds. Cecropins and defensins are examples of AMPs that act by this mechanism.[91] The intracellular antimicrobial mechanism is the other mechanism of action of AMPs. AMPs can translocate across the cell membrane and can interfere with various processes such as DNA, RNA, and protein synthesis. This can cause inhibition of microbial growth or cell apoptosis. Buforin II and histatins are examples of AMPs that act by this mechanism.[119] One of the most important mechanisms of AMPs is immune modulation, where AMPs can modulate the host immune response by affecting the cytokine production and signaling of monocytes, lymphocytes, and polymorphonuclear leukocytes (PMNs). These cells are important for initiating immune responses. AMPs can either enhance or suppress the cytokine secretion of the cells, depending upon the type and concentration of the peptide, the type, and states of the cells, and the presence of other stimuli.[120]

Advantages and limitations of AMP therapy

The main properties that make AMP a promising alternative to antibiotics include: (i) broad spectrum activity, (ii) rapid and potent antibacterial activity, (iii) low level of resistance, and (iv) vast variety of AMP in terms of structure and functionalities, which represents tremendous potential. However, AMPs also face some limitations. The first one is the low bioavailability; AMPs are often degraded by the proteases or blood plasma reducing their activity. They also have low oral absorption and tissue penetration and require high and frequent doses.[91] The second one is high toxicity; AMPs can damage the host cell or tissue by interacting with the cell membrane or intracellular components and causing hemolysis and inflammation. Another limitation is its low specificity; AMPs can bind to both pathogenic and beneficial microbes and disrupt their function and balance. AMPs are expensive to produce by both the chemical and recombinant methods because of their complex structure. It also requires extensive optimization and screening to increase safety, stability, and potency.[135] One of the most important challenges related to AMPs is their purification process. AMPs are produced by a wide range of organisms, which are present in different body parts and secretions. Because of the variety of sources, standardization of the purification process is challenging.[136,137] Changes in temperature and pH during the purification process can have an impact on the structure and function of AMPs. Since the yield of AMPs from natural sources might be low, effective extraction and purification techniques must be developed to get a significant amount.[138] These limitations cause serious problems for developing AMPs as effective and safe antimicrobial agents. However, advances in synthetic chemistry, computer-aided drug design, and drug-delivery systems have provided new strategies to overcome these limitations.[139]

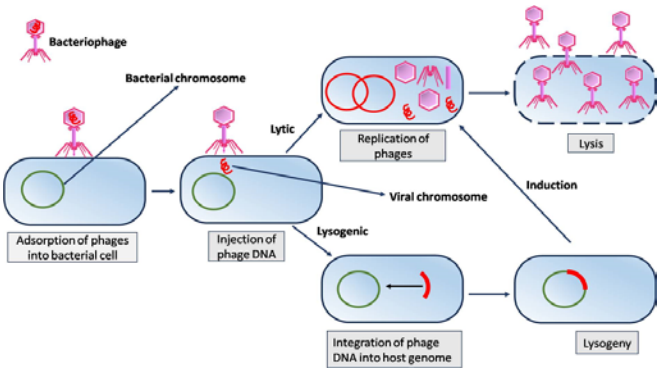

Figure 5. Mechanism of action bacteriophages.

Bacteriophages in the treatment of antibiotic resistance

Felix d'Herelle, first time described bacteriophages. He was a French-Canadian microbiologist who worked at the Pasteur Institute in Paris. He observed that when some mysterious agents infect the culture, it became clear and he named these agents bacteriophages, meaning "bacteria-eater". He published his findings in the journal 'Comptes Rendus - Académie des sciences' in 1917. However, some other sources suggest that Frederick W. Twort, a British bacteriologist had observed the bacteriophage phenomenon before d'Herelle. He observed that some Staphylococcus became transparent when infected with a filtrate from another bacterial culture. He published his observation in The Lancet journal in 1915 but did not name or characterize the agent responsible for it. That's why Felix d'Herelle is considered the first to describe bacteriophages.[140] We now live at a time when the World Health Organization has identified antibiotic resistance as the greatest threat to food security, development, and global health.[141] It is incredibly expensive and takes a long time to create new antibiotics and new classes of drug that function entirely distinct from those that are already on the market.[142] So, phages can be considered as the best alternative for antibiotic resistance. Bacteriophages are viruses that are most prevalent biological species on Earth can infect or kill bacteria. Bacteriophages cannot reproduce themselves, so they require a bacterial host for reproduction. Like most viruses, bacteriophages attack specific bacterial hosts.[143] Bacteriophages may be found in the environment, soil, plants, animals, and even the seas. They can even be found deep beneath the earth's crust. For example, 1 milliliter of ocean water contains ~10^7 phages and approximately ~10^{31} phages are present in the environment.[144] Only 93 bacteriophages with genomes greater than 200 kbp have been identified in the last 100 years since phages were discovered, out of all known bacteriophages. The majority of phages have genomes less than 200 kbp.[145] Phage genomes greater than 200 kbp are referred to as "jumbo phages". Most of the bacteriophage range in size from 24-200 nm in length. An example of one of the largest phages is T4, the size of approximately 200 nm in length and 80-100 nm wide.[146] According to the International Committee on Taxonomy of Viruses (ICTV), bacteriophages are classified based on the

genetic material and virion morphology. More than 95% of the known phages come under the order *Caudovirales*, which contain double-stranded DNA. Based on tail morphology, the order *Caudovirales* is again divided into three families: *Podoviridae* (having a short noncontractile tail), *Shipoviridae* (having a long noncontractile tail), *Myoviridae* (having a long contractile tail).[147] ds-DNA-tailed bacteriophages are again classified into two different categories: lytic and temperate phages. Some bacteriophages do not come under the order *Caudovirales* because of their different morphologies, genomes, and lifestyles. They can be classified based on their nucleic acid type, presence, or absence of envelop capsid symmetry, and host range. Examples of some non-*Caudovirales* phages are the small ssRNA genomes of leviviruses,[148] non-tailed dsDNA autolykiviruses,[149] inoviridae, cystoviridae,[150] tectiviridae, and plasmaviridae.[151]

Mechanism of action

Lytic phages are bacteriophages that infect their bacterial host, they take control of the bacterial machinery and make copies of themselves. As a result, the bacterial cells break, and more new bacteriophages are released. The growth of temperate phages is similar to that of lytic phages. In this phage, there is an alternative outcome: it can act either calmly by forming lysogeny which is the integration of phage genetic material into the bacterial genome, or the formation of circular replication in the bacterial cytoplasm, without causing any harm or it can switch to an aggressive mode causing bacterium to burst.[143] Lytic bacteriophages, such as T4 and MS2 are mainly used in phage therapy because of their ability to invade and kill bacteria.[152] There are 6 steps involved in the lytic phage: attachment, penetration, transcription, mutation, biosynthesis, and lysis.[153] Some bacteriophages such as M13 show a chronic cycle where the phage continuously releases newly formed virions without cell lysis. However, this process affects the growth rate of host cells (Figure 5).[154]

Phage therapy

The use of bacteriophages in the treatment of bacterial infections, when the bacteria become resistant to the currently available drugs is known as phage therapy. When treating bacterial infections, it shows great promise as a substitute for antibiotics. Other than antibiotic resistance, one of the main problems of antibiotics is that they kill bacteria that are beneficial to humans along with the pathogenic bacteria. But bacteriophages are highly specific and target types of bacteria and kill selectively the harmful ones while leaving the beneficial ones unharmed.[155] According to a report published by the 'UC San Diego School of Medicine, the first therapeutic use of phages was evidenced in 1919, when a 12-year-old child suffering from acute dysentery was given a phage cocktail by Felix d'Herelle and a few hospital interns. Within a few days, the youngster recovered completely from a single dose. However, d'Herelle did not publish his findings until 1931[156] The clinical use of phages for the treatment of a wide range of diseases started in the early 1920s.[157] The discovery of the first antibiotic, penicillin gave an alternative to phage therapy, and it faded out. Over the past few decades, phage therapy has gained popularity because of the growing threat of AMR.[158]However, phage therapy has been used for many years in several countries including Poland and Georgia and has gained popularity across other parts of the world.[159] According to a report published in Clinical Infectious Diseases on 20 patients with Mycobacterium infection, 11 out of 20 showed clinical improvement, when treated with phage therapy and 6 out of 20 patients showed microbiological improvement while treated with phage therapy.[160] Another study showed that a 15-year-old girl with cystic fibrosis had undergone a double lung transplant but developed a severe infection and was resistant to all available antibiotics. However, six weeks of phage therapy showed significant improvement in clinical condition. This study includes isolation and testing of 15 phages that can kill bacterial strains that infected the girl.[161]

Characteristics and immune response of therapeutic phages

While selecting a phage for therapeutic use, there are several factors to be considered. Some of these are: first, host specificity; therapeutic phages must be highly specific, it should only kill pathogenic bacteria without harming beneficial ones. Second, the bacteriophage should be of broad spectrum, and capable of eliminating a variety of bacteria within the same species or genus. Third, the phages should be able to rapidly lysis the bacterial cell and release more new phages that cause infection of the bacterial cell. Fourth, therapeutic phages should be able to maintain their activity in different environmental conditions, such as pH, temperature, and pressure. Fifth, sometimes the use of antibiotics causes adverse effects, but the phages should be able to avoid or minimize the adverse effects such as toxicity, autoimmunity, inflammation, and allergic reactions. However, it should be noted that phages may act differently in vitro and in the patient. In vivo, bacteria may form biofilms, which causes poor penetration of phages into the bacteria or is not able to kill the bacteria efficiently.[143,162,163] When used topically, immune responses to phages are not a concerning problem. However, there is a possibility of an immunological reaction when it is administered

Table 4. Name of different bacteriophages under clinical trial with their targeted bacteria.

Bacteriophages	Targeted bacteria	Phases of clinical trial	Ref.
AB-SA01	*S. aureus*	Phase I/II	165
AB-PA01	*P. aeruginosa*	Phase I/II	166
PYO and Intesti	*P. aeruginosa* and *E. coli*	Phase II/III	167
Eliava-1 and Eliava-2	*E. coli* and *Salmonella enterica*	Phase III	168
AP-MP02-1 and AP-MP02-2	*Mycobacterium abscessus*	Phase I/II	169
AB-KP01	*K. pneumoniae*	Phase I/II	170
AB-EC01	*E. coli*	Phase I/II	170
AB-PA02	*P. aeruginosa*	Phase I/II	170
Phagoburn phage cocktail	*P. aeruginosa* and *E. coli*	Phase I/II	170
AP-PA01	*P. aeruginosa*	Phase I/II	171

in other ways, particularly intravenously, which might impact phage activity. As evidenced by the management of a young cystic fibrosis child receiving a bilateral lung transplant, the immune response may be neutralized in immunosuppressed individuals, such as organ transplant recipients.[164]

Bacteriophages under clinical trials

In 2019, intravenously administered phage therapy got approval from the USFDA for the first clinical trial. The trial was conducted by researchers at the University of California, San Diego School of Medicine in collaboration with the AmpliPhi Biosciences Corporation. In this trial, they used AB-SA01, a cocktail of three natural lytic bacteriophages that act against *S. aureus*.[165] Currently, there are various bacteriophages that are under clinical trial (Table 4).

Phage resistance

Phage resistance is the most crucial phenomenon that can affect the outcome and success of phage therapy. Phage therapy has various advantages over conventional antibiotic therapy such as specificity, self-improving and self-replication. However, phages also face some challenges such as phage resistance. There are 4 main types of mechanisms through which bacteria resist phage therapy.[172]

a) Restriction-modification (RM) system

This is the mechanism by which bacteria can resist or evade the infection caused by phages. RM system comprises two types of enzymes, i.e., restriction enzymes (REs) and modification enzymes (MEs).[173] There are four main types of RM systems, type I, II, III, and type IV. All these have different structures and functions. Type II RM system is the most studied and simple.

b) CRISPR-Cas system

CRISPR-Cas system is a bacterial immune system that recognizes and destroys foreign DNA molecules. Due to this reason, the CRISPR-Cas system acts as a source of phage resistance. As bacteria acquire new sequences from the phages and use the CRISPR-Cas system to cleave these sequences. This process is called CRISPR adaptation or spacer acquisition, and it is one of the most important bacterial immune systems against phages.[174]

c) Abortive infection system (Abis)

Abis is a phage resistance mechanism that kills the infected bacteria so that it cannot produce new phages. Abis is also known as programmed cell death or bacterial apoptosis. Examples of some Abis found in bacteria are AbiA, AbiE, AbiF, and AbiG.[175,176]

d) Superinfection exclusion

In this mechanism, the bacteria block the entry of the second phage after the first one. This prevents multiple infections and reduces the chances of further exchange of genetic material and recombination.[172,177]

Advantages and limitations of phage therapy

Advantages

The advantages of phage therapy over conventional antibiotic therapy are as follows: (i) it does not interfere with the normal microbial flora of the human body, (ii) it is also effective against phase-resistance bacterial mutants because phage mutation is significantly higher than the bacteria, and (iii) side-effects are very rare.[178]

Limitations

Firstly, phage therapy is not well-regulated, mainly in the West. This makes it difficult to gain approval from the regulatory bodies and is widely accepted by the medical communities.[157] The classification of phages as antibiotics in legal texts affects how they are produced and how proof of efficiency is provided in randomized controlled trials.[179] A major obstacle in the UK for phage therapy is that phages should be manufactured according to GMP standards.[180] Phage therapy phase challenges in clinical trials due to its unique nature, and getting regulatory clearance may be difficult and time-consuming.[181] Secondly, phage therapy is technically challenging to prepare and administer. Phages are highly specific to their bacterial targets and require testing and careful selection for each infection. Also, phages should be purified, stored, and delivered in the right ways to avoid degradation, contamination, and immune reactions.[182] The third reason is that phage therapy is not well understood by patients, doctors, and researchers. Executing phage therapy requires a vast knowledge of microbiology, virology, immunology, medicine, genetics, etc. which is quite tough. The fourth reason is that phage therapy is not well-funded or supported by the government, institutions, or industries. There is a lack of investment in phage research & development as compared to antibiotics and there is also a lack of collaboration among phage experts around the world.[183] However, there are still some concerns such as the release of large amounts of bacterial endotoxin due to rapid cell lysis, lack of pharmacokinetic data, neutralization of host phage therapy by the host immune system, conversion of lytic phages to the lysogenic phages leads to the bacterial immunity to attack by the corresponding lytic phages and may also change the virulence of the bacteria.[184]

CONCLUSION

Finding the best treatment options to combat bacterial resistance is a very difficult task. Precision medicine offers a promising approach for combating AMR by leveraging the targeted and personalized nature of bacteriophages and AMPs for more effective and tailored treatment strategies. AMPs have broad-spectrum antimicrobial activity with high specificity, and low toxicity and can act on multiple targets. Additionally, they can modulate the body's immune system and promote its defense mechanisms. However, the production and purification of AMPs pose significant challenges. In contrast, bacteriophages are highly specific as they only infect and harm specific pathogenic bacteria. This makes them flexible options that can be adapted to evolving bacterial strains. However, their high specificity is also a disadvantage, as they can only attack one bacterium at a time. The regulatory challenges associated with phage therapy, as well as the choice between bacteriophages and antibiotics, depend on the type and nature of the infection. The current clinical status of phage therapy has shown promising results, but not still widely approved or accepted by the regulatory authorities. The future of phage therapy requires rigorous and extensive research to establish its safety and efficacy. Phage therapy has the potential

to be a viable alternative to antibiotics but requires more clinical data to support it. Future studies should focus on transforming these antimicrobial alternatives into practical clinical substitutes for antibiotics and demonstrating their expected efficacy, safety, and affordability.

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REFERENCES AND NOTES

1. N. Pariente, on behalf of the PLOS Biology Staff Editors. The antimicrobial resistance crisis needs action now. *PLoS Biol.* **2022**, 20 (11), e3001918.
2. N. Sabtu, D.A. Enoch, N.M. Brown. Antibiotic resistance: what, why, where, when and how? *Br. Med. Bull.* **2015**, 116 (1), 105–113.
3. World Health Organization (WHO). Call for urgent agreement on international deal to prepare for and prevent future pandemics, **2024**. Available from: https://www.who.int/news/item/20-03-2024-call-for-urgent-agreement-on-international-deal-to-prepare-for-and-prevent-future-pandemics [Last accessed on Mar 28, 2024].
4. Institute for Health Metrics and Evaluation (IHME). Antimicrobial resistance (AMR), **2019**. Available from: https://www.healthdata.org/research-analysis/health-risks-issues/antimicrobial-resistance-amr [Last accessed on Mar 28, 2024].
5. R. Rosini, S. Nicchi, M. Pizza, R. Rappuoli. Vaccines against antimicrobial resistance. *Front. Immunol.* **2020**, 11, 1048.
6. Our World in Data. Causes of Death, **2018**. Available from: https://ourworldindata.org/causes-of-death [Last accessed on Mar 28, 2024].
7. Institute for Health Metrics and Evaluation (IHME). GBD Results, **2019**. Available from: https://vizhub.healthdata.org/gbd-results/ [Last accessed on Mar 28, 2024].
8. A. Sharma, A. Singh, M.A. Dar et.al. Menace of antimicrobial resistance in LMICs: Current surveillance practices and control measures to tackle hostility. *J. Infect. Public Health* **2022**, 15 (2), 172–181.
9. B. Aslam, M. Khurshid, M.I. Arshad et.al. Antibiotic Resistance: One Health One World Outlook. *Front. Cell Infect. Microbiol.* **2021**, 11, 771510.
10. World Health Organization (WHO). WHO publishes list of bacteria for which new antibiotics are urgently needed, **2017**. Available from: https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed [Last accessed on Mar 28, 2024].
11. H.K. Sharma, P. Gupta, D. Nagpal, M. Mukherjee, V. S. Parmar, V. Lather. Virtual screening and antimicrobial evaluation for identification of natural compounds as the prospective inhibitors of antibacterial drug resistance targets in Staphylococcus aureus. *Fitoterapia* **2023**, 168, 105554.
12. D. Sengupta, A. Raghunathan. Rise of the Superbugs: What We Need to Know: Overview of Antimicrobial Resistance. *Resonance* **2021**, 26 (9), 1251–1266.
13. N.A. Church, J.L. McKillip. Antibiotic resistance crisis: challenges and imperatives. *Biologia (Bratisl)* **2021**, 76 (5), 1535–1550.
14. Britannica. Penicillin, **1998**. Available from: https://www.britannica.com/science/penicillin [Last accessed on Mar 28, 2024].
15. A Brief History of Antimicrobial Resistance: How a Major Medical Miracle turned into the Biggest Public Health Threat of our Time, **2022**. Available from: https://www.researchgate.net/publication/363671979_A_Brief_History_of_Antimicrobial_Resistance_How_a_Major_Medical_Miracle_turned_into_the_Biggest_Public_Health_Threat_of_our_Time [Last accessed on Mar 28, 2024].
16. D. Stekel. First report of antimicrobial resistance pre-dates penicillin. *Nature* **2018**, 562 (7726), 192.
17. K. Iskandar, J. Murugaiyan, D.H. Halat et.al. Antibiotic discovery and resistance: the chase and the race. *Antibiotics (Basel)* **2022**, 11 (2), 182.
18. M.K. Byrne, S. Miellet, A. McGlinn, J. Fish, S. meedya, N. Reynolds, A. M. van Oijen. The drivers of antibiotic use and misuse: the development and investigation of a theory driven community measure. *BMC Public Health* **2019**, 19 (1), 1425.
19. C.J. Murray, K.S. Ikuta, F. Sharara. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* **2022**, 399 (10325), 629–655.
20. Q. Chen, D. Li, C. Beiersmann, F. Neuhann, B. Moazen, G. Lu, O. Muller. Risk factors for antibiotic resistance development in healthcare settings in China: a systematic review. *Epidemiol. Infect.* **2021**, 149, e141.
21. K.C. Sahoo, A.J. Tamhankar, E. Johansson, C.S. Lundborg. Antibiotic use, resistance development and environmental factors: a qualitative study among healthcare professionals in Orissa, India. *BMC Public Health* **2010**, 10, 629.
22. T. Khare, U. Anand, A. Dey, Y. G. Assaraf, Z. Chen, Z. Liu, V. Kumar. Exploring phytochemicals for combating antibiotic resistance in microbial pathogens. *Front. Pharmacol.* **2021**, 12, 720726.
23. S. Mak, Y. Xu, J.R. Nodwell. The expression of antibiotic resistance genes in antibiotic-producing bacteria. *Mol. Microbiol.* **2014**, 93 (3), 391–402.
24. Microbial Facts. 10 mechanisms of antibiotic resistance in Bacteria, **2018**. Available from: https://www.microbialfacts.com/mechanisms-of-antibiotic-resistance/ [Last accessed on Mar 28, 2024].
25. D.G.J. Larsson, C.F. Flach. Antibiotic resistance in the environment. *Nat. Rev. Microbiol.* **2022**, 20, 257–269.
26. W. Arber. Genetic variation: molecular mechanisms and impact on microbial evolution. *FEMS Microbiol. Rev.* **2000**, 24 (1), 1–7.
27. T. Oz, A. Guvenek, S. Yildiz, E. Karaboga, Y.T. Tamer, N. Mumcuyan, V.B. Ozan, G.H. Sentruk, M. Cokol, P. Yeh, E. Toprak. Strength of selection pressure is an important parameter contributing to the complexity of antibiotic resistance evolution. *Mol. Biol. Evol.* **2014**, 31 (9), 2387–2401.
28. W. Xiong, Y. Sun, X. Ding, M. Wang, Z. Zeng. Selective pressure of antibiotics on ARGs and bacterial communities in manure-polluted freshwater-sediment microcosms. *Front. Microbiol.* **2015**, 6 (MAR), 129617.
29. C. Rancurel, L. Legrand, E.G.J. Danchin. Alienness: Rapid Detection of Candidate Horizontal Gene Transfers across the Tree of Life. *Genes* **2017**, 8 (10), 248.
30. E.P.C. Rocha, D. Bikard. Microbial defenses against mobile genetic elements and viruses: Who defends whom from what? *PLoS Biol.* **2022**, 20 (1), e3001514.
31. S. Khedkar, G. Smyshlyaev, I. Letunic, O. M. Maistrenko, L. P. Coelho, A. Orakov, S. K. Forslund, F. Hildebrand, M. Luetge, T. S. B. Schmidt, O. Barabas, P. Bork. Landscape of mobile genetic elements and their antibiotic resistance cargo in prokaryotic genomes. *Nucleic Acids Res.* **2022**, 50 (6), 3155–3168.
32. M. Emamalipour, K. Seidi, S. Vahed, A. Esfahlan, M. Jaymad, H. Majdi, Z. Amoozgar, L. Chitkushev, T. Javaheri, R. Jahanban-Esfahlan, P. Zare. Horizontal gene transfer: from evolutionary flexibility to disease progression. *Front. Cell Dev. Biol.* **2020**, 8, 507646.
33. LibreTexts Biology. 20.3B: Horizontal Gene Transfer, **2023**. Available from: https://bio.libretexts.org/Bookshelves/Introductory_and_General_Biology/Book%3A_General_Biology_%28Boundless%29/20%3A_Phylogenies_and_the_History_of_Life/20.03%3A_Perspectives_on_the_Phylogenetic_Tree/20.3B%3A_Horizontal_Gene_Transfer [Last accessed on Sep 14, 2023].
34. Britannica. Transduction, **1998**. Available from: https://www.britannica.com/science/transduction-microbiology [Last accessed on Sep 14, 2023].
35. M. Llosa, F.X. Gomis-Rüth, M. Coll, F. De la Cruz. Bacterial conjugation: a two-step mechanism for DNA transport. *Mol. Microbiol.* **2002**, 45 (1), 1–8.
36. S.H. Kumar, M. Varela. Molecular mechanisms of bacterial resistance to antimicrobial agents. **2013**.
37. M. Mora-Ochomogo, C.T. Lohans. β-Lactam antibiotic targets and resistance mechanisms: from covalent inhibitors to substrates. *RSC Med. Chem.* **2021**, 12 (10), 1623–1639.
38. Microbe Online. ESBL and Classification of β-lactamases, **2023**. Available from: https://microbeonline.com/betalactamase-classification/#google_vignette [Last accessed on Sep 10, 2023].
39. S.M. Khalifa, A.M. Abd El-Aziz, R. Hassan, E.S. Abdelmegeed. β-lactam resistance associated with β-lactamase production and porin alteration in clinical isolates of E. coli and K. pneumoniae. *PLoS One* **2021**, 16 (5), e0251594.
40. E. Peterson, P. Kaur. Antibiotic resistance mechanisms in bacteria: Relationships between resistance determinants of antibiotic producers, environmental bacteria, and clinical pathogens. *Front. Microbiol.* **2018**, 9, 426686.
41. G. Gosset. Improvement of Escherichia coli production strains by modification of the phosphoenolpyruvate: sugar phosphotransferase system. *Microb. Cell. Fact.* **2005**, 4 (1), 1–11.
42. J.X. Zhong, H. R. Zheng, Y.Y. Wang, L.L. Bai, X.L. Du, Y. Wu, J.X. Lu. Molecular characteristics and phylogenetic analysis of Clostridium perfringens from different regions in China, from 2013 to 2021. *Front. Microbiol.* **2023**, 14:1195083.

43. R. Leclercq. Mechanisms of resistance to macrolides and lincosamides: Nature of the resistance elements and their clinical implications. *Clin. Infect. Dis.* **2002**, 34 (4), 482–492.
44. E.A. Campbell, N. Korzheva, A. Mustaev, K. Murakami, S. Nair, A. Goldfarb, S. A. Darst. Structural mechanism for rifampicin inhibition of bacterial rna polymerase. *Cell*. **2001**, 104 (6), 901–912.
45. H.G. Floss, T.W. Yu. Rifamycin-mode of action, resistance, and biosynthesis. *Chem. Rev.* **2005**, 105 (2), 621–632.
46. N. Mapara, M. Sharma, V. Shriram, R. Bhardwaj, K.C. Mohite, V. Kumar. Antimicrobial potentials of Helicteresisora silver nanoparticles against extensively drug-resistant (XDR) clinical isolates of Pseudomonas aeruginosa. *Appl. Microbiol. Biotechnol.* **2015**, 99 (24), 10655–10667.
47. H. Qiu, Z. Si, Y. Luo, P. Feng, X. Wu, W. Hou, Y. Zhu, M.B. Chan-Park, L. Xu, D. Huang. The Mechanisms and the Applications of Antibacterial Polymers in Surface Modification on Medical Devices. *Front. Bioeng. Biotechnol*. **2020**, 8: 571162.
48. Microbe Online. Mechanisms of Action of Antibiotics: An Overview, **2022**. Available from: https://microbeonline.com/mechanisms-of-action-of-antibiotics-an-overview/ [Last accessed on Sep 10, 2023].
49. T.J. Foster. Antibiotic resistance in Staphylococcus aureus. Current status and future prospects. FEMS Microbiol Rev 2017, 41 (3), 430–449.
50. M.O. Ahmed, K.E. Baptiste. Vancomycin-Resistant Enterococci: A review of antimicrobial resistance mechanisms and perspectives of human and animal health. *Microb. Drug Resist.* **2018**, 24 (5), 590–606.
51. A. Bartsch, C.M. Ives, C. Kattner, F. Pein, M. Diehn, M. Tanabe, A. Munk, U. Zachariae, C. Steinem, S. Llabres. An antibiotic-resistance conferring mutation in a neisserial porin: Structure, ion flux, and ampicillin binding. *Biochim. Biophys. Acta- Biomembr*. **2021,** 1863 (6), 183601.
52. U. Choi, C.R. Lee. Distinct Roles of Outer Membrane Porins in Antibiotic Resistance and Membrane Integrity in Escherichia coli. *Front. Microbiol.* **2019**, 10: 458574.
53. L. McMurry, R.E. Petrucci, S.B. Levy. Active efflux of tetracycline encoded by four genetically different tetracycline resistance determinants in Escherichia coli. *Proc. Natl. Acad. Sci. USA* **1980**, 77 (7), 3974–3977.
54. M. Alcalde-Rico, S. Hernando-Amado, P. Blanco, J.L. Martinez. Multidrug efflux pumps at the crossroad between antibiotic resistance and bacterial virulence. *Front. Microbiol.* **2016**, 7: 1483.
55. J.M. Munita, C.A. Arias. Mechanisms of antibiotic resistance. *Microbiol. Spectr*. **2016**, 4 (2).
56. S. Chetri. The culmination of multidrug-resistant efflux pumps vs. meager antibiotic arsenal era: Urgent need for an improved new generation of EPIs. *Front. Microbiol.* **2023**, 14, 1149418.
57. D. Du, X. Wang-Kan, A. Neuberger, H.W. van Veen, K.M. Pos, L.J.V. Piddock, B.F. Luisi. Multidrug efflux pumps: structure, function and regulation. *Nat. Rev. Microbiol*. **2018**, 16 (9), 523–539.
58. T. Rana, K. pathania, U. Farooq. A review on efflux pump inhibitors of medically important bacteria from plant sources. *Int. J. Pharm. Sci. Rev. Res.* **2014**, 26(2), 101–111.
59. M.C. Roberts. Update on acquired tetracycline resistance genes. *FEMS Microbiol. Lett.* **2005**, 245 (2), 195–203.
60. K. Poole. Efflux-mediated antimicrobial resistance. *J. Antimicrob. Chemother*. **2005**, 56 (1), 20–51.
61. F. Iannelli, F. Santoro, M. Santagati, J.D. Docquier, E. Lazzeri, G. Pastore, M. Cassone, M. R. Oggioni, G. M. Rossolini, S. Stefani, G. Pozzi. Type M resistance to macrolides is due to a two-gene efflux transport system of the ATP-binding cassette (ABC) superfamily. *Front. Microbiol.* **2018**, 9, 1–9.
62. A. Savoldi, E. Carrara, L.J.V. Piddock, F. Franceschi, S. Ellis, M. Chiamenti, D. Bragantini, E. Righi, E. Tacconelli. The role of combination therapy in the treatment of severe infections caused by carbapenem resistant gram-negatives: a systematic review of clinical studies. *BMC Infect. Dis.* **2021**, 21 (1), 545.
63. P.N.T. Thu, M.N.T. Huong, N.T. Thi, H.N. Thanh, K.P. Minh. Combination antibiotic therapy versus monotherapy in the treatment of acute exacerbations of chronic obstructive pulmonary disease: an open-label randomized trial. *BMC Infect. Dis*. **2021**, 21 (1), 1019.
64. N. Wang, J. Luo, F. Deng, Y. Huang, H. Zhou. Antibiotic combination therapy: a strategy to overcome bacterial resistance to aminoglycoside antibiotics. *Front. Pharmacol.* **2022**, 13, 839808.
65. T. Umemura, H. Kato, M. Hagihara, J. Hirai, Y. Yamagishi, H. Mikamo. Efficacy of combination therapies for the treatment of multi-drug resistant gram-negative bacterial infections based on meta-analyses. *Antibiotics (Basel)*. **2022**, 11 (4), 524.
66. M. Bassetti, M. Peghin, A. Vena, D.R. Giacobbe. Treatment of infections due to MDR gram-negative bacteria. *Front. Med.* **2019**, 6, 452726.
67. B.A. Pontefract, H.T. Ho, A. Crain, M.K. Kharel, S.E. Nybo. Drugs for Gram-Negative Bugs From 2010–2019: A Decade in Review. *Open Forum Infect. Dis*. **2020**, 7 (7), ofaa276.
68. I. Karaiskos, S. Lagou, K. Pontikis, V. Rapti, G. Poulakou. The "Old" and the "New" antibiotics for MDR Gram-negative pathogens: For whom, when, and how. *Front. Public Health.* **2019**, 7, 460782.
69. I. Nicolas, V. Bordeau, A. Bondon, M. Baudy-Floc'h, B. Felden. Novel antibiotics effective against gram-positive and -negative multi-resistant bacteria with limited resistance. *PLoS Biol.* **2019**, 17 (7), e3000337.
70. A. Matlock, J.A. Garcia, K. Moussavi, B. Long, S.Y.T. Liang. Advances in novel antibiotics to treat multidrug-resistant gram-negative bacterial infections. *Intern. Emerg. Med.* **2021**, 16 (8), 2231–2241.
71. S. Groß, F. Panter, D. Pogorevc, C.E. Seyfert, S. Deckarm, C.D. Bader, J. Hermann, R. Muller. Improved broad-spectrum antibiotics against Gram-negative pathogens via darobactin biosynthetic pathway engineering. *Chem. Sci.* **2021**, 12 (35), 11882–11893.
72. Compound Interest. A Brief Overview of Classes of Antibiotics, **2014.** Available from: https://www.compoundchem.com/2014/09/08/antibiotics/ [Last accessed on Oct 2, 2023].
73. F. Menichetti. Current and emerging serious Gram-positive infections. *Clin. Microbiol. Infect.* **2005**, 11 (3), 22–28.
74. D. Koulenti, E. Xu, I. Mok, A. Song, D. Karageorgoloulos, A. Armaganidis, J. Lipman, S. Tsiodras. Novel antibiotics for multidrug-resistant gram-positive microorganisms. *Microorganisms* **2019**, 7(8), 270.
75. A.P. Kulkarni, V.C. Nagvekar, B. Veeraraghavan, A. R. Warrier, D. Ts, J. Ahdal, R. Jain. Current perspectives on treatment of gram-positive infections in India: What is the way forward? *Interdiscip. Perspect. Infect. Dis.* **2019**, 7601847.
76. C. Elias, L. Moja, D. Mertz, M. Loeb, G. forte, N. Magrini. Guideline recommendations and antimicrobial resistance: the need for a change. *BMJ Open* **2017**, 7 (7), e016264.
77. R.R. Watkins. Antibiotic stewardship in the era of precision medicine. *JAC Antimicrob. Resist.* **2022**, 4 (3), dlac066.
78. M. Merker, L. Tueffers, M. Vallier, E.E. Groth, L. Sonnenkalb, D. Unterweger, J. F. Baines, S. Niemann, H. Schulenburg. Evolutionary approaches to combat antibiotic resistance: opportunities and challenges for precision medicine. *Front. Immunol.* **2020**, 11, 1938.
79. N. Naithani, S. Sinha, P. Misra, B. Vasudevan, R. Sahu. Precision medicine: Concept and tools. *Med J Armed Forces India.* **2021**, 77 (3), 249-257.
80. World Health Organization (WHO). GLASS whole-genome sequencing for surveillance of antimicrobial resistance, **2020**. Available from: https://www.who.int/publications/i/item/9789240011007 [Last accessed on Mar 2, 2024].
81. S.P. Djordjevic, V.M. Jarocki, T. Seemann, M.L. Cummins, A.E. Watt, B. Drigo, E.R. Wyrsch, C.J. Reid, E. Donner, B.P. Howden. Genomic surveillance for antimicrobial resistance- A one health perspective. *Nat. Rev. Genet.* **2023**, 25 (2), 142–157.
82. W. Slikker. Biomarkers and their impact on precision medicine. *Exp. Biol. Med.* **2018**, 243 (3), 211.
83. H. Barabadi, E. Mostafavi, M. Saravanan. Pharmaceutical Nanobiotechnology for Targeted Therapy (Nanotechnology in the Life Sciences). Springer Nature, **2022**.
84. C. Delpierre, T. Lefèvre. Precision and personalized medicine: What their current definition says and silences about the model of health they promote. Implication for the development of personalized health. *Front. Sociol*. **2023**, 8, 1112159.
85. M. Prosperi, J.S. Min, J. Bian, F. Modave. Big data hurdles in precision medicine and precision public health. *BMC Med. Inform. Decis. Mak.* **2018**, 18 (1), 1–15.
86. A.A. Seyhan, C. Carini. Are innovation and new technologies in precision medicine paving a new era in patients centric care? *J. Transl. Med.* **2019**, 17 (1), 1–28.
87. C.W. Seymour, H. Gomez, C.C.H. Chang et.al. Precision medicine for all? Challenges and opportunities for a precision medicine approach to critical illness. *Crit. Care* **2017**, 21 (1), 1–11.
88. A. Breckenridge, H.G. Eichler, J.P. Jarow. Precision medicine and the changing role of regulatory agencies. *Nat. Rev. Drug Discov.* **2016**, 15 (12), 805–806.

89. J. Wang, X. Dou, J. Song, Y. Lyu, X. Zhu, L. Xu, W. Li, A. Shan. Antimicrobial peptides: Promising alternatives in the post feeding antibiotic era. *Med. Res. Rev.* **2019**, 39 (3), 831–859.
90. Y. Huan, Q. Kong, H. Mou, H. Yi. Antimicrobial peptides: Classification, design, application and research progress in multiple fields. *Front. Microbiol.* **2020**, 11, 582779.
91. Q.Y. Zhang, Z. B. Yan, Y.M. Meng et.al. Antimicrobial peptides: mechanism of action, activity and clinical potential. *Mil. Med. Res.* **2021,** 8 (1), 1–25.
92. J. Mwangi, X. Hao, R. Lai, Z. Y. Zhang. Antimicrobial peptides: new hope in the war against multidrug resistance. *Zool. Res.* **2019**, 40 (6), 488–505.
93. J. Lei, L. Sun, S. Huang, C. Zhu, P. Li, J. He, V. Mackey, D. H. Coy, Q. He. The antimicrobial peptides and their potential clinical applications. *Am. J. Transl. Res.* **2019**, 11 (7), 3919.
94. F. Costa, C. Teixeira, P. Gomes, M.C.L. Martins. Clinical application of AMPs. *Adv. Exp. Med. Biol.* **2019**, 1117, 281–298.
95. A.T.R. Mattick, A. Hirsch, N.J. Berridge. Further observations on an inhibitory substance (nisin) from lactic streptococci. *The Lancet* **1947**, 250(6462), 5–8.
96. A. Gharsallaoui, N. Oulahal, C. Joly, P. Degraeve. Nisin as a Food Preservative: Part 1: Physicochemical Properties, Antimicrobial Activity, and Main Uses. *Crit. Rev. Food Sci. Nutr.* **2016**, 56(8), 1262–1274.
97. A. Essig, D. Hofmann, D. Münch et.al. Copsin, a novel peptide-based fungal antibiotic interfering with the peptidoglycan synthesis. *J. Bio. Chem.* **2014**, 289 (50), 34953–34964.
98. S. Srivastava, K. Dashora, K. Ameta et.al. Cysteine-rich antimicrobial peptides from plants: The future of antimicrobial therapy. *Phytother. Res.* **2021**, 35 (1), 256–277.
99. J. Li, S. Hu, W. Jian, C. Xie, X. Yang. Plant Antimicrobial Peptides: Structures, Functions, and Applications. *Bot. Stud.* **2021**, 62(1), 5.
100. K. Höng, T. Austerlitz, T. Bohlmann, H. Bohlmann. The thionin family of antimicrobial peptides. *PLoS One* **2021**, 16 (7), e0254549.
101. R. van Harten, E. van Woudenbergh, A. van Dijk, H. Haagsman. Cathelicidins: immunomodulatory antimicrobials. *Vaccines.* **2018**, 6(3), 63.
102. J. Ageitos, A. Sánchez-Pérez, P. Calo-Mata, T.G. Villa. Antimicrobial peptides (AMPs): Ancient compounds that represent novel weapons in the fight against bacteria. *Biochem. Pharmacol.* **2017**, 133, 117–138.
103. C. Chen, A. Wang, F. Zhang et.al. The protective effect of fish-derived cathelicidins on bacterial infections in zebrafish, Danio rerio. *Fish Shellfish Immunol.* **2019**, 92, 519–527.
104. C. Pérez-Peinado, S.A. Dias, M.M. Domingues et.al. Mechanisms of bacterial membrane permeabilization by crotalicidin (Ctn) and its fragment Ctn(15–34), antimicrobial peptides from rattlesnake venom. *J. Bio. Chem.* **2018**, 293 (5), 1536–1549.
105. K.V.R. Reddy, R.D. Yedery, C. Aranha. Antimicrobial peptides: premises and promises. *Int. J. Antimicrob. Agents* **2004**, 24 (6), 536–547.
106. J. Michael Conlon, M. Mechkarska. Host-Defense peptides with therapeutic potential from skin secretions of frogs from the family Pipidae. *Pharmaceuticals (Basel).* **2014**, 7 (1), 58–77.
107. P. Dutta, R.K. Sahu, T. Dey, M.D. Lahkar, P. Manna, J. Kalita. Beneficial role of insect-derived bioactive components against inflammation and its associated complications (colitis and arthritis) and cancer. *Chem. Biol. Interact.* **2019**, 313, 108824.
108. J. Cao, C. De La Fuente-Nunez, R.W. et.al. Yeast-Based Synthetic Biology Platform for Antimicrobial Peptide Production. *ACS Synth. Biol.* **2018**, 7 (3), 896–902.
109. C. Li, C. Zhu, B. Ren et.al. Two optimized antimicrobial peptides with therapeutic potential for clinical antibiotic-resistant Staphylococcus aureus. *Eur. J. Med. Chem.* **2019**, 183.
110. L.N. Shwaiki, E.K. Arendt, K.M. Lynch. Anti-yeast activity and characterisation of synthetic radish peptides Rs-AFP1 and Rs-AFP2 against food spoilage yeast. *Food Control* **2020**, 113, 107178.
111. Y. Jung, B. Kong, S. Moon et.al. Envelope-deforming antiviral peptide derived from influenza virus M2 protein. *Biochem. Biophys. Res. Commun.* **2019**, 517 (3), 507–512.
112. H. Madanchi, M. Shoushtari, H.H. Kashani, S. Sardari. Antimicrobial peptides of the vaginal innate immunity and their role in the fight against sexually transmitted diseases. *New Microbes New Infect.* **2020**, 34, 100627.
113. F. Abbassi, Z. Raja, B. Oury, E. Gazanion, C. Piesse, D. Sereno, P. Nicolas, T. Foulon, A. Ladram. Antibacterial and leishmanicidal activities of temporin-SHd, a 17-residue long membrane-damaging peptide. *Biochimie* **2013**, 95 (2), 388–399.
114. M. Arias, E.F. Haney, A.L. Hilchie et.al. Selective anticancer activity of synthetic peptides derived from the host defence peptide tritrpticin. *Biochim. Biophys. Acta Biomembr.* **2020**, 1862 (8), 183228.
115. M. Mattiuzzo, A. Bandiera, R. Gennaro et.al. Role of the Escherichia coli SbmA in the antimicrobial activity of proline-rich peptides. *Mol. Microbiol.* **2007**, 66 (1), 151–163.
116. N. Dong, C. Wang, T. Zhang, L. Zhang, C. Xue, X. Feng, C. Bi, A. Shan. Bioactivity and Bactericidal Mechanism of Histidine-Rich β-Hairpin Peptide Against Gram-Negative Bacteria. *Int. J. Mol. Sci.* **2019**, 20 (16), 3954.
117. A. Walrant, A. Bauzá, C. Girardet et.al. Ionpair-π interactions favor cell penetration of arginine/tryptophan-rich cell-penetrating peptides. *Biochim. Biophys. Acta Biomembr.* **2020**, 1862 (2), 183098.
118. J. Lei, L.C. Sun, S. Huang et.al. The antimicrobial peptides and their potential clinical applications. *Am. J. Transl. Res.* **2019**, 11 (7), 3919-31.
119. T. Singh, P. Choudhary, S. Singh. Antimicrobial Peptides: Mechanism of Action. *In Insights on Antimicrobial Peptides.* **2022**.
120. D.I. Duarte-Mata, M.C. Salinas-Carmona. Antimicrobial peptides´ immune modulation role in intracellular bacterial infection. *Front. Immunol.* **2023**, 14, 1119574.
121. J.M. Shin, J.W. Gwak, P. Kamarajan, J.C. fenno, A.H. Rickard, Y.L. Kapila. Biomedical applications of nisin. *J. Appl. Microbiol.* **2016**, 120 (6), 1449–1465.
122. A.V. Gurov, K.E. Borovkova, K.L. Kryshen, L.R. Nikiforova, J.V. Salmova. Evaluation of the bactericidal activity of gramicidin S against Streptococcus pneumoniae and Staphylococcus aureus clinical isolates with single and multiple exposure. *Antibiot. Chemother.* **2022**, 67 (7–8), 8–18.
123. J. Swierstra, V. Kapoerchan, A. Knijnenburg, A. van Belkum, M. Overhand. Structure, toxicity and antibiotic activity of gramicidin S and derivatives. *Eur. J. Clin. Microbiol. Infect. Dis.* **2016**, 35 (5), 763.
124. S.N. Avedissian, J. Liu, N.J. Rhodes, A. Lee, G.M. Pais, A.R. Hauser, M.H. Scheetz. A Review of the Clinical Pharmacokinetics of Polymyxin B. *Antibiotics (Basel)* **2019**, 8 (1), 31.
125. K. Cave, I. Gould. Daptomycin. *Comprehensive Pharmacology* **2022**, 7, 106–122.
126. L.J.V. Piddock. Teixobactin, the first of a new class of antibiotics discovered by iChip technology? *J. Antimicrob. Chemother.* **2015**, 70 (10), 2679–2680.
127. P. Askari, M.H. Namaei, K. Ghazvini, M. Hosseini. In vitro and in vivo toxicity and antibacterial efficacy of melittin against clinical extensively drug-resistant bacteria. *BMC Pharmacol. Toxicol.* **2021**, 22 (1), 1–12.
128. M.K. Kim, N. Kang, S.J. Ko et.al. Antibacterial and Antibiofilm Activity and Mode of Action of Magainin 2 against Drug-Resistant Acinetobacter baumannii. *Int. J. Mol. Sci.* **2018**, 19 (10), 3041.
129. H. Memariani, M. Memariani. Antibiofilm properties of cathelicidin LL-37: an in-depth review. *World J. Microbiol. Biotechnol.* **2023**, 39 (4).
130. C.B. Park, H.S. Kim, S.C. Kim. Mechanism of action of the antimicrobial peptide buforin II: buforin II kills microorganisms by penetrating the cell membrane and inhibiting cellular functions. *Biochem. Biophys. Res. Commun.* **1998**, 244 (1), 253–257.
131. E.R. Cobo, K. Chadee. Antimicrobial Human β-Defensins in the Colon and Their Role in Infectious and Non-Infectious Diseases. *Pathogens* **2013**, 2 (1), 177–192.
132. N. Orsi. The antimicrobial activity of lactoferrin: current status and perspectives. *Biometals* **2004**, 17 (3), 189–196.
133. H.B. Koo, J. Seo. Antimicrobial peptides under clinical investigation. *Peptide Science* **2019**, 111 (5), e24122.
134. A. Lauwers, L. Twyffels, R. Soin, C. Wauquier, V. Kruys, C. Gueydan. Post-transcriptional regulation of genes encoding anti-microbial peptides in drosophila. *J. Biol. Chem.* **2009**, 284 (13), 8973–8983.
135. B.H. Gan, J. Gaynord, S.M. Rowe, T. Deingruber, D.R. Spring. The multifaceted nature of antimicrobial peptides: current synthetic chemistry approaches and future directions. *Chem. Soc. Rev.* **2021**, 50 (13), 7820–7880.
136. C.H. Chen, T.K. Lu. Development and Challenges of Antimicrobial Peptides for Therapeutic Applications. *Antibiotics (Basel)* **2020**, 9 (1), 24.
137. S. Suda, D. Field, N. Barron. Antimicrobial peptide production and purification. *Methods Mol. Biol.* **2017**, 1485, 401–410.

138. Y. Zhang, Z. Li, L. Li, B. Rao, L. Ma, Y. Wang. A Method for Rapid Screening, Expression, and Purification of Antimicrobial Peptides. *Microorganisms* **2021**, 9(9), 1858.
139. C. Deshayes, M.N. Arafath, V. Apaire-Marchais, E. Roger. Drug Delivery Systems for the Oral Administration of Antimicrobial Peptides: Promising Tools to Treat Infectious Diseases. *Front. Med. Technol.* **2021**, 3, 778645.
140. W.C. Summers. The Discovery of Bacteriophages and the Historical Context. In: Harper, D., Abedon, S., Burrowes, B., McConville, M. (eds) Bacteriophages. Springer, Cham. *Bacteriophages* 2017, 1–15.
141. World Health Organization (WHO). Antibiotic resistance, **2019**. Available from: https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance [Last accessed on Sep 24, 2023].
142. K. Lewis. The Science of Antibiotic Discovery. *Cell* **2020**, 181 (1), 29–45.
143. G.F. Hatfull, R.M. Dedrick, R.T. Schooley. Phage Therapy for Antibiotic-Resistant Bacterial Infections. *Annu. Rev. Med.* **2022**, 73, 197–211.
144. A.R. Mushegian. Are There 1031 Virus Particles on Earth, or More, or Fewer? *J. Bacteriol.* **2020**, 202 (9), 2192–2197.
145. S. Reardon. Phage therapy gets revitalized. *Nature* **2014**, 510 (7503), 15–16.
146. Microbiology and Immunology On-line. Bacteriophage, **2016**. Available from: https://www.microbiologybook.org/mayer/phage.htm [Last accessed on Sep 24, 2023].
147. L. Kaliniene, E. Šimoliūnas, L. Truncaitė, A. Zajanckauskaite, J. Nainys, A. Kaupinis, M. Valius, R. Meskys. Molecular Analysis of Arthrobacter Myovirus vB_ArtM-ArV1: We Blame It on the Tail. *J. Virol.* **2017**, 91 (8).
148. J. Callanan, S.R. Stockdale, A. Shkoporov, L.A. Draper, R.P. Ross, C.Hill. Expansion of known ssRNA phage genomes: From tens to over a thousand. *Sci. Adv.* **2020**, 6 (6), eaay5981.
149. K. Kauffman, F. Hussain, J. Yang et.al. A major lineage of non-tailed dsDNA viruses as unrecognized killers of marine bacteria. *Nature* **2018** 554 (7690), 118-22.
150. D. Turner, A.M. Kropinski, E.M. Adriaenssens. A Roadmap for Genome-Based Phage Taxonomy. *Viruses.* **2021**, 13, 506.
151. I. Tolstoy, A.M. Kropinski, J.R. Brister. Bacteriophage taxonomy: An evolving discipline. *Methods Mol. Biol.* **2018**, 1693, 57–71.
152. P. Rogovski, R.D. Cadamuro, R. da Silva et.al. Uses of Bacteriophages as Bacterial Control Tools and Environmental Safety Indicators. *Front. Microbiol.* **2021**, 12, 793135.
153. I. Ul Haq, W.N. Chaudhry, M.N. Akhtar, S. Andleeb, I. Qadri. Bacteriophages and their implications on future biotechnology: A review. *Virol. J.* **2012**, 9 (1), 1–8.
154. L. Qv, S. Mao, Y. Li, J. Zhang, L. Li. Roles of Gut Bacteriophages in the Pathogenesis and Treatment of Inflammatory Bowel Disease. *Front. Cell. Infect. Microbiol.* **2021**, 11, 755650.
155. N. Chanishvili, D. Myelnikov, T.K. Blauvelt. Professor Giorgi Eliava and the Eliava Institute of Bacteriophage. Phage (New Rochelle). **2022**, 3 (2), 71–80.
156. UC San Diego School of Medicine, IPATH. Phage 101, **2020**. Available from: https://medschool.ucsd.edu/som/medicine/divisions/idgph/research/center-innovative-phage-applications-and-therapeutics/research/Pages/Phage%20101.aspx [Last accessed on Sep 26, 2023].
157. D.P. Pires, A.R. Costa, G. Pinto, L. Meneses, J. Azeredo. Current challenges and future opportunities of phage therapy. *FEMS Microbiol. Ver.* **2020**, 44 (6), 684–700.
158. F.L. Gordillo Altamirano, J.J. Barr. Phage therapy in the postantibiotic era. *Clin. Microbiol. Rev.* **2019**, 32 (2), e00066-18.
159. P. Knezevic, N.S. Hoyle, S. Matsuzaki, A. Gorski. Editorial: Advances in Phage Therapy: Present Challenges and Future Perspectives. *Front Microbiol.* **2021**, 12, 701898.
160. R. Dedrick, B. Smith, M. Cristinziano et.al. Phage therapy of Mycobacterium infections: compassionate use of phages in 20 patients with drug-resistant mycobacterial disease. *Clin. Infect. Dis.* **2023**, 76 (1), 103-112.
161. S. Crunkhorn. Phage therapy for Mycobacterium abscesses. *Nat. Rev. Drug Discov.* **2019**, 18 (7), 500.
162. J.J. Bull, J.J. Gill. The habits of highly effective phages: Population dynamics as a framework for identifying therapeutic phages. *Front Microbiol.* **2014**, 5, 109443.
163. K. Bhargava, G. Nath, A. Bhargava, G.K. Aseri, N. Jain. Phage therapeutics: from promises to practices and prospectives. *Appl. Microbiol. Biotechnol.* **2021**, 105 (24), 9047–9067.
164. R. M. Dedrick, C.A. Guerrero-Bustamante, R. A. Garlena et.al. Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant Mycobacterium abscessus. *Nat. Med.* **2019** 25, 5.
165. R. Voelker. FDA Approves Bacteriophage Trial. *JAMA* **2019**, 321 (7), 638.
166. M.L. Ooi, A.J. Drilling, S. Morales, S. Fong, S. Moraitis, L. Macias-Valle, S. Vreudge, A.J. Psaltis, P.J. Wormald. Safety and Tolerability of Bacteriophage Therapy for Chronic Rhinosinusitis Due to Staphylococcus aureus. *JAMA Otolaryngol. Head Neck Surg.* **2019**, 145 (8), 723–729.
167. A. Górski, J. Borysowski, R. Międzybrodzki. Phage Therapy: Towards a Successful Clinical Trial. *Antibiotics (Basel)* **2020**, 9 (11), 827.
168. J. Gabard, P. Jault. How to achieve a good phage therapy clinical trial? Phage Therapy: A Practical Approach. **2019**, 147–168.
169. ScienceDaily. Clinical trial of phage therapy for cystic fibrosis begins, **2022**. Available from: https://www.sciencedaily.com/releases/2022/10/221004134330.htm [Last accessed on Oct 2, 2023].
170. K. Diallo, A. Dublanchet. A Century of Clinical Use of Phages: A Literature Review. *Antibiotics* **2023**, 12 (4), 751.
171. S. Trend, A.M. Fonceca, W.G. Ditcham, A. Kicic, A. CF. The potential of phage therapy in cystic fibrosis: Essential human-bacterial-phage interactions and delivery considerations for use in Pseudomonas aeruginosa-infected airways. *J. Cystic Fibrosis* **2017**, 16 (6), 663–670.
172. A. Ambroa, L. Blasco, M. López, O. Pacios, I. Bleriot, L. Fernandez-Garcia, M. G. de Aledo, C. Ortiz-Cartagena, A. Millard, M. Tomas. Genomic Analysis of Molecular Bacterial Mechanisms of Resistance to Phage Infection. *Front. Microbiol.* **2022**, 12, 784949.
173. J.E. Egido, A.R. Costa, C. Aparicio-Maldonado, P.J. Haas, S.J.J. Brouns. Mechanisms and clinical importance of bacteriophage resistance. *FEMS Microbiol. Rev.* **2022**, 46 (1), 1–16.
174. C. Duan, H. Cao, L.H. Zhang, Z. Xu. Harnessing the CRISPR-Cas Systems to Combat Antimicrobial Resistance. *Front. Microbiol.* **2021**, 12, 716064.
175. M. Tangney, G.F. Fitzgerald. Effectiveness of the lactococcal abortive infection systems AbiA, AbiE, AbiF and AbiG against P335 type phages. *FEMS Microbiol. Lett.* **2002**, 210 (1), 67–72.
176. R.L. Dy, R. Przybilski, K. Semeijn, G.P.C. Salmond, P.C. Fineran. A widespread bacteriophage abortive infection system functions through a Type IV toxin–antitoxin mechanism. *Nucleic Acids Res.* **2014**, 42 (7), 4590–4605.
177. M. Hunter, D. Fusco. Superinfection exclusion: A viral strategy with short-term benefits and long-term drawbacks. *PLoS Comput. Biol.* **2022**, 18 (5), e1010125.
178. S. Matsuzaki, M. Rashel, J. Uchiyama et.al. Bacteriophage therapy: a revitalized therapy against bacterial infectious diseases. *J. Infect. Chemother.* **2005**, 11 (5), 211–219.
179. C. Brives, J. Pourraz. Phage therapy as a potential solution in the fight against AMR: obstacles and possible futures. *Palgrave* Commun. **2020**, 6:100.
180. J.D. Jones, C. Trippett, M. Suleman, M.R. Clokie, J.R. Clark. The Future of Clinical Phage Therapy in the United Kingdom. *Viruses* **2023**, 15 (3).
181. L.L. Furfaro, M.S. Payne, B.J. Chang. Bacteriophage Therapy: Clinical Trials and Regulatory Hurdles. *Front. Cell. Infect. Microbiol.* **2018**, 8, 418978.
182. J. Anomaly. The Future of Phage: Ethical Challenges of Using Phage Therapy to Treat Bacterial Infections. *Public Health Ethics* **2020**, 13 (1), 82–88.
183. S. Le, X. He, Y. Tong. Editorial: Phage Biology and Phage Therapy. *Front. Microbiol.* **2022**, 13, 891848.
184. A. Parisien, B. Allain, J. Zhang, R. Mandeville, C.Q. Lan. Novel alternatives to antibiotics: bacteriophages, bacterial cell wall hydrolases, and antimicrobial peptides. *J. Appl. Microbiol.* **2008**, 104 (1), 1–13.