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Review Article

A Comprehensive Review of Antibiotic Resistance: Mechanisms, Causes, and Novel Therapeutic Approaches

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A B S T R A C T

Antibiotic resistance is a major global health concern that threatens the effective treatment of bacterial infections. The misuse and overuse of antibiotics in human medicine and agriculture have accelerated the emergence of resistant bacterial pathogens such as Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa. Various mechanisms, including genetic mutations and horizontal gene transfer, contribute to the spread of antimicrobial resistance. This review discusses the causes and mechanisms of antibiotic resistance as well as emerging strategies to combat it, including bacteriophage therapy, antimicrobial peptides, and advanced genomic technologies. Strengthening antimicrobial stewardship, improving surveillance systems, and developing new therapeutic approaches are essential to control the spread of antibiotic resistance and ensure effective treatment in the future.

Keywords: Antimicrobial Resistance (AMR), Antibiotic Resistance, Multidrug-Resistant Bacteria, Bacteriophage Therapy, Antimicrobial Stewardship, Novel Antimicrobial Strategies.

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INTRODUCTION

Antibiotic resistance has become a persistent global health concern that continues to threaten public health worldwide. Addressing this issue requires coordinated efforts that include policy development, legislative actions, advancement of therapeutic strategies, and educational programs. Healthcare providers, policymakers, and researchers face significant challenges in controlling antibiotic resistance, particularly because the development of new treatments for bacterial infections remains limited. Effective solutions involve strengthening monitoring systems, improving surveillance of prescribing practices, implementing supportive policies, and promoting the development of new treatment options in both medical and agricultural sectors. The complexity of antibiotic resistance highlights the necessity for a comprehensive and multidisciplinary approach to improve healthcare outcomes [1].

antibiotic resistance remainsa criticalchallenge in global healthcare, threateningthe effectiveness of treatments and increasing the burden of resistant infections. While no single approach cancompletely eliminatethis problem, various strategies can help mitigate its spread and impact. Antibiotic overuse isa majordriver ofresistance evolution, asepidemiological studies have showna direct link between consumption andthe emergenceof resistant strains [2].

Antimicrobial resistance among bacterial pathogens is a major global challenge and is associated with increased morbidity and mortality. The rise of multidrug-resistant Gram-positive and Gram-negative bacteria has led to infections that are difficult to manage with standard antimicrobial treatments. In many healthcare environments, early identification of the causative microorganisms and their susceptibility patterns is often unavailable, which leads to the frequent and sometimes unnecessary use of broad-spectrum antibiotics. This practice contributes to the rapid emergence of resistant strains. When combined with poor infection

control practices, resistant bacteria can spread easily among patients and within healthcare settings. Therefore, access to updated epidemiological data on antimicrobial resistance in common bacterial pathogens is essential for guiding appropriate treatment decisions and for developing effective antimicrobial stewardship programs in hospitals [3]. The increasing resistance of bacterial pathogens to commonly used antimicrobial drugs, along with the emergence of multidrug-resistant organisms, is occurring at an alarming rate. This situation creates major challenges in the treatment of bacterial infections and related diseases. The limited availability of effective drugs, insufficient preventive measures, and the small number of new antibiotics currently in development highlight the need for innovative treatment strategies and alternative antimicrobial approaches. Improved understanding of bacterial virulence mechanisms and the molecular pathways involved in infection provides new opportunities to target key pathogenic factors.

Such strategies may interfere with bacterial virulence while reducing the selective pressure that often drives the development of resistance.The rapid global increase in antibiotic-resistant bacteria has become a serious challenge for both public health and the life sciences community. Many infections caused by resistant microorganisms no longer respond effectively to conventional therapies, and even last-resort antibiotics are losing their effectiveness. At the same time, the pharmaceutical industry has produced relatively few new antibiotics in recent decades. Global initiatives, including campaigns led by the World Health Organization such as “Combat drug resistance: no action today means no cure tomorrow,” have stimulated increased research aimed at restoring effective treatment options against resistant bacterial pathogens [4].

Research has also shown that antibiotic resistance genes are not limited to clinical pathogens but are present in a larger genetic reservoir known as the resistome. This reservoir includes pathogenic, commensal, and environmental bacteria, as well as mobile genetic elements and bacteriophages. Through horizontal gene transfer, resistance genes can move between different bacterial species, allowing pathogenic bacteria to acquire resistance traits from environmental or non-pathogenic organisms. While transformation and transduction were previously considered less significant mechanisms, recent studies suggest that they may play a greater role in the spread of resistance than previously believed. Understanding the resistome and the mechanisms that facilitate gene transfer is therefore critical for controlling the spread of antibiotic resistance [5].

Table 1: Major Bacterial Pathogens Associated with Antibiotic Resistance

S. No.	Bacterial Pathogen	Type	Common Infections	Resistance Concern
1	*Staphylococcus aureus*	Gram-positive	Skin infections, pneumonia	MRSA, VRSA [30,33]
2	*Escherichia coli*	Gram-negative	UTIs, sepsis	ESBL, carbapenem resistance [30,60]
3	*Pseudomonas aeruginosa*	Gram-negative	Burn infections, pneumonia	MDR, biofilm formation [29,46]
4	*Klebsiella pneumoniae*	Gram-negative	Pneumonia, bloodstream infections	Carbapenem-resistant (KPC) [42]
5	*Acinetobacter baumannii*	Gram-negative	ICU infections	XDR, PDR strains [60]
6	*Streptococcus pneumoniae*	Gram-positive	Pneumonia, meningitis	Penicillin resistance [50]

The growing prevalence of multidrug-resistant bacteria has become a major concern due to the serious health problems they cause. Infections caused by these organisms contribute to increased morbidity and mortality, creating an urgent need for effective solutions to address bacterial resistance. Various mechanisms contribute to antibiotic resistance, including reduced drug uptake, biofilm formation, and other adaptive bacterial strategies. To overcome these challenges, several approaches have been proposed, such as the development of new generations of antibiotics, combination therapies, the use of natural antimicrobial compounds, and the application of nanoparticle-based antimicrobial systems [6].

Environmental factors, including exposure to biocides, may also contribute to the development of antimicrobial resistance. Studies have demonstrated that exposure to certain biocidal compounds, such as triclosan, can increase the risk of resistance and cross-resistance in bacteria like *Staphylococcus aureus* and *Escherichia coli*. In contrast, exposure to other agents such as chlorhexidine or hydrogen peroxide under normal use conditions may not produce the same effect. However, prolonged exposure to low concentrations of hydrogen peroxide may still promote the emergence of antibiotic resistance. These findings highlight the importance of evaluating the effects of biocide exposure on antimicrobial resistance, in line with recommendations from regulatory authorities such as the U.S. FDA and the European Union Biocidal Products Regulation [7].

Antibiotics: past, present and future

The rapid increase in antimicrobial resistance (AMR) has become one of the most serious global health threats of the 21st century. The growing prevalence of resistant bacterial strains significantly complicates the treatment of infectious diseases and reduces the effectiveness of existing antibiotics. In recent years, pharmaceutical companies have encountered numerous scientific, financial, and regulatory challenges associated with the development of new antimicrobial agents. One of the major issues is the limited understanding of how to design effective antibiotics capable of targeting highly resistant bacterial pathogens. Because of the high costs of research and development combined with relatively low economic returns, many pharmaceutical companies have reduced their investment in antibiotic discovery programs or abandoned them entirely [8,9]. As a consequence, experts have raised concerns that humanity may be moving toward a potential “post-antibiotic era,” a scenario in which common bacterial infections could once again become life-threatening due to the lack of effective treatments [9]. Despite these concerns, there has been a gradual resurgence of interest in antibiotic

innovation in recent years. Governments, research organizations, and international health agencies have begun increasing financial support for antimicrobial research, antibiotic discovery, and improved diagnostic technologies. Large collaborative initiatives between academic institutions, biotechnology companies, and pharmaceutical industries have been established to accelerate the development of new antimicrobial agents. For example, programs such as New Drugs for Bad Bugs (ENABLE) and CARB-X (Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator) are actively supporting the research and development of new antibiotics and rapid diagnostic tools to combat resistant pathogens [10,11].

In addition to conventional antibiotics, scientists are exploring several alternative therapeutic strategies that may help address the growing problem of AMR. These include bacteriophage therapy, antimicrobial peptides, and other biologically derived antimicrobial compounds [10]. Bacteriophages are viruses that specifically infect and destroy bacterial cells, while antimicrobial peptides are naturally occurring molecules capable of disrupting bacterial membranes and inhibiting microbial growth. Although these alternatives demonstrate promising antimicrobial activity, their clinical applications remain limited due to challenges related to safety, stability, regulatory approval, and large-scale production. Nevertheless, these innovative approaches may serve as valuable complementary therapies alongside traditional antibiotics in the future.

Future Approaches

To effectively address the growing threat of antimicrobial resistance, researchers are exploring several novel strategies that involve a deeper understanding of bacterial resistance mechanisms, disease transmission, and infection prevention [12,13,14]. One of the most significant technological advancements in this field is whole genome sequencing (WGS). This powerful molecular technique enables scientists to analyze the complete genetic makeup of microorganisms, allowing rapid identification of resistance genes and mutations responsible for antibiotic resistance.

By providing detailed insights into the genetic mechanisms underlying bacterial resistance, WGS plays a crucial role in accelerating drug discovery, improving surveillance systems, and guiding the development of targeted antimicrobial therapies [15]. Another promising approach being investigated is the quorum-quenching (QQ) strategy, which focuses on disrupting bacterial communication systems. Many bacteria communicate with each other through chemical signaling processes known as quorum sensing, which regulate important functions such as biofilm formation, virulence factor production, and infection development. Quorum-quenching techniques interfere with these signaling pathways, thereby preventing bacteria from coordinating harmful activities and reducing their ability to cause infections [16].

This approach has the potential to control bacterial infections without directly killing the microorganisms, which may also help reduce the selective pressure that drives the emergence of antibiotic resistance.Among the alternative therapies currently gaining renewed attention is bacteriophage therapy. Bacteriophages, commonly referred to as phages, are viruses that specifically infect bacterial cells and destroy them through replication within the host bacterium. One of the major advantages of phage therapy is its high specificity, as phages selectively target pathogenic bacteria while leaving beneficial microorganisms, such as the normal gut microbiota, largely unaffected. This selectivity reduces the risk of opportunistic infections and minimizes damage to the host's natural microbial balance [17].

Historically, phage therapy was widely used for the treatment of bacterial infections prior to the widespread introduction of antibiotics, particularly in countries such as Russia and Georgia. With the global rise of antibiotic resistance, phage therapy is currently being re-evaluated as a promising alternative or complementary treatment strategy for resistant bacterial infections [15].In addition to phage therapy, advances in biotechnology and molecular medicine have contributed to the development of humanized monoclonal antibodies as potential antimicrobial agents. These antibodies are engineered proteins designed to specifically recognize and neutralize bacterial pathogens or their toxins. Due to rapid progress in genetic sequencing technologies and recombinant DNA techniques, monoclonal antibodies have become one of the fastest-growing categories of biotechnology-derived therapeutic molecules currently undergoing clinical trials.

Targeted immune therapies, including monoclonal antibody injections or the administration of specialized immune cells that recognize bacterial pathogens, offer promising opportunities for treating difficult bacterial infections. However, the high cost of production and limited accessibility remain major challenges for their widespread clinical use [18]. Furthermore, structural biology techniques have also provided valuable insights into the design of next-generation antimicrobial drugs. For instance, researchers have used X-ray crystallography to determine the three-dimensional structures of ribosomal components from the bacterium Staphylococcus aureus. These structural studies revealed unique molecular patterns specific to this bacterial species, which could serve as important targets for the development of novel antimicrobial agents. Such pathogen-specific drug design strategies may enable scientists to create environmentally friendly, degradable antimicrobial compounds that selectively target harmful bacteria while minimizing adverse effects on beneficial microorganisms and the surrounding environment [13].

CAUSES OF THE ANTIBIOTIC RESISTANCE CRISIS

Overuse

As early as 1945, **Alexander Fleming** warned about the dangers of excessive antibiotic use, stating that once these drugs became widely available, the public would start demanding them and this could lead to widespread misuse.[19,20] The excessive use of antibiotics is a major

factor contributing to the development of antibiotic resistance.[21,22] Epidemiological studies have shown a clear association between the level of antibiotic consumption and the emergence as well as spread of resistant bacterial strains.[23]

In bacteria, resistance genes may be inherited from related organisms or obtained from unrelated bacteria through mobile genetic elements such as plasmids.[22] This process, known as horizontal gene transfer (HGT), enables resistance traits to spread among different bacterial species. Resistance may also develop naturally through spontaneous genetic mutations.[22] When antibiotics eliminate drug-susceptible bacteria, resistant bacteria survive and continue to multiply due to natural selection.[22]Despite repeated warnings about excessive antibiotic use, antibiotics continue to be widely overprescribed across the world.[23]In the **United States**, the high number of antibiotic prescriptions suggests that significant efforts are still required to reduce their usage.[24]

Data from the IMS Health Midas database, which estimates antibiotic consumption based on antibiotic sales in retail and hospital pharmacies, showed that in 2010 approximately 22.0 standard units of antibiotics were prescribed per person.[25]A standard unit represents a single dose, such as one pill, capsule, or ampoule.In many other countries, antibiotics are not strictly regulated and can be purchased over the counter without a prescription.[23,26] This lack of control makes antibiotics easily available, inexpensive, and abundant, which further encourages their excessive use.[26] Additionally, the availability of antibiotics through online purchasing has made them accessible even in countries where strict regulations exist.[26]

Inappropriate Prescribing

Incorrect prescribing of antibiotics also contributes significantly to the development of antibiotic-resistant bacteria.[21] Research has shown that in approximately 30% to 50% of cases, the indication for treatment, the choice of antibiotic, or the duration of therapy is inappropriate.[21,27] A study conducted in the **United States** reported that among 17,435 patients hospitalized with community-acquired pneumonia (CAP), the specific pathogen responsible for infection was identified in only 7.6% of cases.[20] In contrast, researchers at the **Karolinska Institute** in **Sweden** were able to determine the probable pathogen in 89% of CAP patients using molecular diagnostic techniques such as polymerase chain reaction (PCR) and semiquantitative PCR.[20]Furthermore, studies have indicated that 30% to 60% of antibiotics prescribed in intensive care units (ICUs) are unnecessary, inappropriate, or not optimally selected.[27]

Incorrect antibiotic prescriptions often provide limited therapeutic benefit and may expose patients to unnecessary risks and complications associated with antibiotic therapy.[28]Subinhibitory or subtherapeutic concentrations of antibiotics can promote antibiotic resistance by encouraging genetic changes, including alterations in gene expression, horizontal gene transfer, and mutations.[29] Alterations in antibiotic-induced gene expression may increase bacterial virulence, while enhanced mutagenesis and horizontal gene transfer facilitate the development and spread of antibiotic resistance. Low antibiotic concentrations have also been shown to promote strain diversification in bacteria such as *Pseudomonas aeruginosa*. Additionally, subinhibitory levels of piperacillin and/or tazobactam can trigger extensive proteomic changes in *Bacteroides fragilis*.[29]

The Action Mechanisms of Antibiotics and Antibiotic Resistance

Damage to the Cell Membrane

The plasma membrane of microorganisms is selectively permeable and facilitates active transport, which generates energy in the form of ATP. It also regulates cytoplasmic contents, including micro- and macromolecules and ions, through integral transporter proteins. When antimicrobial agents disrupt the selective permeability of the membrane, ions leak out, the cellular ion gradient is disturbed, and the microorganism suffers cellular damage leading to death.[30]Bacterial membranes are composed of fatty acids that can be synthesized internally or taken from the environment. Antimicrobials often target steps in fatty acid synthesis or membrane phospholipids. Polymyxin B, a bactericidal antibiotic, is used to treat Gram-negative bacteria such as *Pseudomonas*spp.[31]

Table 2: Mechanisms of Antibiotic Resistance

Mechanism	Description	Example	Ref
Enzymatic degradation	Enzymes destroy antibiotics	β-lactamase	[30,32]
Target modification	Alter binding site	MRSA (PBP change)	[32]
Efflux pumps	Drug pumped out	Tetracycline resistance	[29]
Reduced permeability	Prevent drug entry	Gram-negative bacteria	[30]
Biofilm formation	Protective barrier	*P. aeruginosa*	[46]

It contains detergent-like peptides with lipophilic and hydrophilic groups that disrupt phosphatidylethanolamine in the membrane. Valinomycin, an ionophore, forms pores in the membrane, disturbing the cellular membrane potential essential for oxidative phosphorylation. Daptomycin, used to treat bloodstream, wound, and soft tissue infections caused by β-lactam-resistant bacteria like vancomycin-resistant *Staphylococcus aureus*, causes membrane depolarization, resulting in potassium ion efflux from the cytoplasm.[4] Other antibiotics such as daptomycin, amphotericin B, colistin, imidazoles, and triazoles also function by inhibiting or damaging the cell membrane.[31,30]

Antibiotic Effects on the Cell Wall

Inhibition of Cell Wall Synthesis

Microbial cell walls are primarily made of peptidoglycan, with glycan polysaccharide strands linked by peptide cross-bridges attached to N-acetylmuramic acid (NAM). During cell wall synthesis, bactoprenol, a membrane-bound carrier, transports UDP-NAM-pentapeptide and UDP-NAG from the cytoplasm to the outer membrane. Penicillin-binding proteins (PBPs), which are DD-peptidases associated with the membrane, catalyzetransglycosylation and transpeptidation to assemble peptidoglycan.[32]

Disruption of Cell Wall Structure and Function

Certain antibiotics, including β-lactams, inhibit PBPs by acting as structural analogs of acyl-D-alanyl-D-alanine. These drugs bind to the active site of PBPs, blocking the transpeptidation reaction and inactivating the enzymes, thereby preventing peptidoglycan synthesis and causing bacterial death.[32].

Table 3: Causes of Antibiotic Resistance

Cause	Explanation	Ref
Overuse of antibiotics	Excessive prescribing	[21,23]
Inappropriate prescribing	Wrong drug/dose/duration	[21,27]
OTC availability	Easy access without prescription	[26]
Agricultural use	Use in livestock	[64]
Poor infection control	Spread in hospitals	[3]
Subtherapeutic doses	Promotes mutation	[29]

β-Lactamases and β-Lactam Resistance Mechanisms

β-lactamases are enzymes produced by many Gram-positive and Gram-negative bacteria that hydrolyze the β-lactam ring of antibiotics, inactivating them.[30] These enzymes can be encoded on plasmids or chromosomes. For example, penicillinases in *Staphylococcus aureus* are plasmid-mediated, while many Gram-negative bacteria produce chromosomal β-lactamases.

Plasmid-mediated β-lactamases can be transferred between bacterial species, whereas chromosomal β-lactamases may be constitutive (e.g., in *Bacteroides* and *Acinetobacter*) or inducible (e.g., in *Enterobacter*, *Citrobacter*, *Pseudomonas*). Extended-spectrum β-lactamases (ESBLs) can hydrolyze β-lactams such as cefotaxime, ceftazidime, and aztreonam, and are found in Gram-negative species like *Klebsiella pneumoniae* and *Escherichia coli*.[30] The blaZ gene encodes β-lactamase and is regulated by blaI and blaRI genes located on plasmids or transposons. In the absence of β-lactams, BlaI binds the promoter-operator region of the blaI-blaRI operon, preventing blaZtranscription.[3] When β-lactam antibiotics are present, they bind BlaRI, activating the intracellular zinc metalloprotease domain, releasing BlaI from the operator. This triggers blaZ upregulation and β-lactamase production, leading to bacterial resistance.[32].

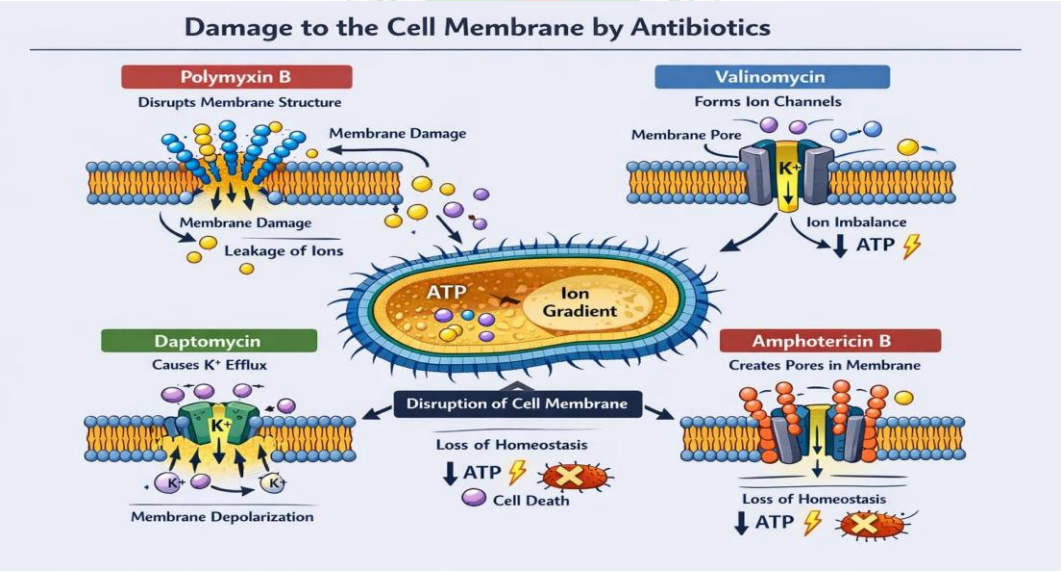

Figure 1: Damage by Antibiotics

Inhibition of Metabolic Compound Synthesis

Antibiotics can inhibit microbial metabolic pathways by acting as competitive inhibitors of enzymes. Structural analogs of natural substrates bind to enzyme active sites, blocking normal metabolic reactions.For example, para-aminobenzoic acid (PABA) is a substrate for folic acid synthesis, which is crucial for purine, pyrimidine, and amino acid production. Drugs such as sulfanilamide and 3,4,5-trimethoxybenzylpyrimidine inhibit these metabolic pathways. Sulfonamides (sulfa drugs) are used in infections like urinary tract infections and are often

combined with other drugs, such as silver sulfadiazine for burn infections.[31] Trimethoprim-sulfamethoxazole (TMP-SMZ) is another widely used combination therapy because of its synergistic effect. Trimethoprim and sulfamethoxazole block different steps in the synthesis of DNA and RNA precursors, inhibiting protein production.[32]

Multidrug resistance of bacterial

Multidrug-resistant (MDR) bacteria are widely recognized as a major public health concern today. The Infectious Diseases Society of America states that antimicrobial resistance represents one of the greatest threats to human health worldwide[33]. Several factors contribute to the seriousness of this problem. First, patients infected with MDR bacteria often experience poorer outcomes compared with those infected by antibiotic-susceptible organisms[34,35]. Increasing antibacterial resistance therefore affects many aspects of modern medicine and may reduce the success of important medical interventions such as cancer therapy, organ transplantation, and surgical procedures[36]. Second, infections caused by resistant organisms impose significant economic costs. In the United States, the additional annual expenses related to these infections are estimated to range from $21 billion to $34 billion[33]. Third, the occurrence of certain MDR bacteria is strongly associated with the frequent use of broad-spectrum antibiotics for both empirical and definitive therapy[37].

Greater use of these drugs promotes the emergence of resistant bacteria, which in turn requires further antibiotic use, creating a continuing cycle of resistance.

Traditionally, MDR bacteria have been linked mainly with hospital-acquired infections.However, some resistant organisms have increasingly become causes of community-acquired infections. This shift is important because the spread of MDR bacteria in the community increases the number of individuals at risk and leads to a greater number of resistant infections.

Moreover, when resistance rates among bacteria responsible for community infections exceed a certain level, clinicians may need to prescribe broader-spectrum antibiotics or combination therapy as empirical treatment. This review therefore focuses on the trends and epidemiology of MDR bacteria circulating in community settings.Infections are commonly classified as either community-onset or nosocomial (hospital-acquired). The usual distinction is based on whether the infection develops within the first 48 hours after hospital admission (community-onset) or later (nosocomial).

However, this classification has certain limitations, since the 48-hour cutoff is somewhat arbitrary and also depends on the timing of diagnostic testing. When cultures are performed early during hospitalization, more infections may be categorized as community-onset.Community-onset infections can be further divided into community-acquired and healthcare-associated infections, based on research conducted by Morin and Friedman[38,39].

Table 4: Mechanism of Action of Antibiotics

Target Site	Mechanism	Example Drugs	Ref
Cell wall synthesis	Inhibits peptidoglycan	Penicillin, Cephalosporins	[32]
Cell membrane	Disrupts membrane	Polymyxin B, Daptomycin	[31]
Protein synthesis	Ribosome inhibition	Tetracycline, Aminoglycosides	[31]
DNA/RNA synthesis	Blocks replication	Fluoroquinolones	[31]
Metabolic pathways	Folic acid inhibition	Sulfonamides, TMP-SMX	[32]

An infection is generally considered healthcare-associated if the patient was hospitalized for two or more days within the previous 90 days, lived in a nursing home or long-term care facility, received intravenous antibiotics, chemotherapy, or wound care within the last 30 days, or regularly attended a hospital or hemodialysis clinic[40].Patients who develop community-onset infections but do not meet these healthcare-associated criteria are classified as having community-acquired infections. However, these definitions may not fully explain the origin of MDR bacteria in community settings. In many cases, infections occur from organisms that previously colonized the patient.

Therefore, the timing of colonization may be more important than the time at which the infection is diagnosed when determining the origin of MDR bacteria. Studies involving screening of healthy individuals have provided insight into colonization patterns of certain MDR bacteria in different populations.Research has shown that MDR organisms share several risk factors with opportunistic pathogens such as Clostridium difficile and fungi like Candida species, as described by Safdar and Maki[41].

Numerous studies examining risk factors for MDR bacteria have found considerable overlap. Exposure to antibiotics is one of the most consistently identified risk factors in studies with sufficient statistical power. However, the specific antibiotic class associated with a particular resistance pattern may differ. In many cases, the use of a specific antibiotic is directly linked with resistance to that same drug.

For example, in patients infected with carbapenem-resistant *Klebsiella pneumoniae*, treatment with tigecycline has been shown to lead to the development of tigecycline resistance in the same bacteria[42].Certain epidemiological study designs, such as case-case-control studies, are often required to accurately determine the contribution of antibiotic exposure to resistance development[43,44]. In some situations, the relationship between antibiotic use and resistance can be complex.

For instance, the use of ceftriaxone—but not other cephalosporins—has been associated with bloodstream infections caused by vancomycin-resistant Enterococci (VRE)[45]. These findings emphasize the importance of antimicrobial stewardship in hospitals, community healthcare settings, and even non-medical contexts to control the spread of antimicrobial resistance.Exposure to

healthcare environments is another major risk factor for MDR bacteria.

The presence of medical devices such as urinary catheters, feeding tubes, endotracheal tubes, and vascular lines is frequently linked with colonization or infection by resistant organisms[41]. Additional risk factors include immunosuppressive conditions such as solid-organ transplantation, hematopoietic stem-cell transplantation, and chronic illnesses like renal failure. However, the impact of these factors is sometimes difficult to determine because they often overlap with antibiotic exposure and healthcare contact.For MDR bacteria to spread widely in community environments, the traditional hospital-related risk factors must become less important. One key requirement is that the MDR phenotype remains stable even in the absence of strong antibiotic pressure typically present in hospitals or nursing homes.

Table 5: Multidrug-Resistant (MDR) Bacteria and Impact

Factor	Description	Ref
Clinical impact	Increased morbidity/mortality	[34,35]
Economic burden	High treatment cost	[33]
Hospital stay	Prolonged hospitalization	[36]
Treatment failure	Limited options	[37]
Spread	Community + hospital	[38,39]

This stability allows resistant bacteria to compete successfully with antibiotic-susceptible strains while maintaining the genetic elements responsible for resistance. Resistance genes that significantly reduce bacterial fitness are less likely to spread widely unless compensatory genetic changes occur or the resistance mechanism is inducible. An example of inducible resistance is the erythromycin resistance methylase (erm) genes found in mycobacteria and *Staphylococcus aureus*.

These genes produce resistance proteins only when bacteria are exposed to certain antibiotics, resulting in rapid phenotypic resistance.In addition, MDR bacteria that successfully spread in community environments must be able to survive without relying on biofilm formation on artificial surfaces.

Instead, they must compete with normal microbial populations present in the skin, nasal passages, mouth, and gastrointestinal tract. Nevertheless, biofilm formation remains an important factor in bacterial persistence and contributes to several common infections, including periodontal disease, gastric infection caused by *Helicobacter pylori*, middle ear infections, and urinary cystitis[46]. MDR bacteria capable of forming biofilms even without foreign materials are more likely to become established in community settings.Finally, community-associated MDR bacteria must be able to survive within healthy individuals without obvious immune suppression. However, variations in host immune genes may influence susceptibility to colonization. In the case of persistent nasal carriage of *Staphylococcus aureus*, host genetic factors have even been suggested to play a predominant role in determining colonization[47].

Burden of Antibiotic Resistance

Antimicrobial resistance is widely recognized as one of the most significant public health challenges of the 21st century[48,49]. However, reliable estimates of the overall global health burden caused by bacterial resistance to antibiotics are still lacking. Although many studies have attempted to measure the burden associated with specific combinations of diseases, bacterial pathogens, antibiotics, and healthcare environments—mainly in hospitals within developed countries—the approaches used in these studies vary widely.

Differences in measurement methods, incomplete geographical coverage, and inconsistent research methodologies make it difficult to generate accurate global estimates. Some studies have attempted to estimate resistance-related mortality and other health outcomes in regions such as Europe[50], the United States[51], and globally[52]. Nevertheless, because these estimates often rely on limited data and require extrapolation from small-scale studies, they should be interpreted cautiously.Several indicators are used to measure the burden of infectious diseases. These include mortality rates, morbidity, disability-adjusted life years (DALYs), duration of hospital stay, and the economic cost of treatment. In this discussion, the focus is primarily on mortality, although similar principles apply to other indicators.

A key step in assessing the burden of antibiotic resistance is to clearly define what is meant by this burden. The most appropriate definition is the number of deaths that occur due to the failure of antibiotic treatment caused by bacterial resistance. It is important to note that this measure does not equal the total number of deaths among patients who have antibiotic-resistant infections. In fact, the number may be considerably lower for two main reasons.

First, not all patients with resistant infections receive the appropriate antibiotic treatment. Second, even when appropriate antibiotics are used, the difference in clinical outcomes between patients with resistant infections and those with susceptible infections may sometimes be relatively small.More specifically, the burden of antibiotic resistance can be described using the concept of the population attributable fraction (PAF), also known as the aetiological fraction. This represents the proportion of deaths that would not occur if antibiotic resistance were completely eliminated.

Calculating the PAF for mortality related to antibiotic resistance requires several types of data. These include the number of patients with resistant infections, the number of deaths among those patients, and information about the broader population under study, including individuals who survived or had infections caused by susceptible bacteria. Determining this population requires additional data on the incidence of the clinical condition, the causative organisms, and the extent to which recommended antibiotic treatments are used. Because such detailed information is rarely available, the PAF method is seldom applied to estimate the global burden of antibiotic resistance.

Table 6: Novel Therapeutic Approaches

Approach	Description	Advantage	Limitation	Ref
Bacteriophage therapy	Virus kills bacteria	High specificity	Regulatory issues	[17,18]
Antimicrobial peptides	Membrane disruption	Broad spectrum	Stability issues	[10]
Monoclonal antibodies	Target toxins	High specificity	Expensive	[19]
Whole genome sequencing	Detect resistance genes	Rapid diagnosis	Costly	[15]
Quorum quenching	Block signaling	Reduce virulence	Early-stage	[16]

One recent study used this approach to evaluate neonatal sepsis[49], but it had to rely on extrapolated data derived from observations in a single hospital.Global antibiotic consumption has been estimated to exceed **70 billion doses annually**[53].

In terms of total usage, the most commonly consumed antibiotic groups in 2010 included **penicillins, cephalosporins, macrolides, fluoroquinolones, trimethoprim, and tetracyclines**.These figures are based on pharmacy sales data and therefore do not directly associate antibiotic use with the treatment of particular clinical conditions. The **World Health Organization** last released general guidelines for antibiotic therapy in 2001[54].

Although these guidelines and later national or international recommendations provide direction for antibiotic use, they are generally not highly prescriptive. Instead, they emphasize adapting treatment decisions according to local circumstances, especially local patterns of antibiotic resistance. As a result, antibiotic usage patterns may differ significantly between regions. In some countries, data on antibiotic use are available at the hospital level; however, these records are rarely connected with detailed information about the specific diseases being treated [55].Current patterns of antibiotic use are strongly influenced by existing levels of antibiotic resistance. For instance, **aminopenicillins** alone are often no longer suitable for treating severe infections caused by gram-negative bacteria. In such cases, additional or alternative antibiotics may be required if they are available. Under these circumstances, resistance to aminopenicillins would not necessarily contribute to the **population attributable fraction (PAF)** defined earlier, although it can still be considered part of the broader burden associated with antibiotic

Global Threat of Antimicrobial Resistance: Challenges and Solutions

Over the decades, numerous antimicrobials have been developed and introduced to treat infections ranging from mild to severe. The accidental discovery of **penicillin** in the late 1920s paved the way for the development of a variety of antibiotics, including modifications of penicillin itself. Research has also produced new **antiviral drugs** for previously untreatable diseases such as AIDS, as well as **antifungal** and **antiparasitic agents**, which have become essential in combating infections [56,57].

Table 7: Antibiotic Combination Strategies

Combination	Purpose	Example	Ref
β-lactam + Aminoglycoside	Synergy	Penicillin + Gentamicin	[67,68]
β-lactam + Fluoroquinolone	Broad coverage	Ceftriaxone + Ciprofloxacin	[66]
β-lactam + BLI	Overcome resistance	Amoxicillin + Clavulanic acid	[72]
Colistin combinations	Last-resort therapy	Colistin + Rifampicin	[76]

Although these drugs have significantly improved health outcomes and life expectancy, their effectiveness has been increasingly undermined by the rise of **antimicrobial resistance (AMR)**. AMR reduces the efficacy of treatments, making infections harder to manage and increasing the risk of disease spread, severe illness, and mortality. Many pathogens are now **multi-drug-resistant (MDR)**, while some have become **extensively drug-resistant (XDR)** or **pan-resistant (PDR)**, rendering standard therapies largely ineffective. The **WHO** has recognized the growing threat of ineffective antibiotics and other antimicrobial agents due to AMR [56]. The **OIE** (World Organization for Animal Health) also acknowledged the importance of regulating antimicrobial agents for veterinary use during its 75th general session in 2007 [57].AMR imposes considerable **pharmaco-economic burdens**. For instance, the **IDSA** reported that in 2017, antibiotic-resistant infections among the U.S. Medicare population resulted in $1.9 billion in healthcare costs, 400,000 hospital days, and 10,000 deaths [58]. Similarly, the 2014 **UK Review on Antimicrobial Resistance**, chaired by Lord Jim O'Neill, estimated 700,000 annual deaths from resistant infections, projecting a rise to 10 million deaths per year and an economic loss of $100 trillion by 2050 if no preventive measures are implemented [59]. A 2019 global assessment covering 204 countries estimated that AMR was associated with 4.95 million deaths, with 1.27 million directly attributable to antibiotic resistance. The highest burden was predicted in sub-Saharan Africa and

the lowest in Australasia. **MRSA** alone accounted for approximately 500,000 deaths, while six major pathogens—*Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*—were responsible for between 50,000 and 100,000 deaths each [60].

Table 8: Global Burden of Antibiotic Resistance

Parameter	Data	Ref
Annual antibiotic consumption	>70 billion doses	[53]
Global deaths (2019)	4.95 million	[60]
Direct AMR deaths	1.27 million	[60]
Projected deaths (2050)	10 million/year	[59]
Major pathogens	ESKAPE pathogens	[62]

AMR is a **global public health challenge** affecting countries regardless of risk level. Its spread has implications for the environment, food production, poverty, health security, and the UN's Sustainable Development Goals (SDGs), highlighting the need for a **multisectoral One Health approach** [61]. Rising AMR, particularly among clinically significant **ESKAPEE pathogens** (*Enterococcus* spp., *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* spp., and *Escherichia coli*), has placed immense pressure on human healthcare, veterinary medicine, and agriculture, making AMR one of the most urgent global health threats [62,63]. In a One Health context, the transmission of resistant bacteria from food animals may substantially impact both animal and human health [64]. Given the global threat posed by MDR, XDR, and PDR infections, new strategies are being adopted to manage these infections, as even last-resort antibiotics are increasingly failing in clinical settings [65].

Antibiotic Combinations

Several antibiotic combinations have traditionally been employed to manage **MDR infections**. **β-lactam antibiotics**, due to their broad spectrum and synergistic properties, are often combined with other antibiotic classes. For instance, the combination of a β-lactam with an **aminoglycoside** is well-studied and commonly used to treat various Gram-negative infections [66]. In this combination, the β-lactam disrupts **peptidoglycan synthesis**, which enhances aminoglycoside uptake and intracellular concentration in bacterial cells [67,68].

Other frequently used combinations include **β-lactam/fluoroquinolone** and **β-lactam/tetracycline** pairings. Additionally, the aminoglycoside **amikacin** has shown synergy when used with **colistin**, though its clinical use is limited by nephrotoxicity [69]. While some antibiotic combinations are believed to be more effective than monotherapy, their true efficacy remains uncertain due to evolving resistance mechanisms [66,70]. Therefore, the effectiveness of such combinations, as well as emerging alternatives, should be continuously evaluated to address AMR [71].

Antibiotic Combinations with β-Lactamase Inhibitors

To treat infections resistant to β-lactams, combining **β-lactam antibiotics** with **β-lactamase inhibitors (BLIs)**—such as **sulbactam, clavulanic acid, and tazobactam**—can restore antibiotic activity. This approach is referred to as **β-lactam/β-lactamase inhibitor (BLBLI) therapy**. Newer BLIs, including **avibactam, relebactam, taniborbactam, tazobactam, vaborbactam, enmetazobactam,** and **zidebactam**, have been developed to treat **carbapenem-resistant bacteria** or to serve as carbapenem-sparing options [72].

Table 9: Classification of Resistance

Type	Definition	Ref
MDR	≥3 drug classes resistant	[33]
XDR	Resistant except 1–2 classes	[62]
PDR	Resistant to all drugs	[75]

For example, the **aztreonam–avibactam** combination is effective against **NDM, VIM, and IMP-producing bacteria**, which inactivate carbapenems, and is used clinically for **carbapenem-resistant Enterobacteriaceae (Enterobacterales)** [73]. Similarly, the activity of **cefepime**, a fourth-generation cephalosporin, is restored when combined with **enmetazobactam** [74].Over the past decade, resistance among **ESKAPE pathogens** has escalated, and **PDR infections** have become more common [75]. Few last-resort options remain, but some studies report that combining **colistin** with **rifampicin, meropenem,** or **tigecycline** improves treatment outcomes for PDR infections [76].

Combination of Antibiotics with Biocides

Combining antibiotics with **biocides** (including disinfectants, antiseptics, and preservatives) has theoretical potential against MDR bacteria, but has been largely underexplored [77]. In one study testing three antibiotics with seven biocides against **Pseudomonas aeruginosa**, the combinations exhibited effects ranging from **synergistic to antagonistic** [78]. Future research should investigate the evolutionary implications of these interactions, as antibiotic-biocide combinations may provide a promising approach to countering AMR using existing agents.

Future Perspectives

Since 2017, only two of the eight newly approved antibiotics have introduced a completely new chemical scaffold [79]. The remaining antibiotics are derivatives of existing classes, offering advantages over traditional drugs. All eight exhibit activity against ESBL (extended spectrum β-lactamase) enzymes, with most effective against carbapenem-resistant Enterobacteriaceae (KPC producers), while very few are active against carbapenem-resistant Pseudomonas aeruginosa and multidrug-resistant Acinetobacter baumannii. Consequently, therapeutic options for these latter pathogens remain extremely limited. These new antibiotics are primarily used to treat complicated urinary

tract infections (cUTI) and complicated intra-abdominal infections (cIAI), though further clinical studies are needed to determine their effectiveness against other infections. Notably, the combination of vaborbactam, meropenem, and plazomycin has been included in the WHO Model List of Essential Medicines.Research progress is evident, as the number of new antibiotics effective against Gram-negative bacteria has increased.

Most compounds approved or in clinical development since 2017 targeting pathogens listed by the WHO in 2016 (critical, high, and medium priority) are combinations of β-lactams and β-lactamase inhibitors. Cefiderocol is currently the only antibiotic active against all three critical-priority pathogens, along with SPR-206 Phase I, a polymyxin analogue with a broad antibacterial spectrum. By the end of 2020, 43 antibiotics were in clinical development: 15 in Phase I, 13 in Phase II, and 13 in Phase III. Nineteen of these antibiotics have demonstrated in vitro activity against ESKAPE pathogens, including Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species, which are responsible for the major nosocomial infections [80].It is critical that newly developed antibiotics avoid cross-resistance with existing compounds. Efforts to modify traditional antibiotics rely on knowledge of resistance mechanisms, though discovering innovative chemical structures with novel targets and binding sites remains difficult and yields fewer results [81].

Table 10: Future Strategies to Combat AMR

Strategy	Description	Ref
Antimicrobial stewardship	Rational use	[28]
Surveillance systems	Monitoring resistance	[3]
Drug discovery	New antibiotics	[8,10]
Infection control	Hygiene practices	[41]
One Health approach	Human-animal-environment	[61]

Beyond small and large molecules, alternative approaches—such as fecal microbiota transplantation for recurrent Clostridioides difficile infections—show potential. Other non-traditional strategies, including immunomodulators and phage therapies, have yet to enter clinical development due to significant challenges. Market trends remain unfavorable: despite modest increases in public investment from countries like Germany, the UK, and the USA via organizations such as BARDA, CARB-X, and GARDP, private investment has declined. Many pharmaceutical companies are withdrawing from antibiotic research due to high development costs. Considering the long timelines for clinical development, 11 new antibiotics are expected to gain approval within the next five years, while many candidates may stagnate in Phase II or III because of financial constraint

CONCLUSION

Antibiotic Resistance has emerged as a serious global public health problem that threatens the successful treatment of bacterial infections. The increasing spread of resistant bacteria is largely caused by the inappropriate and excessive use of antibiotics, along with genetic mutations and mechanisms such as horizontal gene transfer. The rise of multidrug-resistant microorganisms has made many infections harder to manage and has contributed to higher rates of illness and death. To address this growing issue, coordinated strategies are required, including the discovery of new antimicrobial drugs, better diagnostic tools, responsible antibiotic use, and strong infection control practices. Furthermore, emerging approaches such as nanotechnology, bacteriophage therapy, and natural antimicrobial agents may provide promising alternatives for the future. Therefore, collaboration among scientists, healthcare providers, and policymakers worldwide is crucial to reduce the spread of resistance and preserve the effectiveness of antibiotics for future generations.

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