REVIEW ARTICLE

Innovative Strategies to Combat Antimicrobial Resistance: Advances in Drug Discovery, Alternative Therapies and Immune Modulation

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Abstract

The escalating threat of drug-resistant microorganisms poses a significant challenge to global health, necessitating an urgent and comprehensive review of current strategies and innovations aimed at combating antimicrobial resistance (AMR). AMR not only undermines the effectiveness of existing antibiotics but also complicates treatment protocols, leading to increased morbidity, mortality, and healthcare costs. This review explores the latest advancements and methodologies being developed to address this critical issue, highlighting the multifaceted approaches essential for maintaining the efficacy of antimicrobial therapies. A major focus of current work is to review the discovery and development of novel antibiotics with unique mechanisms of action. Noteworthy examples include teixobactin, which targets Gram-positive bacteria by disrupting cell walls, and Lefamulin, a pleuromutilin effective against drug-resistant *Streptococcus pneumoniae*. In addition, Zoliflodacin and Cefiderocol represent promising candidates for treating infections caused by *Neisseria gonorrhoeae* and Gram-negative bacteria, respectively. Despite these advancements, the development of new antibiotics is fraught with challenges, such as the complexity of clinical trials, the need for combination therapies, and the risk of rapid resistance development. Bacteriophage therapy and engineered lysins offer alternative approaches to traditional antibiotics by specifically targeting bacterial pathogens and minimizing collateral damage to beneficial microbiota. Similarly, combination therapies, which employ multiple antibiotics with distinct mechanisms, aim to enhance treatment efficacy and mitigate resistance. Examples such as trimethoprim–sulfamethoxazole and beta-lactam/beta-lactamase inhibitor combinations illustrate the effectiveness of this strategy. Immune modulation represents another innovative approach, leveraging the body's natural defenses to combat infections. Techniques include the use of immunomodulatory compounds, such as interferon-gamma and granulocyte-colony stimulating factor, and the development of vaccines targeting drug-resistant strains. Monoclonal antibodies, such as bezlotoxumab and altastaph, target specific bacterial toxins and proteins, offering precise and effective treatment options. Nanoparticles, with their ability to disrupt microbial membranes and deliver targeted drug therapies, present a versatile and potent means of combating infections. However, the antimicrobial research faces significant limitations, including the scarcity of novel antibiotic discoveries, the rapid development of resistance, and the economic and regulatory challenges associated with drug development. To address these issues, a coordinated international effort is essential, akin to the Montreal Protocol for chlorofluorocarbons, to manage the evolution of resistance and sustain the efficacy of antimicrobial therapies. In conclusion, the fight against drug-resistant microorganisms requires

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a multifaceted and innovative approach, integrating new drug discoveries, alternative therapies, immune modulation, and international cooperation.

Key words: Drug development, drug-resistance, health care, micro-organisms

INTRODUCTION

The rise of drug resistance represents one of the most significant challenges to global public health anticipated in the coming decades.[1] This phenomenon undermines the efficacy of treatments for infections that were once severe or fatal before the advent of antimicrobial therapies, consequently threatening advancements in surgery, cancer therapy, and immunosuppression that rely on effective infection management.[2] Over billions of years, through countless generations, microbes-including bacteria, mycobacteria, parasites, fungi, and viruses-have evolved mechanisms to shield themselves from harm and transfer these protective traits to other microorganisms, even across species. The rapid increase in antimicrobial resistance (AMR) observed in the 20th and 21st centuries can be attributed to these robust evolutionary processes, exacerbated by human activities such as the extensive production and use of antimicrobial drugs.[3]

Resistance varies in severity; low levels can often be countered with higher doses or prolonged treatment durations. The impact of resistance is also influenced by the availability of alternative treatments; when second-line drugs are accessible, initial resistance to first-line drugs may seem less alarming. However, the recent emergence of strains of key pathogens that exhibit high levels of resistance to nearly all available treatments (such as extensively drug-resistant tuberculosis [TB] and pan-resistant Gram-negative bacteria) poses a critical public health threat.[4] Addressing drug resistance involves ethical considerations due to the significant role of human actions and omissions in its development, the substantial and unevenly distributed impact on human health and well-being, and the need to balance policies aimed at reducing resistant pathogens with other ethical considerations, risks, burdens, and benefits. This review seeks to delve into the ethical dimensions of drug resistance, emphasizing its complex causes and serious consequences, and demonstrating how ethical and conceptual analysis can inform and enhance policy responses. Additionally, this chapter connects these discussions with the broader themes explored in this volume and suggests future directions for ethicists, empirical scientists, and public health policymakers.

NOVEL DRUGS FOR RESISTANCE

The development of drug resistance is influenced by numerous factors, including the increased use of antibiotics and antimalarials, lax regulation of drug prescriptions, poor adherence to treatment regimens, improper dosing, insufficient infection control measures, and the growing frequency and speed of travel, which contribute to the rapid dissemination of resistant organisms. Additionally, there is often a lack of motivation for patients, healthcare providers, or governments to address the rising resistance.[5] It is crucial to distinguish between the factors that lead to the emergence of resistance and those that contribute to the spread of existing resistance.[6]

Understanding the molecular basis of resistance can indicate how likely it is for resistance to develop. For example, if a single mutation in DNA can cause resistance, this type of resistance is likely to become prevalent, especially if the mutation carries a low biological effect.[7] *De novo* or acquired resistance results in the emergence of a resistant strain in an individual patient. This strain can then be transmitted to others, leading to cases of primary resistance from the start of infection.[8] This process contributes to the prevalence of multidrug-resistant bacteria or TB (MDR-TB) through independent, cumulative events.[9] A similar mechanism applies to antimalarials; resistance arises when drug concentrations are sufficient to eliminate susceptible parasites but fail to stop the multiplication of naturally resistant strains. Commonly used antimalarial drugs do not cause mutations.[10]

For many years, even when the rise of drug resistance was recognized, the response from clinicians and policymakers was often based on an unfounded belief that new antimicrobial drugs would be developed, making resistance to older drugs less significant. Despite early warnings, the excessive use of antimicrobials continued and even increased in humans, animals, and agriculture.[11] The restricted use of new antimicrobials as "reserve" agents, while potentially slowing the emergence of resistance, creates disincentives for profit-driven research and development of new antimicrobials.[12] As a result, few new antibiotic classes or agents have been developed in recent decades. To encourage more relevant research and development, greater public effort and funding may be necessary, along with realigning pharmaceutical companies' incentives to make profit-making more compatible with developing products critical to global public health.[13]

New drugs (or other treatments/prevention methods) are urgently needed for infections that have become nearly pan-resistant, such as extensively drug-resistant TB and multi-resistant Gram-negative bacteria.[14] Compared to other responses targeting specific causal pathways (e.g., prescription restrictions or agricultural use limitations), new drugs offer a comprehensive solution

to drug resistance by addressing the issue regardless of its specific mechanisms.[15] However, policymakers and patients cannot rely solely on new drugs to solve the problem of drug resistance because (i) the development of new antimicrobial drugs has been slow and relatively unsuccessful in recent decades, (ii) the underlying challenges of drug development have proven difficult to overcome, and (iii) without other measures to curb the rise of drug resistance, we face an ongoing need to find new drugs. Therefore, addressing drug resistance requires a multifaceted and global policy response that is also tailored to the specific issues and mechanisms of resistance in a particular microbe and context.[16]

ANTIBIOTIC RESISTANCE

Drug-resistant infections

Drug-resistant infections arise when pathogens adapt in ways that make antimicrobial drugs ineffective, allowing the pathogens to survive and proliferate. Antimicrobials have been crucial in treating infections and containing their spread, saving hundreds of millions of lives since their widespread adoption over 70 years ago.[17] However, the increasing loss of drug efficacy due to AMR is becoming a significant issue in both developed and developing countries. If this trend continues unchecked, many infectious diseases may become untreatable, posing a severe global health crisis.[18]

Antibiotic resistance in bacteria

The rise in antibiotic resistance worldwide is severely compromising the effectiveness of standard antibiotics against common bacterial infections. The 2022 Global AMR and use surveillance system report highlights concerning resistance rates among key bacterial pathogens.[19] For instance, median resistance rates in many countries are reported over 50% for third-generation cephalosporin-resistant *Escherichia coli* and methicillin-resistant *Staphylococcus aureus* (MRSA).[20] In 2020, 1 in 5 urinary tract infections caused by *E. coli* showed reduced susceptibility to commonly used antibiotics such as ampicillin, co-trimoxazole, and fluoroquinolones (FQs), complicating treatment efforts.[21] *Klebsiella pneumoniae*, a bacterium commonly found in the gut, has also exhibited increased resistance to critical antibiotics. This trend may lead to greater reliance on last-resort drugs like carbapenems, for which resistance is also rising in several regions.[22] As these essential drugs lose their effectiveness, the risk of untreatable infections grows. According to the Organization for Economic Cooperation and Development, resistance to last-resort antibiotics is expected to double by 2035 compared to 2005 levels, highlighting the urgent need for stringent antimicrobial stewardship and enhanced global surveillance.[23]

Fungal drug resistance

The increase in drug-resistant fungal infections is also concerning, prompting WHO to monitor their prevalence and public health impact. Treating fungal infections can be particularly challenging due to potential drug–drug interactions, especially in patients with other infections like human immunodeficiency virus (HIV).[24] The emergence and spread of multi-drug-resistant *Candida auris*, an invasive fungal pathogen, is especially troubling.[25] The WHO's Fungal Priority Pathogens List development included an extensive review of global fungal infections and resistance patterns.[26]

Resistance in HIV, TB, and malaria

HIV drug resistance (HIVDR) arises from genetic changes in HIV that reduce the efficacy of antiretroviral (ARV) drugs. This resistance can be transmitted at infection or acquired through poor adherence to treatment or drug-drug interactions, leading to increased HIV infections and related morbidity and mortality.[27] WHO advises routine HIVDR surveys to guide the optimal selection of ARV regimens for prevention and treatment. TB significantly contributes to AMR. MDR-TB, resistant to isoniazid and rifampicin-the two most potent first-line TB drugs-poses a public health crisis. MDR-TB is treatable with second-line drugs, but these are costly, toxic, and sometimes lead to further drug resistance.[28,29] TB that resists the most effective second-line drugs leaves patients with limited treatment options. In 2022, majority of those with drug-resistant TB received effective treatment.[30]

The rise of drug-resistant parasites is a significant challenge for malaria control. Artemisinin-based combination therapies (ACTs) are the first-line treatment for uncomplicated *Plasmodium falciparum* malaria and are widely used in endemic regions.[31] The emergence of partial resistance to artemisinin and partner drugs complicates treatment choices and necessitates close monitoring. Since 2001, partial resistance to artemisinin or its analogs has been confirmed in several countries within the Greater Mekong Subregion.[31,32] In the eastern region of Sudan, resistance to sulfadoxine–pyrimethamine has led to treatment failures, prompting a switch to alternative therapies.[33] In Africa, mutations associated with artemisinin partial resistance have been detected in several countries.[34] While tested ACTs remain effective, the spread of resistance poses a significant public health challenge, underscoring the need for improved surveillance.

Drug resistance in neglected tropical diseases (NTDs)

Drug resistance threatens control, elimination, and eradication programs for NTDs, which disproportionately affect

vulnerable populations.[35] Resistance has been reported in treatments for leprosy (dapsone, rifampicin, and clofazimine) in several countries, as well as in anti-helminthics (resistance observed in animals, posing concerns for human use), and in drugs for human African trypanosomiasis (melarsoprol) and leishmaniasis (pentavalent antimonials, miltefosine).[36-40] Monitoring resistance and drug efficacy, implementing strategies to delay or curb resistance, and strengthening the development pipeline for second-line NTD medications are crucial. WHO provides guidance for resistance surveillance in global leprosy elimination programs and supports the controlled distribution, standardized use, safety, and efficacy monitoring of medicines, including those donated for NTD programs.[41]

MECHANISMS OF DRUG RESISTANCE

Antibiotics fundamentally alter the biochemistry and physiology of microbial cells to inhibit their growth or induce cell death. They achieve this by targeting various cellular processes, such as cell wall synthesis, protein synthesis, and nucleic acid synthesis. For instance, some antibiotics disrupt cell walls by targeting β-lactam and glycopeptide components, while others inhibit protein synthesis by binding to ribosomal units. Common antibiotics affecting cell walls include aminoglycosides, tetracyclines, linezolid, chloramphenicol, and macrolides. In contrast, antibiotics like rifampin and FQs target nucleic acid synthesis and other cellular machinery. Further, antibiotics such as folic acid analogs, daptomycin, polymyxins, and sulfonamides interfere with metabolic pathways and disrupt cell membrane integrity [Table 1].[42]

Research indicates that the evolution of antibiotic resistance mechanisms can lead to cross-resistance among antibiotics and other substances. MDR bacteria, for example, may develop resistance to a broad range of chemical compounds unrelated to antibiotics, including quaternary ammonium compounds, sodium dodecyl sulfate, ethidium bromide, acridine, and uncouplers. This multidrug resistance affects bacterial physiology and provides resistance to various metabolic byproducts, such as bile acids. Some biological functions contributing to antibiotic resistance remain unidentified, further complicating treatment efforts [Figure 1].[43]

Drug inactivation or modification

Some bacteria have evolved the ability to neutralize or modify antimicrobial agents, rendering them ineffective. A prime example is the production of β-lactamases by certain penicillin-resistant bacteria. These enzymes break the β-lactam ring found in Penicillin G and other β-lactam antibiotics, which is crucial for their bactericidal activity. By deactivating this ring, the antibiotic is rendered harmless,

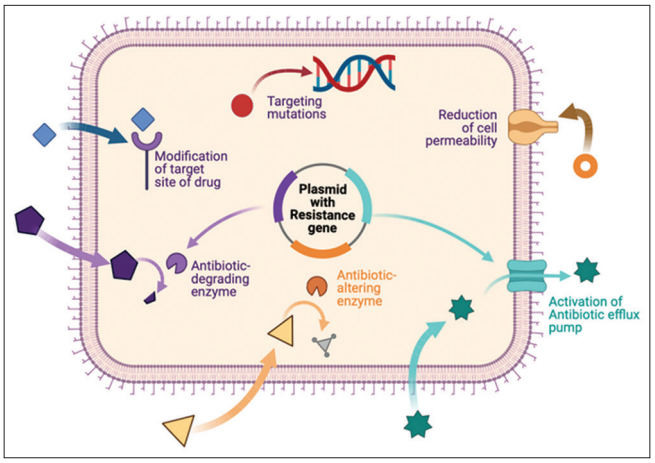

Figure 1: Mechanisms of antibiotic resistance

allowing the bacteria to survive and proliferate despite the presence of the drug.[44]

Alteration of the target site

Antibiotics typically function by binding to specific targets within bacterial cells. However, bacteria can alter these target sites through mutations, reducing the binding affinity of the antibiotic. For instance, MRSA and other penicillin-resistant bacteria modify their penicillin-binding proteins (PBPs), which are the targets of penicillins. These alterations prevent the antibiotic from effectively binding to the PBPs, thereby negating its ability to disrupt cell wall synthesis and kill the bacteria.[45]

Alteration of metabolic pathway

Some bacteria can develop resistance by altering their metabolic pathways to bypass the step targeted by the antibiotic. Sulfonamides, for example, inhibit the synthesis of folic acid by competing with para-aminobenzoic acid (PABA). However, certain sulfonamide-resistant bacteria have acquired the ability to utilize preformed folic acid from their environment instead of synthesizing it from PABA. This adaptation allows them to continue producing essential nucleic acids and proteins even in the presence of sulfonamides, which would otherwise inhibit their growth.[46]

Reduced drug accumulation

Bacteria can also resist antibiotics by limiting the intracellular concentration of the drug. This can be achieved through two main strategies: decreasing drug permeability and increasing drug efflux. Decreased permeability involves altering the bacterial cell membrane or cell wall to prevent the drug from entering the cell. On the other hand, increased efflux involves the use of efflux pumps, which actively expel the antibiotic from the cell, reducing

Table 1: Overview of mechanism of action (MoA) and drug resistance in various antimicrobial drugs

Mechanism	Antimicrobial agent	Drug action	Mechanism of resistance	References
Drug inactivation/ modification	Aminoglycosides	Binds to the 30S ribosomal subunit, inhibiting protein synthesis	Plasmid-encoded enzymes chemically alter the drug (e.g., through acetylation or phosphorylation), inactivating it.	[42]
	Beta-lactam antibiotics (penicillin and cephalosporins)	Bind to penicillin-binding proteins, inhibiting peptidoglycan synthesis	Plasmid-encoded beta-lactamases open the beta-lactam ring, inactivating the drug.	[45]
	Chloramphenicol	Binds to the 50S ribosomal subunit, inhibiting peptide bond formation	Plasmid-encoded enzymes acetylate the drug, rendering it inactive.	[42]
Alteration of drug targets	Aminoglycosides	Binds to the 30S ribosomal subunit, inhibiting protein synthesis	Bacteria produce altered 30S ribosomal subunits that do not bind the drug.	[42]
	Beta-lactam antibiotics (penicillin and cephalosporins)	Bind to penicillin-binding proteins, inhibiting peptidoglycan synthesis	Bacteria produce altered penicillin-binding proteins that do not bind the drug.	[45]
	Erythromycin	Binds to the 50S ribosomal subunit, inhibiting protein synthesis	Bacteria produce a modified 50S ribosomal subunit that does not bind the drug.	[42]
	Quinolones	Bind to DNA topoisomerase, essential for DNA synthesis	Bacteria produce altered DNA topoisomerases that do not bind the drug.	[21]
	Rifampicin	Binds to RNA polymerase, inhibiting initiation of RNA synthesis	Bacteria produce altered RNA polymerases that do not bind the drug.	[29]
	Trimethoprim	Inhibits dihydrofolate reductase, blocking the folic acid pathway	Bacteria produce altered dihydrofolate reductase enzymes that do not bind the drug.	[42]
Inhibits drug entry or removes drug	Penicillin	Bind to penicillin-binding proteins, inhibiting peptidoglycan synthesis	Bacteria alter outer membrane porin proteins, preventing drug entry.	[45]
	Erythromycin	Binds to the 50S ribosomal subunit, inhibiting protein synthesis	Bacteria develop new membrane transport systems that prevent drug entry.	[42]
	Tetracycline	Binds to the 30S ribosomal subunit, inhibiting protein synthesis by blocking tRNA	Bacteria develop new membrane transport systems that actively pump the drug out of the cell.	[42]

its intracellular concentration to sub-lethal levels. Together, these mechanisms prevent the drug from reaching its target site in sufficient quantities to be effective. Each of these mechanisms reflects the adaptive strategies bacteria employ to survive in the presence of antimicrobial agents. Understanding these mechanisms is crucial for developing new strategies to combat antibiotic resistance and ensure the continued efficacy of existing treatments.[47]

STRATEGIES AGAINST DRUG-RESISTANCE

The escalating threat of drug-resistant bacteria has prompted significant research and innovation among scientists and healthcare professionals. Addressing this critical issue requires a multifaceted approach, integrating advanced methodologies and strategies. Recent efforts in combating

antibiotic resistance have focused on diverse techniques, including bio-nanotechnology, combinatorial drug therapies, and other innovative methods. The widespread emergence of AMR is increasingly compromising the efficacy of existing antibiotics and treatment protocols, with far-reaching consequences across social, economic, medical, and ecological domains [Table 2].

Bio-nanotechnology

Nanoparticles

Engineered nanoparticles, such as silver and gold nanoparticles, exhibit potent antibacterial properties and can enhance the delivery and effectiveness of existing antibiotics. Nanotechnology also facilitates the development of novel diagnostic tools for detecting resistant strains.[48]

Nanocarriers

These systems improve the bioavailability and controlled release of antibiotics, potentially overcoming barriers to drug penetration in resistant bacteria.

Combinatorial drug therapies

Synergistic combinations

Combining antibiotics with adjuvants or other drugs can enhance their efficacy. For instance, β-lactamase inhibitors are used in conjunction with β-lactam antibiotics to restore their effectiveness against resistant strains.[49]

Dual or triple therapy

Administering multiple drugs simultaneously can reduce the likelihood of resistance development by targeting different bacterial pathways.

Alternative therapeutic approaches

Bacteriophage therapy

Utilizing bacteriophages to specifically target and destroy drug-resistant bacteria offers a promising alternative to traditional antibiotics.

Antimicrobial peptides

These naturally occurring peptides exhibit broad-spectrum activity against bacteria, including resistant strains, and are being explored as new therapeutic agents.[50]

Targeted drug design

Structure-based drug design

Advanced computational techniques are used to design drugs that specifically target resistant bacterial enzymes or altered cellular targets.

High-throughput screening

This method allows for the rapid identification of new compounds with potential activity against resistant pathogens.[51]

Table 2: Strategies for combating the antibiotic resistance

Strategy	Safety	Efficacy	Commercial Viability	References
Novel antibiotics	Broad spectrum activity; potential microbiome disruption and side effects	Effective against many infections; resistance reduces efficacy	Established market; resistance, long development, and low profits impact viability	[55-58]
Antimicrobial peptides	Generally safe; minimal toxicity; concerns at high doses	Effective against some strains; ongoing development	Potential viability with further research and development	[50]
Probiotics	Generally safe; risk for immunocompromised individuals	Effective for certain infections; efficacy varies	Commercial traction in dietary supplements and functional foods; needs investment for infection targeting	[58]
Bacteriophages	Generally safe; minimal side effects	Variable efficacy; phage-specific	Potential viability with ongoing research and investment	[59]
Phage therapy	Generally safe; minimal side effects	Variable efficacy; depends on specificity and research	Increasing interest and investment with ongoing studies	[59]
Monoclonal antibodies	Highly safe; minimal side effects	Effective in targeting specific pathogens; reduces infection risks	Costly R and D; potential regulatory challenges	[60]
Nanoparticles	Long-term safety needs evaluation	Effective against some strains; ongoing development	High-quality production is costly, affecting commercial viability	[61]

Improved antibiotic stewardship

Optimal use guidelines

Developing and implementing stringent guidelines for antibiotic use helps to prevent misuse and overuse, which contributes to resistance.

Education and awareness

Increasing awareness among healthcare providers and patients about the risks of antibiotic resistance and the importance of adhering to prescribed treatments.[52]

Monitoring and surveillance

Resistance tracking

Enhanced surveillance systems are critical for tracking the emergence and spread of resistant strains, informing treatment protocols, and guiding public health responses.[53]

Genomic surveillance

Analyzing the genetic makeup of resistant bacteria can provide insights into resistance mechanisms and facilitate the development of targeted therapies.

Environmental management[54]

Waste management

Proper disposal of antibiotics and reducing their environmental contamination can help mitigate the development of resistance in environmental bacteria.

Agricultural practices

Restricting the use of antibiotics in agriculture and veterinary medicine can reduce the selection pressure on bacteria, slowing the spread of resistance.

Novel antibiotics

Researchers are continually developing new antibiotics to combat drug-resistant bacteria, an essential task in the fight against growing AMR. A notable discovery is teixobactin, identified in 2015, which effectively targets a broad spectrum of drug-resistant Gram-positive bacteria by disrupting bacterial cell walls, thus reducing the likelihood of resistance.[55] Lefamulin, approved by the Food and Drug Administration in 2019, is another innovative antibiotic used to treat community-acquired bacterial pneumonia, including drug-resistant *Streptococcus pneumoniae*, by inhibiting bacterial protein synthesis.[56] Zoliflodacin, from the spiroketone class, is being studied for its effectiveness against drug-resistant *Neisseria gonorrhoeae* by targeting DNA replication.[57] Cefiderocol, a siderophore cephalosporin, has shown significant efficacy against drug-resistant Gram-negative bacteria, including carbapenem-resistant Enterobacteriaceae, by disrupting bacterial cell walls and aiding iron uptake.[58]

Bacteriophages

Bacteriophages, viruses that infect bacteria, utilize lysins to break down bacterial cell walls, leading to bacterial death. Engineered lysins show promise against specific bacterial strains, including antibiotic-resistant ones, although challenges like lysin resistance and potential side effects from bacterial toxin release remain. Phage therapy, which involves using specific phages to treat bacterial infections, has been successful in treating antibiotic-resistant infections, especially in regions with a history of phage use. However, the need for tailored treatments, phage stability, and regulatory hurdles pose challenges.

Combination therapies

Combining multiple antibiotics is a promising strategy to enhance treatment efficacy and prevent antibiotic resistance. For example, Trimethoprim-Sulfamethoxazole isrupts bacterial folate synthesis, proving effective against a range of infections, including MRSA. Beta-lactam/beta-lactamase inhibitor combinations, such as ampicillin/sulbactam and piperacillin/tazobactam, allow beta-lactam antibiotics to remain effective against beta-lactamase-producing organisms.

Immune modulation

Immune modulation aims to boost the immune response to enhance bacterial infection clearance, addressing antibiotic resistance by fortifying the body's natural defenses. Strategies include using immunomodulatory compounds like cytokines (e.g., interferon-gamma) and interleukins to activate macrophages and combat infections. Vaccination against specific bacterial pathogens has significantly reduced the prevalence of drug-resistant infections, while immunostimulants like granulocyte-colony stimulating factor enhance white blood cell production to fight infections more effectively.[59]

Antibody therapies

Monoclonal antibodies nd antibody-derived molecules target bacterial pathogens, offering precise and targeted treatment methods. For instance, Bezlotoxumab, approved for preventing recurrent Clostridium difficile infections, binds to the toxin B, reducing infection risk. Altastaph, targeting *S. aureus*, neutralizes the pathogen, addressing MRSA infections. Innovative approaches include lysibodies, which target a broad spectrum of bacteria, and antibody-toxin conjugates,

such as those targeting *Pseudomonas aeruginosa*, offering promising alternatives to conventional antibiotics.[60,62]

Nanotechnology

Nanoparticles have emerged as promising antimicrobials with diverse mechanisms of action. They can disrupt microbial cell membranes, release ions that interfere with DNA replication, generate reactive oxygen species and inhibit biofilm formation. Nanoparticles can also be used for drug delivery, enhancing drug stability and bioavailability. However, challenges include ensuring biocompatibility, high production costs, regulatory hurdles, and environmental impact concerns.[61]

CHALLENGES IN NOVEL ANTIBIOTIC DEVELOPMENT

Therapeutic strategy

Antibiotics aim to halt bacterial growth or survival by targeting DNA/RNA synthesis, protein synthesis, or cell wall maintenance. However, as bacteria evolve, they develop mechanisms to resist these drugs. The use of antibiotics as a "last resort" or in high dosages is sometimes necessary to combat MDR microorganisms. Biofilm-associated infections further complicate treatment, often requiring aggressive physical removal and high-dose antibiotic therapy. The associated risks of adverse effects, resistance, and treatment failure contribute to high costs in drug development.

Research insufficiency

Literature reports that 42 new antibiotics are in various stages of development. However, only 13 of these are expected to reach the market.[63] Many new antibiotics are either reformulations of existing drugs or lack novel mechanisms of action, limiting their effectiveness against resistant pathogens. Only 31% of these drugs target ESKAPE pathogens, whereas 33% might address immediate-danger pathogens identified by the Centers for disease control.[64]

Economic factors

Major pharmaceutical companies have largely exited the antibiotic market, focusing instead on more lucrative therapeutic areas. Small and medium-sized enterprises have attempted to fill this gap but often lack the resources for extensive research and development. The costly and challenging task of developing new antibiotics with innovative mechanisms remains largely unmet.

Development progress

According to the infectious diseases society of America (2013), the number of antibiotics in advanced stages of development is limited.[65] Efforts are more focused on Gram-negative pathogens like Enterobacteriaceae, *P. aeruginosa*, and *Acinetobacter baumannii*, rather than on MRSA. This shift reflects the urgent need for effective treatments against rapidly spreading resistance.

Cost and time

Developing a new antibiotic is a costly and lengthy process, often requiring some millions and sometimes billions of dollars and over a decade of research. Given the urgency of combating antibiotic resistance, alternative strategies are being explored, such as preventing infections and developing new therapeutic approaches.[66]

CONCLUSION

Modern medicine's efficacy hinges on the availability of effective anti-infective drugs. However, the inevitable consequence of drug use is the selective pressure that leads the development of resistance. This growing resistance poses a significant threat to public health globally especially when the infections are concerned. Sustaining our ability to treat infections requires substantial investment in both extending the therapeutic life of existing drugs and discovering new ones. Immediate interventions, such as improved infection control, affordable vaccines, and proper dosing, can provide immediate benefits to patients. Simultaneously, long-term strategies, like developing combination treatments and investing in novel drug discovery, are essential for future resilience against resistant pathogens. The development of new antibiotics and antimicrobial drugs faces several challenges, including complex clinical trials, and the rise of antibiotic-resistant bacteria. In conclusion, without a sustainable, long-term vision and novel solutions to combat resistance, our ability to control infectious diseases is at risk. Governments and international bodies must prioritize and coordinate efforts to ensure that the effectiveness of current and future anti-infective treatments is preserved.

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