CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.22047385

Available online at: http://www.iajps.com Review Article

EMERGING ANTIBIOTICS FOR THE TREATMENT OF MULTIDRUG-RESISTANT BACTERIAL INFECTIONS: A NARRATIVE REVIEW

Shajith khan.S[1], Dr M K Sundar Sri[2]

[1]Pharm D, VELS Institute of Science Technology and Advanced Studies, VISTAS.
Shajithkhan2001@gmail.com

[2]Assistant Professor, Pharmacy practice, Clinical research, VELS Institute of Science Technology and Advanced Studies, VISTAS. sundarsri.sps@vistas.ac.in

Abstract:
Antimicrobial resistance is one of the biggest problems that healthcare has had to face recently. It has made the conventional antibiotics ineffective and increased the prevalence of bacteria that are multidrug-resistant. The continuous emergence of multidrug-resistant strains such as methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, carbapenem-resistant Enterobacterales, multidrug-resistant Pseudomonas aeruginosa, and Acinetobacter baumannii makes it imperative to find newer drugs to deal with the infections. Newer antibiotics developed through recent advancements include beta-lactam/beta-lactamase inhibitors, new cephalosporins, derivatives of tetracycline, oxazolidinones, lipoglycopeptides, siderophore antibiotics, and several others. There are also some emerging strategies that could be considered as unconventional, which include bacteriophage therapy, antimicrobial peptides, CRISPR antimicrobials, monoclonal antibodies, and nanotechnology.

Keywords: *Antimicrobial resistance; Multidrug-resistant bacteria; Emerging antibiotics; β-lactamase inhibitors; Cefiderocol; Antimicrobial stewardship; Novel antibacterial agents; Drug resistance.*

Corresponding author:
Shajith Khan.S,
Pharm D,
VELS Institute of Science Technology and Advanced Studies,
VISTAS. Shajithkhan2001@gmail.com

QR CODE

Please cite this article in press ***Shajith Khan.S*** *et al.,* ***Emerging Antibiotics For The Treatment Of Multidrug-Resistant Bacterial Infections: A Narrative Review****. Indo Am. J. P. Sci, 2026; 13(08).*

INTRODUCTION:

The discovery of antibiotics is considered to be among the biggest breakthroughs in medicine due to the ability of these drugs to efficiently treat bacterial infections that were earlier life-threatening conditions. The use of antibiotics has helped make many clinical practices such as surgeries, organ transplants, cancer chemotherapy, and critical care treatment much safer thanks to the prevention and management of infections. Over time, however, the improper and unreasonable use of antibiotics in clinics, communities, veterinary practice, and agriculture has led to the development of antibiotic-resistant bacteria. Many bacterial strains have started gaining resistance to antibiotics that were efficient earlier, hence making the treatment less effective. As a result, it is becoming harder to control infections which leads to increased length of hospitalization, increased costs of medical care, more patient discomfort and mortality. The issue of antimicrobial resistance (AMR) is nowadays considered to be one of the major global public health problems.

The development of multidrug resistant (MDR) infections is one of the most alarming challenges that the problem of antimicrobial resistance poses. Multidrug resistant bacteria are those that can withstand several types of antibiotics, which provides little scope for treatment. Methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), carbapenem-resistant Enterobacterales (CRE), multidrug-resistant Pseudomonas aeruginosa, and Acinetobacter baumannii have become the most prevalent sources of MDR infections across the world. This group of organisms causes bloodstream infections, pneumonia, urinary tract infections, wound infections, and intra-abdominal infections, primarily among critical patients, elderly people, and immunocompromised individuals. The spread of these resistant bacteria makes available antibiotics ineffective and increases the risk of failure of their action.

As a result, there have been many advances in the field of new antibiotics that are created specifically to defeat common methods of drug resistance. In the past decade, there have been a number of antimicrobials developed and approved for medical application, which includes novel β-lactam/β-lactamase inhibitors, new cephalosporins, tetracycline derivatives, aminoglycoside derivatives, oxazolidinones, lipoglycopeptides, and pleuromutilins. A large portion of these antibiotics have better effects on highly drug-resistant Gram-positive and Gram-negative bacteria, improved pharmacodynamics, and are safer for use. Apart from the recently approved drugs, there are many other new antimicrobials that are still under development and undergoing clinical trials. Additionally, there are new alternative methods of dealing with multidrug-resistant infections such as bacteriophage therapy, antimicrobial peptides, anti-virulence approach, monoclonal antibodies, and antibiotic discovery based on artificial intelligence.

ANTIMICROBIAL RESISTANCE: AN OVERVIEW

Antimicrobial resistance (AMR) stands for the capacity of microbes, including bacteria, viruses, fungi, and parasites, to survive and reproduce even after coming into contact with the antimicrobial agents used to kill them. In cases of bacterial infections, antibiotic resistance happens due to the development of specific traits in bacteria, which make them immune to the action of antibiotics. Consequently, infections become hard to treat, as they may require extended periods of therapy, increased costs, and even the use of combinations of various antibiotics. The process of developing antibiotic resistance happens in a natural way due to the evolution of bacteria. At the same time, the problem has been accelerated significantly by the overuse and inappropriate use of antibiotics in human medicine, veterinary medicine, farming, and livestock management. Presently, AMR is considered one of the biggest health threats in the world because it reduces the effectiveness of medical treatment and causes infections.

EVOLUTION OF ANTIMICROBIAL RESISTANCE

It is an evolutionary process that occurs due to the action of natural selection. As bacteria are introduced to antibiotics, those lacking the resistance genes die while those possessing these genes remain alive and reproduce. Resistant bacteria become a threat to healthcare institutions, communities, and even the environment. Other than genetic mutations, bacteria are able to obtain resistance genes from one another through horizontal gene transfer, which occurs via conjugation, transformation, and transduction. It has made it possible for bacteria to share their resistance characteristics among themselves thus facilitating the emergence of multi-drug resistant bacteria. Some of the factors that have facilitated this process include over prescription of antibiotics, self-medicating, suboptimal treatments, inadequate infection control measures, poor sanitations, and extensive use of antibiotics on livestock.

GLOBAL BURDEN OF ANTIMICROBIAL RESISTANCE

Resistance to antimicrobials is now a serious problem on a global scale in the developed as well as developing world. Every year millions of infections occur as a result of antibiotic resistance causing an increase in admissions in hospitals, prolongation of illnesses, rise in costs of health care and ultimately deaths. Antibiotic resistant infections make patients stay in hospitals for long periods, need intensive care and second or third choice antibiotics which can prove ineffective and toxic. According to WHO, AMR is among one of the major threats facing the world today in terms of health because it reverses all gains made in medicine during decades. If antibiotics continue to remain ineffective, there would be high risks involved in surgical procedures, organ transplantation, chemotherapy, neonatal care and intensive care treatment.

TYPES OF RESISTANCE

Intrinsic Resistance : Intrinsic resistance refers to the natural resistance of some types of bacteria to certain antibiotics. It does not require any previous exposure of bacteria to antibiotics, nor does it involve genetic modification. For example, Gram-negative bacteria have natural resistance to vancomycin due to their outer membrane, while Mycoplasma bacteria have natural resistance to β-lactam antibiotics due to the lack of bacterial cell wall.

Acquired Resistance : Acquired resistance occurs when previously nonresistant bacteria become resistant as a result of genetic modifications, or as a result of the acquisition of resistance genes from other bacteria by means of conjugation, transformation, or transduction. This enables bacteria to inactivate antibiotics, modify their targets, or limit antibiotic uptake. MRSA and CRE are examples of acquired resistance.

Adaptive Resistance : Adaptive resistance is a temporary and reversible mechanism which enables bacteria to survive in stressful environments including the presence of antibiotics or limitation of nutrients. Bacteria do not undergo any permanent genetic modifications; they regulate gene expression, increase the activity of efflux pumps, limit membrane permeability, or create biofilm.

CLASSIFICATION OF RESISTANT ORGANISMS

Multidrug-Resistant (MDR) Organisms : The organisms with multidrug resistance (MDR) are those bacteria that are resistant to at least one antimicrobial drug in three or more categories of antibiotics. Although there are some available treatments for these infections, they are difficult to treat and require broad spectrum or combination antibiotics. Some of the MDR organisms include MRSA and multidrug-resistant Pseudomonas aeruginosa.

Extensively Drug-Resistant (XDR) Organisms : Organisms with extensively drug-resistance (XDR) are those that are resistant to almost all the classes of available antibiotics but still have resistance to only one or two antibiotics. These infections pose a great problem because treatment options are very limited. Some examples of XDR organisms include XDR Acinetobacter baumannii, Pseudomonas aeruginosa, and extensively drug-resistant Mycobacterium tuberculosis.

Pan-Drug-Resistant (PDR) Organisms : Pan-drug-resistant (PDR) organisms are resistant to all existing antibiotics from all classes of antimicrobial drugs. This is the highest stage of resistance in bacteria. PDR organisms cause serious infections, long-term hospital stay, and high mortality. Such pathogens leave doctors with practically no options to choose from among effective antibiotic therapy.

MECHANISMS OF ANTIMICROBIAL RESISTANCE

Enzymatic Drug Inactivation : Enzymatic drug inactivation is one of the main mechanisms that lead to bacteria resistance to antibiotics. The mechanism is based on bacteria synthesis of enzymes that chemically destroy or alter antibiotic molecule before it reaches its target site. The most common are enzymes such as β-lactamases, extended-spectrum β-lactamases (ESBLs), carbapenemases, metallo-β-lactamases, and aminoglycoside-modifying enzymes. The enzymes destroy chemical structure of antibiotics, making them non-effective. Consequently, bacteria survive and reproduce despite of being treated with antibiotics. Rapid development of antibiotic-resistance genes in enzymes producing bacteria, especially Gram-negative pathogens, becomes a challenging problem in clinical practice requiring either use of new antibiotics or combination with β-lactamase inhibitors.

Alteration of Drug Targets : Alteration of the bacterial drug target is another way in which antimicrobial resistance develops. Antibiotics function by binding to some bacterial proteins or enzymes that are required for survival. Bacteria, on the other hand, have the ability to undergo mutations or acquire target proteins that do not bind antibiotics but retain their normal functioning. In doing so,

antibiotics are rendered unable to exert their effect on the bacteria. For example, in Methicillin Resistant Staphylococcus Aureus (MRSA), an altered penicillin binding protein (PBP2a) is made and thus makes β-lactam antibiotics useless.

Reduced Membrane Permeability : Membrane permeability reduction is one of the mechanisms of resistance that involve bacteria restricting the access of antibiotics into the cell. This is a common mechanism for Gram-negative bacteria due to the presence of an additional layer of the membrane – the outer membrane. Antibiotics gain entry into the bacteria through porins which are proteins. Alterations in the number, size or shape of porins decrease the entry of antibiotics into the bacteria. The result is that the antibiotics do not achieve the appropriate concentration within the bacteria to act. Membrane permeability usually occurs alongside another mechanism of resistance.

Efflux Pump Overexpression : Efflux pumps are transport proteins that expel antibiotics out of the bacterial cell before they reach effective intracellular levels. Some bacteria have efflux pumps naturally, whereas some enhance their numbers through mutations and regulatory alterations. Overproduction of efflux pumps reduces the amount of accumulated antibiotic in the bacteria, hence rendering the antibiotics less effective. Resistance by efflux system mainly involves tetracycline, fluoroquinolone, macrolide, chloramphenicol, and many other classes of antibiotics. Some multidrug resistant bacteria have efflux pumps that enable expulsion of many different antibiotics at once.

Biofilm Formation : Formation of biofilms is one of the significant mechanisms that allows bacteria to evade antibiotics and the immune response of the host body. Biofilms are defined as bacterial colonies that are surrounded by a self-generated matrix, which comprises of polysaccharides, proteins, and DNA. The formation of this layer prevents the entry of antibiotics, decreases the metabolic activities of bacteria and results in creation of a niche where bacteria are resistant to antibiotics. Bacteria in biofilms are able to withstand antibiotics in concentrations which would otherwise be lethal for planktonic bacteria. Formation of biofilms occurs in many sites like urinary catheters, central venous catheters, prosthetic joints, heart valves, and chronic wounds.

Horizontal Gene Transfer : Horizontal gene transfer is one of the most critical processes causing the fast spread of resistance to antibiotics in bacteria. Contrary to the vertical transmission where genes are transferred from one generation to another in the same bacteria, in the horizontal transfer process, bacteria transfer their genetic information directly to other bacteria, even different species, through conjugation, transformation, and transduction. The resistant genes contained in plasmids, transposons, and integrons are spread rapidly in hospital and community settings. There are many clinically important resistance determinants like carbapenemases, ESBLs, and colistin resistance that have been spread by horizontal gene transfer.

Persister Cells and Dormancy : Persister cells are a minority group of dormant bacteria that survive antibiotics without having any inherent resistance through genetics. Because antibiotics usually attack fast-growing bacteria, dormant bacteria are left untouched during antibiotic administration. When the exposure to antibiotics is finished, persister cells become active, reproduce very quickly, and result in the onset of infection. Persister cells can be found in biofilms and are mostly related to persistent infections of implanted medical devices, chronic wounds, and pulmonary infections. Despite the fact that persister cells are not genetically resistant, their high survival rate makes the process of getting rid of bacteria very difficult.

MAJOR MULTIDRUG-RESISTANT BACTERIAL PATHOGENS

Methicillin-Resistant Staphylococcus aureus (MRSA) : Methicillin-resistant Staphylococcus aureus (MRSA) is a multi-drug resistant Gram-positive bacteria, which causes skin infections, pneumonia, blood stream infections, and surgical site infections. Resistance occurs due to the presence of mecA gene that produces altered penicillin binding protein (PBP2a). MRSA is resistant to many β-lactams and is treated using vancomycin, linezolid, daptomycin, and ceftaroline.

Vancomycin-Resistant Enterococci (VRE): Vancomycin-resistant Enterococci (Enterococcus faecium and Enterococcus faecalis), are common nosocomial pathogens. Resistance is due to vanA and vanB genes, which alter targets in the bacterial cell wall. Vancomycin resistant Enterococci often cause urinary tract infections, bacteremia, and endocarditis. Linezolid, daptomycin, and tigec

Carbapenem-Resistant Enterobacterales (CRE) : Resistance against carbapenems by Enterobacterales encompasses the resistance shown by strains of Klebsiella pneumoniae, Escherichia coli, and Enterobacter species. The organisms produce

carbapenemases like KPC, NDM, and OXA-48, which makes carbapenem antibiotics ineffective against them. CRE causes life-threatening infections in the bloodstream, lungs, urinary tract, and abdominal cavity with high mortality rates. Novel β-lactam/β-lactamase inhibitor combinations are useful for the treatment.

Multidrug-Resistant Pseudomonas aeruginosa : Pseudomonas aeruginosa is a Gram-negative opportunistic pathogen, which possesses intrinsic and acquired antibiotic resistance capabilities to an amazing extent. Decreased membrane permeability, efflux pumps, β-lactamases, and biofilm formation are responsible for the multidrug resistance property. This organism causes common infections like ventilator

Multidrug-Resistant Acinetobacter baumannii : Acinetobacter baumannii is a multidrug-resistant Gram-negative bacteria that frequently affects patients in intensive care units. This bacterium is responsible for ventilator-associated pneumonia, bloodstream infections, wound infections, and meningitis. Resistance develops due to carbapenemases production, efflux pumps, porin loss, and biofilms formation. Newly available medications such as sulbactam-durlobactam and cefiderocol offer more treatment options.

Neisseria gonorrhoeae: Neisseria gonorrhoeae bacteria have become resistant to penicillins, tetracyclines, fluoroquinolones, and macrolides due to target modification and efflux pumps. The development of resistance to cephalosporins is a problem across the world. Unrecovered infection can result in infertility, pelvic inflammatory disease, and complications in infants. Ceftriaxone is the recommended initial drug for most uncomplicated gonococcal infections.

Mycobacterium tuberculosis : There are multidrug-resistant TB and extensively drug-resistant TB strains among the species of Mycobacterium tuberculosis, which are hard to cure. The reason for drug resistance is genetic modification, insufficient therapy, and lack of adherence. Long-term multidrug treatments are required. Recently released drugs such as bedaquiline, delamanid, and pretomanid have greatly increased success rates of treatment.

LIMITATIONS OF CONVENTIONAL ANTIBIOTICS

Increasing Antimicrobial Resistance : Inappropriate use of conventional antibiotics has led to an increase in the development of antibiotic resistance among many bacteria. Many bacteria have developed ways in which conventional antibiotics do not work, hence causing a reduction in the effectiveness of treatments. Treatment of resistant infections is hard and expensive due to the need for new or combination therapy of antibiotics.

Treatment Failure : Common antibiotics are ineffective in treating infections resulting from multidrug-resistant bacteria. The failure of bacteria to be cleared in time can result in recurrent infections, prolonged stays in hospitals, and even death. In critical situations, patients have to take repeated doses or combinations of antibiotics, thus complicating the management of infections.

Toxicity and Adverse Effects : The majority of conventional antibiotics have many side effects, especially with prolonged usage and high dosage. These side effects range from nephrotoxicity, hepatotoxicity, ototoxicity, gastrointestinal side effects, allergies, and C. difficile infection. These side effects could limit the duration of therapy and also cause problems for patients undergoing treatment.

Narrow Therapeutic Options

With the emergence of resistant bacteria, there has been a marked decrease in the efficacy of several first-line antibiotics. There is an increased dependency on some few reserve antibiotics that might not be easily available, expensive, or even have some adverse effects on the patient's health.

Limited Activity Against Biofilms : Common antibiotics have poor effectivity on bacteria residing in a biofilm. The extracellular matrix acts as a barrier to the entry of antibiotics and protection from the host defense mechanism of the body. Infections caused by biofilms such as infections of catheters, prosthetic joints, heart valves, and chronic wounds usually become chronic.

Slow Development of New Antibiotics : The rate of creation and development of new antibiotics has not been able to keep up with the rapid rise of antimicrobial resistance. The problems associated with science, long trials, cost, and lack of incentive have been some of the factors responsible for the reduced antibiotic pipeline. As a result, there is heavy reliance on currently available antibiotics.

EMERGING ANTIBIOTICS FOR MULTIDRUG-RESISTANT INFECTIONS

New Generation β-Lactam/β-Lactamase Inhibitor Combinations : The development of new β-

lactam/β-lactamase inhibitors has led to an improvement in the management of Gram-negative infections which are resistant to multiple drugs. β-lactam/β-lactamase inhibitors involve the combination of β-lactam antibiotic and a β-lactamase inhibitor, protecting the antibiotic from enzyme-mediated degradation. These antibiotics are useful for treating infections caused by carbapenemase-producing Enterobacterales and resistant Pseudomonas aeruginosa.

Novel Cephalosporins : The novel cephalosporins have improved activity against the resistant strains of Gram-positive and Gram-negative bacteria. The structural changes make these compounds more stable to the β-lactamases enzyme and increase their antibacterial range. Examples include ceftaroline, ceftobiprole, and cefiderocol, which show efficacy against MRSA, multidrug-resistant Enterobacterales, and Pseudomonas aeruginosa.

Novel Tetracycline Derivatives : The novel tetracycline analogs are effective against tetracycline resistance because they target resistance mechanisms like efflux pumps and ribosomal protection protein. The two new tetracyclines, eravacycline and omadacycline, are effective against multidrug-resistant Gram-positive, Gram-negative, anaerobic, and atypical bacteria. They offer a good therapy for complicated intra-abdominal infections, skin infections, and community-acquired bacterial pneumonia.

New Aminoglycosides : Plazomicin is one of the new aminoglycosides which have been designed to circumvent the resistance developed by aminoglycoside-modifying enzymes. The compound exhibits excellent effectiveness against multidrug-resistant Enterobacterales, which include a number of carbapenem-resistant strains as well. Plazomicin is mainly used in the management of complicated urinary tract infections, where other aminoglycosides are ineffective.

New Fluoroquinolones : The newly synthesized fluoroquinolones like delafloxacin and levonadifloxacin have greater antibacterial efficacy against the drug-resistant Gram-positive bacteria like MRSA and at the same time have wide Gram-negative coverage as well. The pharmacokinetics of these drugs allow them to be used in the treatment of various infections, including skin and respiratory infections.

Oxazolidinones : Novel oxazolidinones, like tedizolid and contezolid, target the 50S bacterial ribosome and thus affect protein synthesis in resistant Gram-positive pathogens, including MRSA and VRE. In comparison with linezolid, novel oxazolidinones provide an increased level of safety, less hematologic toxicity, and convenient administration for complicated infections.

New Lipoglycopeptides : Novel lipoglycopeptides, such as dalbavancin and oritavancin, have long half-lives and high efficacy in treatment of resistant Gram-positive pathogens. They block the bacterial cell wall synthesis and affect bacterial cell membrane integrity. Due to their prolonged administration intervals, they can be considered beneficial in treatment of acute bacterial skin and soft tissue infections.

Novel Pleuromutilins

Lefamulin is the first systemic pleuromutilin antibiotic approved for use in humans. Lefamulin inhibits bacterial protein synthesis via interaction with the 50S ribosomal subunit at a novel site, ensuring low cross-resistance with other antibiotics. Lefamulin shows antimicrobial effects against common respiratory microorganisms, such as Gram-positive pathogens and atypical pathogens causing community-acquired pneumonia.

New Siderophore Antibiotics : Cefiderocol is the first approved siderophore cephalosporin antibiotic that uses the iron transport systems of bacteria for its intracellular uptake. This is achieved through the Trojan horse mechanism, which promotes antibiotic transport and bypasses membrane impermeability. Cefiderocol shows excellent activity against carbapenem-resistant Gram-negative pathogens such as Pseudomonas aeruginosa, Acinetobacter baumannii, and Enterobacterales.

Emerging Polymyxin Alternatives : Alternative drugs to polymyxin class are being explored to retain high potency against MDR Gram-negative bacteria and decrease the nephrotoxicity and neurotoxicity of previous-generation polymyxins. Newly synthesized drugs like sulbactam-durlobactam and other drugs in the pipeline show better efficacy against carbapenem-resistant pathogens and may become an option for treatment of HAIs.

NOVEL DRUGS

Novel Drug	Drug Class	Primary Target Organisms	Main Clinical Indication
Ceftazidime–Avibactam	β-lactam/β-lactamase inhibitor	CRE, ESBL-producing Enterobacterales, Pseudomonas aeruginosa	Complicated UTI, cIAI, HAP/VAP
Meropenem–Vaborbactam	Carbapenem/β-lactamase inhibitor	KPC-producing CRE	Complicated UTI, severe Gram-negative infections
Imipenem–Cilastatin–Relebactam	Carbapenem combination	CRE, MDR Pseudomonas aeruginosa	HAP/VAP, cUTI, cIAI
Sulbactam–Durlobactam	β-lactam/β-lactamase inhibitor	Carbapenem-resistant Acinetobacter baumannii	Hospital-acquired and ventilator-associated pneumonia
Cefiderocol	Siderophore cephalosporin	Carbapenem-resistant Gram-negative bacteria	cUTI, HAP/VAP, bloodstream infections
Ceftobiprole	Fifth-generation cephalosporin	MRSA, Streptococcus pneumoniae	Community- and hospital-acquired pneumonia
Ceftaroline	Fifth-generation cephalosporin	MRSA, resistant Gram-positive pathogens	Skin infections, community-acquired pneumonia
Eravacycline	Fluorocycline	MDR Gram-positive, Gram-negative, anaerobes	Complicated intra-abdominal infections
Omadacycline	Aminomethylcycline	MRSA, VRE, atypical bacteria	Skin infections, community-acquired pneumonia
Plazomicin	Next-generation aminoglycoside	CRE, MDR Enterobacterales	Complicated urinary tract infections
Delafloxacin	Fluoroquinolone	MRSA, Gram-negative bacteria	Acute bacterial skin infections, pneumonia
Levonadifloxacin	Benzoquinolizine fluoroquinolone	MRSA, quinolone-resistant Gram-positive bacteria	Skin infections, diabetic foot infections, pneumonia
Tedizolid	Oxazolidinone	MRSA, VRE	Acute bacterial skin infections
Contezolid	Oxazolidinone	Resistant Gram-positive bacteria	Skin and soft tissue infections
Dalbavancin	Lipoglycopeptide	MRSA, Streptococci	Acute bacterial skin and soft tissue infections
Oritavancin	Lipoglycopeptide	MRSA, VRE	Acute bacterial skin infections
Lefamulin	Pleuromutilin	MRSA, atypical respiratory pathogens	Community-acquired bacterial pneumonia
Aztreonam–Avibactam	Monobactam/β-lactamase inhibitor	Metallo-β-lactamase-producing Enterobacterales	Complicated Gram-negative infections
Cefepime–Enmetazobactam	Cephalosporin/β-lactamase inhibitor	ESBL-producing Enterobacterales	Complicated urinary tract infections
Zosurabalpin*	Novel antibacterial (investigational)	Carbapenem-resistant Acinetobacter baumannii	Severe MDR Acinetobacter infections (clinical trials)
Gepotidacin*	Triazaacenaphthylene antibiotic	Drug-resistant Neisseria gonorrhoeae, uropathogens	Gonorrhea, uncomplicated urinary tract infections
Nafithromycin*	Ketolide	Drug-resistant respiratory pathogens	Community-acquired bacterial pneumonia

EMERGING NON-TRADITIONAL ANTIBACTERIAL THERAPIES

Bacteriophage Therapy : Bacteriophage therapy involves the use of viruses that can specifically attack and kill bacteria without affecting human cells and other microorganisms. These phages only reproduce inside their specific bacteria, which makes them very selective in nature. This form of therapy has gained importance in treating infections caused by

multidrug-resistant bacteria and is under study as a replacement for traditional antibiotics.

Antimicrobial Peptides : Antimicrobial peptides are compounds synthesized by humans, animals, plants, and microorganisms, playing an important role in the innate immune system. These compounds can kill bacteria through the disruption of the membrane of the bacteria and inhibition of their physiological processes. Resistance to these antimicrobial compounds is less likely.

CRISPR-Based Antimicrobials : CRISPR antimicrobial therapy employs the use of gene editing techniques to specifically target and eliminate bacterial genes associated with resistance or the DNA itself. As opposed to other antibiotics, this method is specifically designed to destroy only the bacteria that exhibit resistance while keeping useful bacteria intact.

Monoclonal Antibodies : Monoclonal antibodies target and protect through binding to particular toxins or proteins on bacteria. They do not kill bacteria but increase immunity and block bacteria from causing harm. They can lower the intensity of diseases, improve health results, and work well with antibiotics in infections caused by drug-resistant bacteria.

Nanotechnology-Based Antibiotics : Antibiotics can be administered using nanotechnology-based antimicrobials, which help in delivering the antibiotics better, in addition to making them more stable and increasing their permeation through infections and biofilms. The nanocarriers help in releasing the antibiotics right where the infection is found, thus reducing their toxicity in the body and increasing their antibacterial effectiveness.

Probiotics : Probiotics are defined as useful microorganisms that facilitate the preservation of the normal microbial flora and the inhibition of growth of any harmful bacteria. The probiotics work through production of antimicrobials, competition for resources, and strengthening of host immunity. Probiotics can lower recurrent infections and assist in the action of antibiotics.

Microbiome-Based Therapeutics : Therapeutics based on microbiome seek to treat disruptions in the natural balance of microorganisms caused by either antibiotics or diseases by restoring them to their previous state. Through the re-balancing of the microbiota, these treatments can prevent the proliferation of any resistant pathogens and boost host immunity.

Anti-Virulence Drugs : The anti-virulence medications prevent the virulent traits such as toxins, adhesion proteins, or secretion mechanisms from working in bacteria and hence reduce their pathogenicity without directly eliminating the bacteria. This method reduces the likelihood of generating drug resistance while at the same time enabling the body's immune system to kill the infection.

Quorum Sensing Inhibitors

Quorum-sensing inhibitors inhibit the cellular communication networks in bacteria responsible for controlling biofilm development, toxin secretion, and bacterial virulence. This, in turn, helps decrease bacterial virulence and makes the bacteria more susceptible to antibiotics. Such inhibitors have been studied for their ability to serve as co-treatments for chronic bacterial infections.

CHALLENGES IN DEVELOPING EMERGING ANTIBIOTICS

Scientific Challenges : The development of new antibiotics is scientifically challenging due to the continuous mutation of bacteria into resistant forms. It is not easy to find new targets for bacteria that will not be resistant. Besides, the new antibiotics should have the capability of killing bacteria while not affecting the body cells.

Clinical Trial Challenges : Evaluating new antibiotics is done through large and properly designed clinical trials for determination of efficacy and safety. It can be hard to find patients that have certain multidrug resistance infections since such infections are rare in nature and different in various parts of the world. Regulations, time period involved and costs also hinder their approval.

Regulatory Challenges : The approval process for new antibiotics is quite an intensive one that entails an assessment of quality, safety, and efficacy of the antibiotic. This requires extensive research conducted in laboratories and animals as well as clinical trials at different stages. The different regulations governing approval processes in different countries make drug development a costly process.

Economic Challenges : The development of any antibiotic entails huge costs incurred over a long period of time, but the monetary gain that would be realized is often minimal. Antibiotics are different from other medicines which are meant for treating diseases that require continuous treatment. This low commercial value deters drug manufacturers from engaging in antibiotic development.

Rapid Emergence of Resistance

Even newly developed antibiotics could become ineffective in the future due to resistance that bacteria can develop very quickly by mutating or obtaining resistance genes. Improper or excessive use will lead to faster development of antibiotic resistance and reduce the effective period for which the new drug will remain useful.

Limited Pharmaceutical Investment : Numerous drug developers have decreased spending on antibiotic research owing to high costs of development, low-profit margins, and growing regulatory demands. Hence, the worldwide antibiotic pipeline is currently smaller than that of other medical areas. Increased investments and incentives from governments will be necessary to spur further development of antibiotics.

Accessibility in Low- and Middle-Income Countries : Many of the newly approved antibiotics are still out of reach in developing nations owing to expensive prices, scarcity, weak healthcare systems, and slow approval processes. Poor access is a key factor responsible for health disparities and the continued use of old antibiotics. It is vital that these antibiotics become affordable and widely available.

FUTURE PERSPECTIVES

The future of antibiotic therapy will rest on innovations that will help tackle the ever-evolving problem of MD-resistant bacteria. Breakthroughs in molecular biology, genomics, artificial intelligence, and drug discovery are making it easier to discover new antibiotics with a unique mode of action. The antibiotics of the future will be acting through pathways in bacteria which have never been targeted by existing antibiotics. This will ensure that resistance is minimized and cross-resistance will not occur. In addition to this, precision medicine, rapid molecular diagnostic testing, and genome sequencing will allow for quick identification of the resistant bacteria and selection of the best antibiotic therapy.

Apart from the development of new antibiotics, emerging methods of combating the resistant bacteria will also include the adoption of innovative techniques like bacteriophage therapy, antimicrobial peptides, monoclonal antibodies, CRISPR antimicrobials, anti-virulence compounds, and nanotechnology-based drug delivery systems. These techniques have the capability to supplement the existing antibiotic treatments, provide better results, and help avoid the development of resistance. The improvement of global monitoring systems, partnership between private and public sectors, and provision of financial support to antibiotic discovery will go a long way in restoring the research pipeline for antibiotics. Access to new antibiotics in low- and middle-income countries, along with infection prevention and antibiotic stewardship, will become equally critical in the process.

CONCLUSION:

Multidrug-resistant bacteria have become increasingly prevalent across the world, thereby making antimicrobial resistance one of the leading public health threats of the 21st century as it reduces the efficacy of many conventional antimicrobial medications. Despite the fact that the rate at which bacteria develop resistance still exceeds that of the development of new drugs against these pathogens, new developments in antibiotic research have led to a number of novel antibiotics that show promise in overcoming the problem of resistance. The combination of these novel antibiotics along with non-conventional methods of therapy, including bacteriophage therapy, antimicrobial peptides, CRISPR technologies, monoclonal antibodies, and nanotechnology-mediated drug delivery systems, offer some potential solutions to this challenging public health issue.

Nevertheless, future success of new antibiotics lies in the rational use of these drugs. Antimicrobial stewardship programs, adoption of fast diagnosis methods, implementation of infection prevention and control measures, and constant research of antibiotics is of utmost importance in order to ensure the efficiency of these newly introduced drugs. Cooperation between physicians, scientists, pharmaceutical industries, government bodies and public health institutions will be vital in solving problems of antimicrobial resistance. Only a comprehensive strategy involving scientific progress along with sensible antibiotic usage can contribute to a solution of this serious problem.

REFERENCES:

1. Muteeb G, Rehman MT, Shahwan M, Aatif M. Origin of Antibiotics and Antibiotic Resistance, and Their Impacts on Drug Development: A Narrative Review. Pharmaceuticals (Basel). 2023 Nov 15;16(11):1615
2. Marino A, Maniaci A, Lentini M, Ronsivalle S, Nunnari G, Cocuzza S, Parisi FM, Cacopardo B, Lavalle S, La Via L. The Global Burden of Multidrug-Resistant Bacteria. Epidemiologia (Basel). 2025 May 5;6(2):21
3. Machado E, Sousa JC. New Antibiotics for Treating Infections Caused by Multidrug-Resistant Bacteria. Antibiotics (Basel). 2025 Oct 5;14(10):997.

4. Tang KWK, Millar BC, Moore JE. Antimicrobial Resistance (AMR). Br J Biomed Sci. 2023 Jun 28;80:11387.
5. Galgano M, Pellegrini F, Catalano E, Capozzi L, Del Sambro L, Sposato A, Lucente MS, Vasinioti VI, Catella C, Odigie AE, et al. Acquired Bacterial Resistance to Antibiotics and Resistance Genes: From Past to Future. *Antibiotics*. 2025; 14(3):222
6. Nazir A, Nazir A, Zuhair V, Aman S, Sadiq SUR, Hasan AH, Tariq M, Rehman LU, Mustapha MJ, Bulimbe DB. The Global Challenge of Antimicrobial Resistance: Mechanisms, Case Studies, and Mitigation Approaches. Health Sci Rep. 2025 Jul 23;8(7):e71077.
7. Reygaert WC. An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiol. 2018 Jun 26;4(3):482-501.
8. Temesgen AB, Shiferaw SA. Antimicrobial Multidrug Resistance and Mechanisms of Action: An Overview. Biomed Res Int. 2025 Nov 25;2025:8847267.
9. Munita JM, Arias CA. Mechanisms of Antibiotic Resistance. Microbiol Spectr. 2016 Apr;4(2):10.1128/microbiolspec.VMBF-0016-2015.
10. Lopatkin AJ, Sysoeva TA, You L. Dissecting the effects of antibiotics on horizontal gene transfer: Analysis suggests a critical role of selection dynamics. Bioessays. 2016 Dec;38(12):1283-1292
11. Ali Alghamdi B, Al-Johani I, Al-Shamrani JM, Musamed Alshamrani H, Al-Otaibi BG, Almazmomi K, Yusnoraini Yusof N. Antimicrobial resistance in methicillin-resistant staphylococcus aureus. Saudi J Biol Sci. 2023 Apr;30(4):103604.
12. Ibrahim S, Al-Saryi N, Al-Kadmy IMS, Aziz SN. Multidrug-resistant Acinetobacter baumannii as an emerging concern in hospitals. Mol Biol Rep. 2021 Oct;48(10):6987-6998
13. Chavada J, Muneshwar KN, Ghulaxe Y, Wani M, Sarda PP, Huse S. Antibiotic Resistance: Challenges and Strategies in Combating Infections. Cureus. 2023 Sep 26;15(9):e46013
14. Yahav D, Giske CG, Grāmatniece A, Abodakpi H, Tam VH, Leibovici L. New β-Lactam-β-Lactamase Inhibitor Combinations. Clin Microbiol Rev. 2020 Nov 11;34(1):e00115-20. doi: 10.1128/CMR.00115-20. Erratum in: Clin Microbiol Rev. 2021 Jan 27;34(2):e00021-21
15. Koulenti D, Xu E, Song A, Sum Mok IY, Karageorgopoulos DE, Armaganidis A, Tsiodras S, Lipman J. Emerging Treatment Options for Infections by Multidrug-Resistant Gram-Positive Microorganisms. *Microorganisms*. 2020; 8(2):191
16. Ito A, Nishikawa T, Matsumoto S, Yoshizawa H, Sato T, Nakamura R, Tsuji M, Yamano Y. Siderophore Cephalosporin Cefiderocol Utilizes Ferric Iron Transporter Systems for Antibacterial Activity against Pseudomonas aeruginosa. Antimicrob Agents Chemother. 2016 Nov 21;60(12):7396-7401.
17. Venuti F, Romani L, De Luca M, Tripiciano C, Palma P, Chiriaco M, Finocchi A, Lancella L. Novel Beta Lactam Antibiotics for the Treatment of Multidrug-Resistant Gram-Negative Infections in Children: A Narrative Review. *Microorganisms*. 2023; 11(7):1798
18. Durkin MJ, Corey GR. New developments in the management of severe skin and deep skin structure infections - focus on tedizolid. Ther Clin Risk Manag. 2015 May 22;11:857-62.
19. Lin DM, Koskella B, Lin HC. Phage therapy: An alternative to antibiotics in the age of multi-drug resistance. World J Gastrointest Pharmacol Ther. 2017 Aug 6;8(3):162-173.
20. Latif A, Shehzad A, Niazi S, Zahid A, Ashraf W, Iqbal MW, Rehman A, Riaz T, Aadil RM, Khan IM, Özogul F, Rocha JM, Esatbeyoglu T, Korma SA. Probiotics: mechanism of action, health benefits and their application in food industries. Front Microbiol. 2023 Aug 17;14:1216674. doi: 10.3389/fmicb.2023.1216674. Erratum in: Front Microbiol. 2024 Feb 14;15:1378225.
21. Muteeb G, Rehman MT, Shahwan M, Aatif M. Origin of Antibiotics and Antibiotic Resistance, and Their Impacts on Drug Development: A Narrative Review. *Pharmaceuticals*. 2023; 16(11):1615.
22. Sharma S, Chauhan A, Ranjan A, Mathkor DM, Haque S, Ramniwas S, Tuli HS, Jindal T, Yadav V. Emerging challenges in antimicrobial resistance: implications for pathogenic microorganisms, novel antibiotics, and their impact on sustainability. Front Microbiol. 2024 Apr 29;15:1403168
23. Giacobbe DR, Grossi AA, Bassetti M, de la Fuente-Nunez C. The Future of Antibiotics and Artificial Intelligence: Some Thoughts from Discovery to Bedside. Infect Dis Ther. 2026 Feb;15(2):461-475.