MULTIPLE ANTIBIOTIC RESISTANCE: CURRENT PARADIGMS AND FUTURE OUTLOOKS

Abstract

Multiple antibiotic resistance (MAR) in microorganisms poses a significant threat to human health and is a global public health concern. MAR refers to the ability of bacteria to withstand the effects of multiple antimicrobial agents such as antibiotics, rendering traditional treatment ineffective. The key mechanisms of MAR, include efflux pumps, target site alterations, enzymatic inactivation, and biofilm formation. The clinical and economic consequences of MAR emphasize the need for collaborative efforts to address this issue. Herein we explore promising approaches, such as metagenomics, microarrays, proteomics, artificial intelligence/ machine learning, combination therapies, novel drug development, and the use of alternative antimicrobial agents, highlighting the importance initiatives to combat MAR effectively.

Keywords: Multiple Antibiotics Resistance, ESKAPE, Artificial Intelligence (AI), Meta Genomics and Proteomics.

Authors

Ankita Pandey
Department of Microbiology
School of Life Sciences & Biotechnology
CSJM University, Kanpur.

Ashish Kumar Awasthi
Department of Microbiology
School of Life Sciences & Biotechnology
CSJM University, Kanpur.

Puneet Kumar Jha
Department of Microbiology
School of Life Sciences & Biotechnology
CSJM University, Kanpur.

Shilpa Deshpande Kaistha
Department of Biotechnology
School of Life Sciences & Biotechnology
CSJM University, Kanpur.

I. INTRODUCTION

Multiple Drug resistance (MDR) patterns exhibited by some microorganisms to antimicrobial drugs including multiple antibiotics, antifungal, antiviral, and anti-parasitic drugs(Saha & Sarkar, 2021). The statistics of infections caused by MDR bacteria show that the insensitiveness of bacteria toward antimicrobial agents has raised many folds in recent years (Yang et al., 2021). Healthcare providers are faced with a big dilemma because MDR reduces the efficacy of current treatments, making it more challenging to treat infections and disorders. Several reports have emphasized that the resistance faced by antimicrobials is a big risk to human health globally. One of the biggest risks to public health in the twenty-first century is bacterial antimicrobial resistance (AMR), which also refers to bacteria that are resistant to multiple antibiotic treatment. According to reports, AMR may become more lethal than cancer in less than 30 years and may kill 10 million people annually by the year 2050 (Cui et al., 2021)**.**

The ability of bacteria to exhibit an antagonistic action against antibiotic is referred to as Multiple Antibiotic Resistance (MAR) (Pietsch et al., 2021). It happens when bacteria change and adapt in a way that lessens or totally overcomes their susceptibility to the antibiotics that are intended to kill or prevent their growth. Antibiotics are a class of antimicrobial chemical substance produced by a microorganism, which is detrimental to the growth or replication of other microorganisms. Six classical mechanism of action (MOA) categories for antibiotics include: inhibitors of DNA replication (DNA synthesis [DS] and DNA gyrase [DG]), RNA synthesis [RS], protein synthesis (50S [PS50] or 30S [PS30] subunit inhibitors), cell wall biosynthesis (CW), cell membrane biosynthesis (CM), and fatty acid synthesis (FAS) (Sagar et al., 2019). Most bacteria will acquire different mechanism of combating antibiotic modes of action. Multiple Drug Resistance (MDR) is defined as the ability of bacteria to show resistance to 3 or more classes of antibiotics. Pan Drug Resistance (PDR) refers to the ability of bacteria to show resistance to 5 or more classes of antibiotics(Abbasi, Amin & Ozma, Mahdi Asghari, 2022). Multiple antibiotic-resistant bacterial infections must be prevented and treated immediately as bacterial antibiotic resistance spreads.

As per World Health Organization (WHO) six bacterial species together known as ESKAPE infections are known for their capacity to "escape" the effects of antimicrobial medications (Idris & Nadzir, 2023). Numerous antibiotics are no longer effective against these pathogens, which include *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter species,* posing serious problems in healthcare facilities and the general public. It is essential to comprehend and address the multidrug resistance demonstrated by these ESKAPE pathogens if antibiotics are to continue to be effective in treating bacterial illnesses. Recently on 14 April 2023, the second "Surveillance of antimicrobial resistance in Europe" report, published jointly by the European Centre for Disease Prevention and Control (ECDC) and WHO/Europe, shows high percentages of resistance to last-line antibiotics, such as carbapenems, in several countries of the WHO European Region. Other priority organisms showing AMR include VR Staphylococcus aureus, (European Centre for Disease Prevention and Control. & World Health Organization., 2023).

An overview of the MAR classification, mechanisms underlying MAR, the implications for healthcare and society, and potential strategies for combating this emerging challenge are presented.

II. MULTIPLE ANTIBIOTIC RESISTANCE

Multiple antibiotic resistance describes a microorganism's capacity to withstand the effects of multiple antibiotics, which makes it challenging to treat. Medical professionals face serious challenges as a result of this since pathogen bacteria can cause more severe infections that may not be responsive to standard antibiotic therapy. Antibiotics function by focusing on particular bacterial processes. For example β-lactams, inhibit cell wall synthesis, aminoglycosides inhibit protein synthesis, and glycopeptides inhibit cell wall synthesis (Table 1). Bacteria can become resistant to antibiotics in a number of ways (C Reygaert, 2018). They can produce enzymes that modify the antibiotic, they can mutate the genes that encode the target of the antibiotic, or they can develop efflux pumps that expel the antibiotic from the cell. Table 1 shows the different classes of antibiotics, their mechanism of action, and the resistance mechanisms that bacteria can use to become resistant to them. It also provides examples of antibiotics in each class(Mlynarczyk-Bonikowska et al., 2022).

Table 1: Classes of Antibiotics and Their Mode of Actions

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Class of Antibiotic	**Mechanism of Action**	**Resistance Mechanism**	**Select Example**
β lactam	Inhibit Cell Wall Synthesis	Beta-lactamases, modification of penicillin binding proteins (PBPs), efflux pumps and membrane impermeability	Ampicillin (AMP), Amoxicillin (AMX), Dicloxacillin (DCX)
Aminoglycoside	Inhibit Protein Synthesis	Modification of antibiotic by acylation, phosphorylation or adenylation.	Kanamycin (KM), Streptomycin (STP)
Glycopeptide	Inhibit Cell Wall Synthesis	Target modification	Vancomycin
Lipopeptides	Depolarize Cell Membrane	To modify cell surfaces and electrostatic repulsion of the daptomycin calcium complex from the cell surfaces	Daptomycin
Macrolides	50S ribosomal subunit. Inhibits protein synthesis. Bacteriostatic.	Target modification, mutations in 23S rRNA, efflux pumps and enzymatic inactivation.	Erythromycin (ERI)
Sulphonamides	Inhibit Metabolic Pathways	Resistant forms of DHPS enzymes, mutations in dhp gene.	Sulfamethoxazole (SMX)

Tetracycline's	Inhibit Protein Synthesis	Efflux, ribosomal protection and enzymatic inactivation.	Tetracycline (TET)
Fluoroquinolones	Inhibit Nucleic Acid Synthesis	Target modification, efflux pumps.	Ciprofloxacin (CIP), Moxifloxacin
Trimethoprim	Inhibits folate synthesis, dihydrofolate reductase (DHFR).	Resistant forms of the DHFR enzyme. Mutations in gene promoter and upstream genetic elements lead to overexpression of intrinsic DHFR enzyme.	Trimethoprim (TMT)

III. CLASSIFICATION OF MULTIPLE ANTIBIOTIC RESISTANCE (MAR)

Resistance mechanisms can be divided into two categories: acquired and intrinsic mechanisms, which relate to the integral and inherent characteristics of bacteria (Tanwar et al., 2014). MAR can occur due to various factors such as genetic mutations that result in changes to the target DNA allowing them to resist the effects of certain drugs. These mutations can occur spontaneously or be acquired from other resistant organisms(Bale et al., 2023). Bacteria can acquire resistance genes from other bacteria through horizontal gene transfer. This mechanism enables the spread of resistance traits, including those encoding for drug efflux pumps, enzymes that inactivate antibiotics, or alterations in target sites. Misuse and overuse of antibiotics or antivirals can contribute to the emergence of multiple drug. When medications are used inappropriately, such as for viral infections or when not completing the full course of treatment, it creates selective pressure that favours the survival and growth of resistant strains (Terreni et al., 2021). Hospitals, healthcare facilities and inappropriate environmental disposal of biomedical wat can serve as reservoirs for MAR organisms. Factors such as prolonged hospital stays, invasive procedures, and extensive use of antibiotics can promote the selection and transmission of resistant strains.

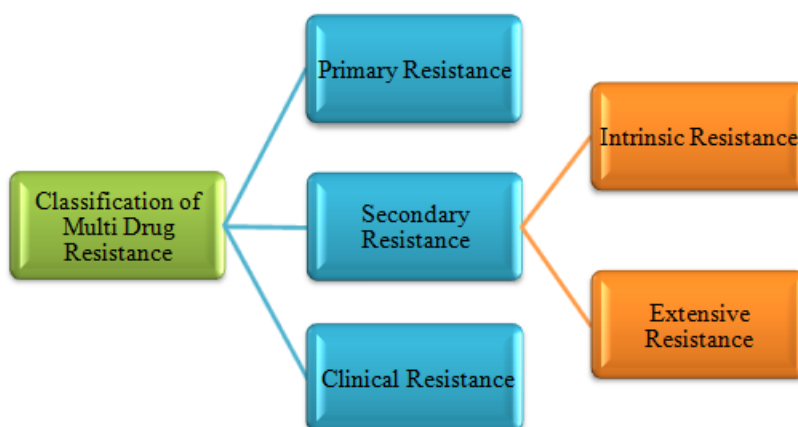Multiple antibiotic resistance in bacteria can be further classified in the following types

Figure 1: Classification of Multi Antibiotic Resistance

1. **Primary Resistance:** Primary resistance simply refers to the fact that some bacteria are inherently less susceptible to specific drugs. It occurs when the organism has never come into contact with the drug of interest in a certain host. The presence of it in bacterial populations without prior selecting pressure from antibiotic use is due to genetic causes. The main resistance to the antibiotic isoniazid in *M. tuberculosis* due to genetic changes in the katG gene. Due to their fundamental resistance, the bacteria are inherently less vulnerable to isoniazid, a crucial medicine in the treatment of tuberculosis (Bhering & Kritski, 2020).

2. **Secondary Resistance:** This term, which is also used to refer to "acquired resistance," is used to indicate resistance that only develops in an organism after a drug exposure. Bacteria can acquire resistance through methods including genetic mutations or the horizontal gene transfer of resistance genes. By acquiring plasmids containing genes expressing fluoroquinolone resistance, Uropathogenic *E. coli* that were previously sensitive to the antibiotic ciprofloxacin can develop secondary resistance (Chegini et al., 2021). Secondary resistance can be further classified into two types:

   - **Intrinsic Resistance:** The efficacy of antibiotics is significantly hampered by intrinsic resistance. Intrinsic resistance, as contrast to acquired resistance, refers to characteristics of bacterial species or strains that make them inherently less vulnerable to specific antibiotics. Acquired resistance is gained by genetic alterations or horizontal gene transfer. Understanding the whole bacterial MDR landscape and creating powerful anti-antibiotic resistance methods require an understanding of the mechanisms of intrinsic resistance(Sadhana Sagar et al., 2019c). Since it happens in species that have never been susceptible to that particular medicine, this is also known as "insensitivity." *Pseudomonas aeruginosa,* gram negative nosocomial pathogen known to exhibit MAR as innate mechanisms that the bacteria have. The existence of efflux pumps is a crucial component of *Pseudomonas aeruginosa's* intrinsic resistance mechanism (Pang et al., 2019).

   - **Extensive Resistance:** MAR can develop as a result of the buildup of several resistance mechanisms, such as efflux pumps, target site modifications, enzymatic inactivation, and decreased drug accumulation. The phrase "extensive resistance" emphasizes the breadth and intricacy of the bacteria's resistance. *Staphylococcus aureus,* which is the cause of many infections, including those of the skin and the bloodstream (Mlynarczyk-Bonikowska et al., 2022). MRSA strains of *Staphylococcus aureus* frequently show considerable resistance to a number of antibiotic classes, including β-lactams like penicillins and cephalosporins (Sagar, Sadhana et al., 2019b).

3. **Clinical Resistance:** It describes the circumstance in which bacterial infections in a clinical context do not respond to antibiotic treatment. Numerous factors including insufficient antibiotic dosage, poor patient compliance, and the existence of additional complicating issues such weakened immune systems can contribute to clinical resistance. Vancomycin, a last-resort medication for treating life-threatening infections, can cause clinical resistance in some strains of the bacteria *Enterococcus faecium.* Clinical resistance may develop as a result of the spread of the VanA gene cluster, which modifies the shape of bacterial cell walls and lowers vancomycin binding, making it less efficient at treating infections brought on by these strains (Sengupta et al., 2023).

IV. MULTIPLE ANTIBIOTICS RESISTANCE MECHANISM AT CELLULAR AND MOLECULAR LEVEL

Recent developments in genomics and transcriptomics have led to better understanding microbial genetics and the processes for genetic modification that a new perspective to the ingenious resistance mechanisms devised as pathogenicity traits (Table 2). The structural and functional understanding of these mechanisms opens up doors for the development of strategies to overcome antibiotic resistance. The different mechanisms for antibiotic resistance are described herewith:

Table 2: Mechanisms for Antibiotic Resistance

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Mechanism	**Bacteria**	**Target**	**References**
Efflux Pumps	*Pseudomonas aeruginosa, Escherichia coli*	MexAB-OprM, AcrAB-TolC	(Nishino et al., 2021)
Target Site Alterations	Methicillin-resistant *Staphylococcus aureus* (MRSA), Erythromycin-resistant *Streptococcus pneumoniae*	Altered penicillin-binding proteins (PBPs), Altered ribosomal target sites	(Saha & Sarkar, 2021)
Enzymatic Inactivation	*Escherichia coli, Klebsiella pneumoniae, Enterobacter spp.*	β-lactamases, Extended-spectrum β-lactamases (ESBLs), New Delhi metallo-β-lactamase (NDM-1)	(Sagar, Sadhana et al., 2019)
Reduced Drug Accumulation	*Acinetobacter baumannii, Pseudomonas aeruginosa*	Impermeable outer membrane	(Bharadwaj et al., 2022)
Horizontal Gene Transfer	*Enterobacteriaceae* carrying extended-spectrum β-lactamase (ESBL) genes	Extended-spectrum β-lactamase (ESBL) genes, Carbapenemase genes	(Parmanik et al., 2022)

1. **Efflux Pump:** Efflux pumps are complex protein networks that are present in bacterial cell membranes and are essential in the development of MAR (Huang et al., 2022). Antibiotics and other toxic compounds are actively transported out of the bacterial cell by these pumps, lowering their intracellular concentration. These pumps help to reduce drug buildup and reduce the efficacy of antimicrobial therapy by effluxing antibiotics. The resistance-nodulation-division (RND) family, the major facilitator superfamily (MFS), and the ATP-binding cassette (ABC) superfamily are just a few of the families into which efflux pumps are divided (Sharma et al., 2019). Bacteria can expel a variety of antibiotics and other hazardous compounds because to the various efflux pump systems found in each family, each of which has specificities for a particular kind of substrate. The MexAB-OprM pump in *Pseudomonas aeruginosa* is a model of the RND family (Nishino et al., 2021). This pump is in charge of ejecting a wide variety of antibiotics, including as

β-lactams, fluoroquinolones, and aminoglycosides, resulting in the development of resistance to numerous drug classes.

2. **Target Site Alterations:** Target site modifications are changes to the cellular structures that antibiotics are meant to attack. These changes might lessen the affinity or ability of antibiotics to bind to their targets. These modifications, which increase antibiotic resistance and reduce antibiotic efficiency, can be brought about by genetic mutations or differences in the target proteins' expression. Methicillin-resistant *Staphylococcus aureus* (MRSA) has target site modification. Penicillin-binding proteins (PBPs), which are the targets of β-lactam antibiotics, are changed in MRSA strains. These modified PBPs are less vulnerable to the inhibitory effects of β-lactam antibiotics due to their decreased affinity for them(Saha & Sarkar, 2021). *Streptococcus pneumoniae* may contain modifications to the ribosomal target site that limit effective binding of macrolide antibiotics (Cillóniz et al., 2018).

3. **Enzymatic Inactivation:** Through this process, bacteria develop enzymes that alter or break down antibiotics, making them useless. These substances are frequently referred to as β-lactamases because they break down the β-lactam ring present in many medicines, such as penicillins and cephalosporins. Extended-spectrum β-lactamases (ESBLs), which have an increased spectrum of action against a wider range of β-lactam antibiotics, are one form of β-lactamase that bacteria can create. The β-lactamases produced by *Escherichia coli, Klebsiella pneumoniae,* and *Enterobacter spp.* are a few examples of clinically significant β-lactamases. The New Delhi metallo-β-lactamase (NDM-1), which imparts resistance to a wide variety of β-lactam antibiotics, including carbapenems, is another example. The spread of MDR is facilitated by enzymatic inactivation by β-lactamases, which is a substantial obstacle in the treatment of bacterial infections(Sagar, Sadhana et al., 2019).

4. **Reduced Drug Accumulation:** Mechanisms that restrict antibiotic uptake or boost antibiotic efflux from bacterial cells reduce drug accumulation by lowering drug concentrations inside the cells. These pathways play a part in the multidrug resistance and decreased effectiveness of antibiotics. The outer membrane of gram-negative bacteria serves as a selective barrier, preventing the entry of antibiotics into the cell. These bacteria are less likely to accumulate drugs due to their impermeable outer membrane and the presence of particular porins with restricted permeability for particular antibiotics. For instance, due to their impermeable outer membranes, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are reported to demonstrate lower drug accumulation (Bharadwaj et al., 2022). Bacteria can increase the efflux of antibiotics through efflux pump systems, as was previously mentioned, in addition to reducing their uptake. Antibiotic intracellular concentrations are aggressively pumped out of the bacterial cell by efflux pumps, which increases multidrug resistance.

5. **Horizontal Gene Transfer:** It is a significant way through which bacteria pick up resistance genes from other bacteria, particularly those that code for multidrug resistance. Through this method, resistance characteristics can spread quickly within bacterial populations, even between distinct species or genera. Plasmids, transposons, and integrons are only a few of the many pathways that can lead to horizontal gene transfer (Mlynarczyk-Bonikowska et al., 2022). These genetic components contain resistance

genes and are easily transmitted from one bacterium to another. As a result, bacteria can develop resistance to a variety of antibiotics, even ones they may not have previously been exposed to. For instance, extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* can spread these genes to other bacterial species or strains, imparting resistance to a variety of -lactam drugs. Similar to this, the horizontal transfer of carbapenemase genes might result in the formation of carbapenem-resistant *Enterobacteriaceae* (CRE) (Parmanik et al., 2022). The spread of multidrug resistance is considerably aided by horizontal gene transfer, which also makes it difficult to effectively treat infections with antibiotics and prevent their occurrence.

6. **Biofilm Formation:** Biofilms are stress resistance community growth forms wherein residents secrete extracellular polysaccharide (EPS) matrix that prevents the entry of antibiotic compound. When compared to equivalent bacteria residing in a planktonic condition, bacteria living in biofilms can exhibit 10- to 1,000-fold higher levels of antibiotic resistance (Baptista et al., 2018). 100% of the isolates in a research looking at *Staphylococcus epidermidis* drug resistance in biofilms were sensitive to the antibiotic vancomycin when tested in a planktonic state (Oliveira et al., 2021). When examined from biofilms, however, over 75% of them were totally resistant to the same antibiotic. Similar trends have been seen for species like *Klebsiella pneumoniae*, which test out as sensitive to particular antibiotics in aqueous solutions but rapidly develop high resistance to those same drugs when tested out in biofilms (Ndagi et al., 2020). The various EPS components combine to diminish or entirely block the efficacy of antibiotics and create resistance in the biofilm. Persistence is the ability of organisms to endure in biofilms in the presence of high antibiotic concentrations due to the interaction of several processes.
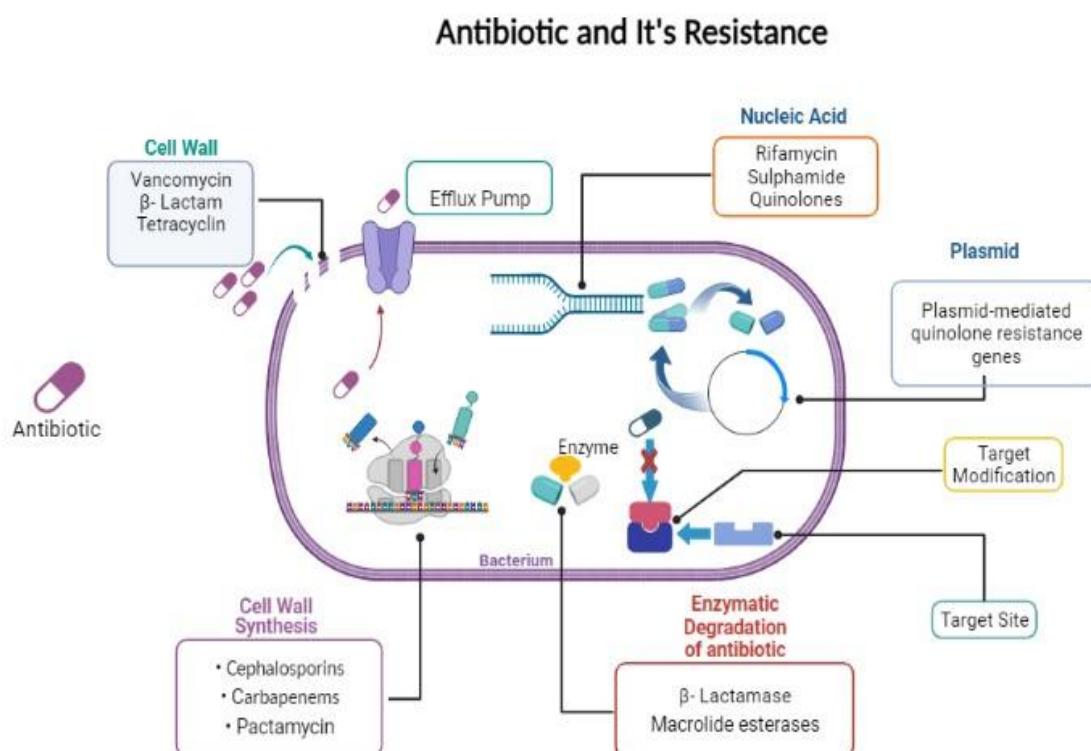

Figure 2: Mechanism of Multiple Antibiotic Resistance (MAR*)*

V. STRATEGIES FOR COMBATING MAR

1. **Understanding New Drug Targets using Metagenomics and Proteomics:** Metagenomics and proteomics have revolutionized our understanding of microbial communities and the mechanisms underlying MAR (Chen et al., 2020). High throughput technologies such as microarrays, next generation sequencing, metagenomics enable the comprehensive study of microbial genetic material and protein expression patterns in complex environments. By analyzing the resistome and proteome of MAR pathogens, researchers gain insights into the genetic basis of resistance and potential targets for drug development (Pillay et al., 2022).

2. **Nanotechnology and Targeted Drug Delivery Systems:** Nanotechnology offers innovative approaches for combating MAR by facilitating targeted drug delivery to specific sites of infection(Sadhana Sagar et al., 2019d). Nano-sized drug carriers can improve drug penetration, increase drug stability, and enhance the therapeutic efficacy of antimicrobial agents against MDR pathogens. These targeted delivery systems hold promise in overcoming drug resistance and reducing the side effects associated with systemic antibiotic administration (Hetta et al., 2023).

3. **Predictive Modeling and Artificial Intelligence:** Predictive modeling and artificial intelligence (AI) play a significant role in understanding and predicting patterns of MAR in bacterial pathogens. These technologies analyze vast amounts of data, including genomic information, epidemiological data, and antimicrobial usage, to identify trends and potential mechanisms of resistance. Predictive modeling and AI can aid in the early detection of emerging MDR strains and guide antimicrobial stewardship efforts(Lv et al., 2021).

4. **Combination Therapy:** Combination therapy is a method of treating MAR infections that involves combining two or more antibiotics with various modes of action. Combination therapy can increase treatment effectiveness and lower the risk of resistance development by attacking the bacteria via numerous mechanisms (Jones et al., 2022). When dealing with bacteria that have developed numerous resistance mechanisms, this strategy is especially helpful. Combination therapy can also help to improve the effectiveness of treatment and prolong the shelf life of already available antibiotics.

5. **Novel Drug Development:** In order to overcome MAR, new antibiotics with different modes of action must be developed. The goal of research is to develop novel medications that target particular bacterial weaknesses while avoiding established resistance mechanisms. The arsenal of current antibiotics is widened by innovative medication development, such as rationale drug designing which also offers efficient alternatives to fight developing MAR infections (Nyerges et al., 2020)**.**

6. **Alternative Antimicrobial Agents:** Alternative antimicrobial agents, such as bacteriophages, antimicrobial peptides, and monoclonal antibodies, are being investigated for their potential to treat MDR infections in addition to conventional antibiotics (Mousavi et al., 2021). Bacteriophages are viruses that attack and eradicate particular bacteria, providing a focused strategy (Rogovski et al., 2021). Small proteins that are found in nature called antimicrobial peptides have strong antibacterial capabilities.

Monoclonal antibodies have the ability to prevent the attachment of bacteria to host cells or neutralize bacterial toxic substances. Through the use of various mechanisms to attack bacterial infections, these alternative medicines demonstrate promise in the fight against MDR(Sagar, Sadhana et al., 2019a).

7. **Surveillance and Stewardship Programs:** MAR control requires strong surveillance and antimicrobial stewardship programs. In order to spot new MAR strains and hotspots of resistance, surveillance entails tracking the presence and trends of antimicrobial resistance (World Health Organization, 2019). Antimicrobial stewardship initiatives seek to optimize therapeutic strategies while promoting appropriate antibiotic use and avoiding needless prescriptions. These initiatives aid in reducing the selection pressure that fuels the emergence and spread of resistance, protecting the effectiveness of currently available antibiotics.

VI. CLINICAL AND SOCIETAL IMPLICATIONS OF MAR

The first WHO regional assessment on health and economic impact of antimicrobial resistance (AMR), emphasizes the importance of prioritizing strategies for treating MAR with due diligence (World Health Organization, 2023). The significant clinical and societal implications of MAR infections are presented below:

1. **Treatment Failures and Increased Morbidity:** Multiple antibiotic resistance (MAR) of bacterial pathogens leads to treatment failure as standard antibiotic therapy becomes ineffective against infections caused by these resistant strains. This can lead to longer sickness for infected people, more severe symptoms, and increased morbidity. Patients with MAR infections may require alternative, more expensive antibiotics, resulting in longer hospital stays and higher medical costs. Furthermore, delayed or ineffective treatment of MAR infections can lead to high complication rates and adverse clinical outcomes (VANESSA study group, on behalf of the Australasian Society for Infectious Diseases (ASID) Clinical Research Network (CRN) et al., 2018).

2. **Spread of Resistant Strains:** MAR bacteria can spread within health care facilities and communities, posing a significant public health threat, and infected individuals can become carriers of resistant strains, facilitating transmission to others at risk. The rapid spread of MAR strains, especially in densely populated areas and areas with inadequate infection control measures, could lead to epidemics, further straining public health resources and containment efforts.

3. **Economic Burden:** The economic burden of MAR is high, affecting both health systems and society. Healthcare costs are rising due to the increased use of expensive alternative antibiotics, longer hospital stays and the need for additional medical interventions. In addition, infection can lead to lost productivity and income as individuals and caregivers are unable to work due to prolonged illness or care for sick family members. The economic impact of MAR goes beyond healthcare costs and can have far-reaching effects on society.

4. **Impact on Healthcare Systems:** MAR poses significant challenges to the healthcare system. Additional resources such as laboratory testing, isolation facilities, and dedicated

infection control measures are required to manage MAR infections. Healthcare facilities must implement strict protocols to prevent the spread of her MAR strain among patients and healthcare workers. MAR burden impacts care capacity, patient flow and overall efficiency, and can lead to increased waiting times and delays in elective procedures.

Table 3: Factors Contributing to the Rise in Multiple Antibiotic Resistance

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S.no	Factors	Detail	Possible Solutions
1.	Overuse and misuse of antibiotics	• Inappropriate antibiotic prescribing and use • Using antibiotics for viral infections • Using antibiotics without proper medical supervision • Livestock and agricultural activities contribute to over-consumption of	• Awareness and Surveillance Campaigns • Strict Regulatory Framework around antibiotic usage/ over the counter sales • Strict Regulatory Laws for Antibiotic disposal
2.	Lack of development of new antibiotics	• Slow development of new antibiotics • Limited investment in research and development • The scientific challenge of finding new antibiotics • Increasing resistance beyond finding effective new drugs	• Investments in innovative and collaborative research for discovery of alternative treatment regimen • Incentives for intellectual property rights and industries in using modified bioproducts
3.	Inadequate infection control practices	• Poor sanitary conditions • Gaps in infection prevention and control procedures • Transmission of MAR bacteria in healthcare settings • Community spread of resistant organisms	• Emphasis on hygiene • Increased regulation related to infection, sanitization, biohazard waste disposal, airventings in hospital settings • Appropriate prescription/ use of antibiotics

VII. CHALLENGES AND FUTURE OUTLOOKS

The rapid evolution of MAR poses challenges for healthcare systems, researchers, and policymakers. However, it also presents opportunities for collaboration, innovation, and the implementation of preventive strategies. Global cooperation and interdisciplinary approaches are crucial in addressing MAR effectively. Addressing MAR requires collaborative efforts involving healthcare professionals, researchers, policymakers, and the public. Multidisciplinary research, sharing of data and knowledge, and international cooperation are key to combating MAR and preserving the effectiveness of antimicrobial agents. Public awareness and education campaigns are essential in promoting responsible antimicrobial use,

infection prevention, and understanding the consequences of MAR. Empowering individuals to make informed decisions can contribute to the global fight against MAR.

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