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Review Article

Antimicrobial resistance and its possible implications in the future: a mini review

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ABSTRACT

The emergence of antimicrobial resistance (AMR) among different species of microbes, or infectious agents, has become a major public health concern worldwide. This alarming trend is due to the rapid development of new resistance mechanisms and the decreasing effectiveness of treating common infectious diseases. As a result, standard treatments often fail to elicit a proper microbial response, leading to prolonged illness, increased healthcare costs, and a higher risk of mortality. Many infectious agents, including bacteria, fungi, viruses, and parasites, have developed high levels of multidrug resistance, resulting in increased morbidity and mortality rates, and being called as "superbugs." While the development of MDR is a natural process, it is exacerbated by the inappropriate use of antimicrobial drugs, inadequate sanitary conditions, improper food handling, and subpar infection prevention and control practices. Given the importance of AMR, this paper enlists the AMR issue along with its significance, mechanism and its possible impact in the future. The creation of innovative treatments to fight these persistent infections should be made easier by a better strategy of educating the population about the drivers of AMR.

Keywords: AMR, MDR, Microbes, Infectious disease, Future

INTRODUCTION

Microbial infections have significantly increased during the last few decades. Several strains of microbes have developed resistance as a result of the usage of antimicrobial medications to treat infections. When a microorganism is insensitive or resistant to an administered antimicrobial medicine despite previous sensitivity to it, it is referred to as multidrug resistance (MDR).[1,2] The world health organization (WHO) reports that antimicrobial medications are unable to effectively treat various resistant microorganisms which causes infections to persist and spread. Despite the fact that the emergence of AMR is a normal process, the rise in immunocompromised conditions including HIV infection, diabetes, organ transplant recipients, and severe burn patients makes the body more vulnerable to infectious diseases contracted in hospitals and accelerates the spread of AMR.

Common infections comprise of pneumonia, bloodstream infections, and UTI are all brought on by drug-resistant strains, as are a significant portion of infections acquired in hospitals.[3,4] Additionally, there are few antifungal drugs available to treat chronic fungal infections, and isolates of *Aspergillus spp., Candida spp.,* etc. and *Pseudomonas aeruginosa* exhibit resistance to medications like flucytosine, DNA and RNA synthesis inhibitors, azole derivatives (itraconazole, fluconazole, ketoconazole, etc.,).[5,6]

There is growing concern over antiviral resistance in immunocompromised patients due to prolonged drug exposure, leading to the emergence of resistant strains and persistent infections. It has been observed in patients infected with viruses such as hepatitis B virus, human immunodeficiency virus (HIV), influenza A virus and many more.[7-9] Malaria, caused by *Plasmodium falciparum*, is a prime example of a disease prone to MDR, as is amoebiasis caused by *Entamoeba spp.*[10,11] Schistosomiasis is also considered a global health threat, similar to malaria and other chronic diseases.[12] This review article aims to highlight the AMR issue along with its possible implications in the future.

AMR AND ITS CONSEQUENCE

Antimicrobial drugs are in use for many years. Surveillance in different parts of the world, including Western Pacific Region, some parts of America, South-East Asia, the Eastern Mediterranean region, Africa, and the Europe, has revealed about evolution of numerous infectious microorganisms over time as well as there are a staggeringly large number of species that are antibiotic-resistant and can withstand the restrain these medicines have. The term "super bug" refers to a group of infectious pathogens (such as bacteria, parasites, viruses and fungi) that use high levels of AMR with increased morbidity and death. AMR poses a huge global danger to public health in view of the fact that deadly diseases including tuberculosis, yeast infections, malaria, influenza, HIV, pneumonia and many others are becoming leading causes of mortality. Due to MTB's resistance to specific drugs, the likelihood of eradicating tuberculosis has reduced, creating a global problem. Another survey indicated that the extensively drug-resistant TB (XDRTB) was present in the 92 countries, with 6% of current infections and 20% of those that had previously been treated having the MDR.[13]

Another bacterial infection, pneumonia, being proven resistant to both carbapenems and cephalosporin by a mechanism mediated by extended spectrum β-lactamases (ESBL), all available therapy with β-lactam antibiotics is no longer effective.[14] Antiretroviral therapy has failed in recent years due to HIV medication resistance, which has resulted in expensive costs and a variety of negative effects. The protozoan parasite that causes malaria had started to develop resistance to several of its most potent medications, including pyrimethamine, artemisinin, and chloroquine.[15] As a result, new drugs have been introduced to replace these old, ineffective ones, increasing the expenses of healthcare. The emergence of antifungal treatment resistance in invasive yeast infections, such as Candidiasis, has increased morbidity and death globally and creating a big economic burden on the world. Microbes do not even respond to common medications due to antimicrobial resistance or multidrug resistance, which lengthens the course of treatment and increases health care expenditures, worsen the situation for those who cannot afford such expenses.

MECHANISM OF AMR

In microbiology, resistance is referred as an ability of microorganism to resist the effects of antimicrobial drug, compared to other isolates of the same species. Despite the introduction of several new drugs, among infectious microorganisms, the emergence of resistance is on the rise, particularly in patients exposed to prolonged drug treatment.[16] Antimicrobial medications often function by blocking a metabolic process, such as nucleotide synthesis, which prevents the production of DNA/RNA, proteins, and cell membranes. As an alternative, they could compete with chitin synthase, an enzyme involved in the creation of cell walls, for its substrate.[17] To withstand the effects of medications as well as endure exposure to them, microbes have evolved a number of defense mechanisms (Table 1). This section will go through the defense mechanisms that micro-organisms have created to counteract the anti-microbial drugs' lethal effects.

The cell wall is a critical component of bacteria and fungi, essential for their survival. As previously mentioned, medicines can stop the synthesis of cell walls by attaching to the peptidoglycan layer in bacteria or altering the production of ergosterol (such as polyenes) in fungus, which stops the development and division of cells.[35] These organisms experience a variety of modifications, such as transformation or conjugation or chromosomal mutations[36]. These modifications can lead to changes in the composition of cell membranes, which reduces permeability and drug uptake.[1,7,14] Unavailability of active target sites for medications like echinocandins in fungi to bind to can also be caused by changes in membrane composition, such as changes in the amount of β-1,3 glucan and lipid across cell membranes.[35] The target molecules can also be modified at the molecular level by mutations in the genes that encode them, lowering their sensitivity to inhibition but preserving cellular function.[1,5]

Resistance to antimicrobial drugs can occur due to various mechanisms (Figure 1). One of them is medication inactivation or enzymatic degradation that occurs when ester or amide linkages are hydrolyzed. β-lactamases are enzymes responsible for the degradation of β-lactams, leading to resistance.[1,7] Antimicrobial compounds may get oxidized or reduced by microorganisms to stop them from interacting with the desired targets.[35] Antiviral drugs can interact differently with the enzyme in drug-resistant mutant strains because these mutations occur in the reverse transcriptase sections of the polymerase gene. Many point mutations or substitutions can cause changed drug targets in parasites like *Toxoplasma gondii* and *Plasmodia spp.*[10,37] Parasites are developing MDR which is creating a global public health issue because to the absence of effective antiparasitic vaccinations and the sluggish development of new medications.

Table 1: Organisms associated with AMR and their mechanisms.

Organisms	Associated in	Resistant to	Mechanisms	References
Acinetobacter baumannii	Bloodstream infections and pneumonia	1. Aminoglycosides, 2. Tetracyclines, 3. Chloramphenicol, 4. Fluoroquinolones, 5. Trimethoprim	1.Enzymatic modification, target site modification and efflux pumps, 2. Target-site gene mutations, efflux pumps and modifying enzyme, 3. Inhibit folic acid metabolism	Mancuso et al, 2021[18], Xu et al, 2019[19]
Campylobacter coli	Gastroenteritis, travel-associated infections, infections acquired domestically	1. Betalactam antimicrobial agents, 2. Fluoroquinolones, 3. Macrolides, 4. Aminoglycosides, 5. Ciprofloxacin, 6. Nalidixic acid	1. Hydrolyses structural lactam ring, 2. Point mutation of Thr86Ile in gyrA gene, 3. Interrupt protein synthesis in bacterial ribosome by targeting 50S subunit and inhibit bacterial RNA-dependent protein synthesis, 4. Binding to decoding region in A-site of bacterial ribosomal 30S subunit, 5 and 6. gyrA mutations	Martin and Kaye 2004[20]
Campylobacter jejuni	Gastroenteritis	1. Macrolides, 2. Aminoglycosides	1. Macrolides interrupt protein synthesis in bacterial ribosome by targeting 50S subunit and inhibit bacterial RNA-dependent protein synthesis. 2. Secondly mediated by enzymatic modification that diminishes affinity of amino-glycosides for rRNA A-site.	Wieczorek and Osek 2013[21]
E. Coli	UTI, gastroenteritis, neonatal meningitis, nosocomial infections	Carbapenems, cephalosporins, aminoglycosides and fluoroquinolones	Acquisition of genes coding for extended-spectrum β-lactamases, carbapenemases, 16S rRNA methylases	Ojdana et al, 2015[22]; Poirel et al, 2018[23]
Enterobacter cloacae	Bloodstream infections and pneumonia	1. Carbapenem, 2. Betalactam antimicrobial agents	1. Produce ESBLs and carbapenems, including VIM, OXA, metallo-β-lactamase-1, and KPC, 2. Depression of ampC β-lactamases	Mancuso et al, 2021[18]; Halat and Moubareck, 2020[24]
Enterococci faecium	Hospital-acquired infections such as catheter-associated urinary tract infections, endocarditis and bacteremia	1. Vancomycin, 2. Fluoroquinolones	1. Van gene clusters such as vanR, vanS, vanH, vanX and vanZ that are responsible for replacement of D-Ala-D-Ala with D-alanyl-D-lactate termini, 2. Point mutations in gyrA and parC genes that encode subunits A of DNA gyrase and topoisomerase IV/ with efflux transporter NorA that pump out these drugs	Mancuso et al. 2021[18]; Jubeh et al, 2020[25]
Group A *Streptococcus*	Strep throat	Erythromycin	Presence of the Fn binding protein F1 gene (prtF1)	Passàli et al, 2007[26]
Group B *Streptococcus*	Neonatal disease	1. Betalactam antibiotics, 2. Fluoroquinolones, 3. Aminoglycosides	1. Reduced access to PBPs, reduced PBP binding affinity or destruction of the antibiotic through beta-lactamases, 2 and 3. Mutations within genes encoding topo-isomerases DNA gyrase and topoisomerase IV beta-lactams mutations within genes encoding penicillin binding proteins, particularly PBP2x	Hayes et al, 2020[27]

Continued.

Organisms	Associated in	Resistant to	Mechanisms	References
Haemophilus influenzae	Ear and bloodstream infection	Beta-lactam antibiotics	Production of a TEM-1 plasmid-mediated beta-lactamase, and in some cases to a new enzyme ROB-1	Bae et al, 2010[28]
Helicobacter pylori	Peptic ulcer and stomach infection	1. Clarithromycin, 2. Levofloxacin, 3. Fluoroquinolones (all)	1-3. Point mutation at DNA gyrase	Mégraud 2012[29]
Klebsiella aerogenes	Bloodstream infections and pneumonia	1. Carbapenem, 2. Betalactam antimicrobial agents	1. Produce ESBLs and carbapenemases, including VIM, OXA, metallo-β-lactamase-1, and KPC, 2. Depression of ampC β-lactamases	Mancuso et al, 2021[18]; Halat and Moubareck 2020[24]
Klebsiella pneumonia	Nosocomial, UTI, pneumonia, liver abscess, surgical site infections and bloodstream infections	1. Carbapenem, 2. Aminoglycosides	1. Carbapenemase encoding blaKPC-3 gene, 2. Alterations in AcrAB-TolC and KpnEF efflux pump systems	Mancuso et al, 2021[18]
Listeria monocytogenes	Food pathogens	1. Tetracyclines, 2. Fluoroquinolones	1. Acquisition of conjugative transposons, 2. Active efflux	Jubeh et al, 2020[25]
Neisseria gonorrhoeae	Sexually transmitted disease	1. Penicillin, 2. Fluoroquinolone	1. Chromosomally mediated resistance (CMRNG) and penicillinase-mediated resistance (PPNG), 2. NorM efflux pump is encoded by norM gene and provides resistance to fluoroquinolones.	Loughlin et al, 2003[30]
Pseudomonas aeruginosa	Respiratory infections in patients with compromised host defenses	1. Carbapenems, 2. Aminoglycoside, 3. β-lactam, 4. Fluoroquinolone	1. Carry mobile genetic element that makes carbapenemase enzyme, 2-4. Overexpression of MexXY–OprM induced by mexZ gene mutation	Mancuso et al, 2021[18]; Pang et al, 2019[31]
Salmonellae	Food poisoning or gastroenteritis	1. Cephalosporin, 2. Fluoroquinolone	1. Production of extended-spectrum β-lactamases (ESBLs), 2. Chromosomal mutations in quinolone resistance-determining regions (QRDRs)	Sriyapai et al, 2021[32]
Shigella spp.	Food poisoning or gastroenteritis	Tetracycline	Acquisition of resistance genes which are often associated with mobile elements	Hayes et al, 2020[27]
Staphylococcus aureus	Bloodstream and surgical-site infections	Methicillin	Horizontal gene transfer, genes mecA and mecC which inactivate methicillin by synthesis of an alternative PBP, designated PBP2a, that has very low affinity for almost all β-lactam antibiotics	Mancuso et al, 2021[18]
Staphylococcus aureus	Bloodstream and surgical-site infections	Penicillin	Plasmid-encoded beta-lactamases capable of hydrolyzing the β-lactam ring of penicillin	Guo et al, 2020[33]
Streptococcus pneumoniae	Ear and sinus infections to pneumonia, meningitis, and bloodstream infections.	1. ß-lactam, 2. Fluoroquinolone	1. Alteration of cell wall PBP, resulting in decreased affinity for penicillin, 2. Spontaneous point mutations in quinolone resistance-determining region (QRDR)	WHO 2017[34]

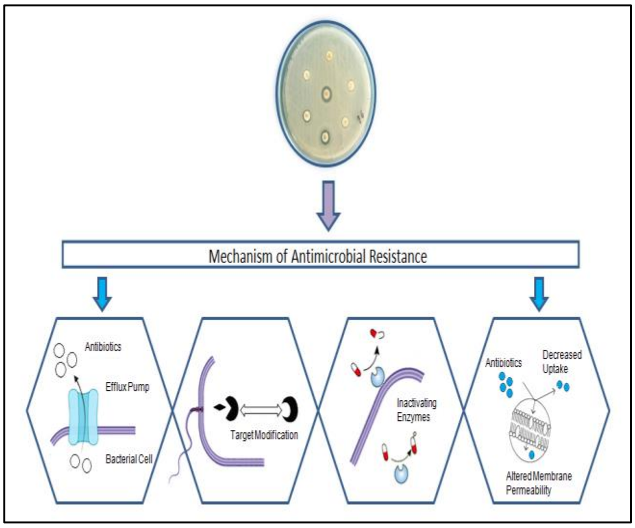

Figure 1: Mechanism of antimicrobial resistance.

FUTURE PERSPECTIVES OF AMR

Global economy

According to two scenarios, the World Bank has produced estimations of the economic effects of AMR between 2017 and 2050. In comparison to the base case, the low-AMR scenario predicts a global GDP decline of 1.0 percent by 2030 and 1.1% by 2050. Global GDP is expected to decline in the high-AMR scenario by 3.2% by 2030 and then continue to decline through 2050, losing 3.8% of GDP compared to the base case.[38] The high-AMR scenario's costs are seen as severe owing to the long-term consequences on the economy, but the low-AMR scenario would result in a sizable economic burden.

According to a world bank estimate, AMR's potential economic harm might be on par with a serious global financial catastrophe. Global GDP in 2050 would be 3.8% lower under the high-AMR scenario than it would be under the base scenario, with low-income nations facing a GDP decline of nearly 5 percent. This would cause significant drops in economic production during the last 20 years. After 2030, the yearly production losses would approach $1 trillion, and by 2050 they would exceed $2 trillion even in the low-AMR scenario. In the high-AMR scenario, losses would be substantially worse, reaching absolute amounts of $3.4 trillion per year by 2030 and $6.1 trillion per year by 2050.[38]

Livestock industry

The livestock production industry accounts for approximately 2% of the global economy, which means its decreased production barely affects the outcome of the simulation as a whole. However, in low- and lower middle-income countries, the sector is relatively more important for their economies and exports than in wealthier countries. The livestock production sector also plays a significant role in development and contributes substantially for nutrition. AMR is expected to worsen animal health. The increased disease burden caused by AMR will result in more frequent and severe infections, leading to increased variability of incomes and reduced income levels, as this becomes the new normal.

Health care expenditures

The impact of AMR on healthcare expenditures would be significant, with both public and private spending expected to rise as a result of increasing disease burdens. Globally, an 8 percent increase in annual healthcare expenditures in 2050, with 25% increase among low-income, 15% for middle income and 6% for high income countries which would amount to an additional $1.2 trillion annually during high AMR scenario. For low-AMR scenario, an additional healthcare expenditure in 2050 would be $0.33 trillion annually.[38,39] While the impact on healthcare spending is significant, it is important to note that this is just one aspect of the overall economic impact of AMR.

Impact on poverty

Extreme poverty is anticipated to rise sharply as a result of AMR's effects on economic growth. This is partly because low-income nations were disproportionately affected by AMR, which resulted in severe and sustained drops in economic production over the simulations. By 2050, majority of 26.2 million will be in severe poverty under high-AMR scenario would reside in low-income nations. Without AMR, the world is moving towards the World Bank Group's goal of having less than 3% of extreme poverty people worldwide and on pace to eradicate extreme poverty by 2030. The AMR, however, would make it more difficult to reach the goal. By 2030, there might be 24.1 million more individuals who are extremely poor, 18.7 million of whom will reside in low-income nations, according to the high-AMR scenario.[38] AMR must be addressed in order to prevent negative repercussions on attempts to reduce global poverty.

AMR PREVENTION

The emergence and spread of AMR has become a complex issue of global concern. Cooperative efforts are required to reduce the escalation and dissemination of AMR through health education and promotion, as diseases that were previously treatable have become significant causes of death in the present era.[1,4] Antibiotic stewardship programmes (ASPs), which are described as coordinated interventions intended for assess and safe use of antibiotics, must be focused on regions that are vulnerable to their inappropriate use (Figure 2). In reality, a number of ASPs are being carried out right now to enhance clinical outcomes, reduce treatment-related costs, minimize or stabilize AMR, and optimize antimicrobial therapy.[40] The treatments made possible by ASPs either limit the accessibility of certain antimicrobial medicines or examine the widespread antibiotics use before ceasing them[41]. For further future success in the fight against AMR, there is a serious demand for assistance as well as cooperation at the global, country, regional and subregional levels.[4]

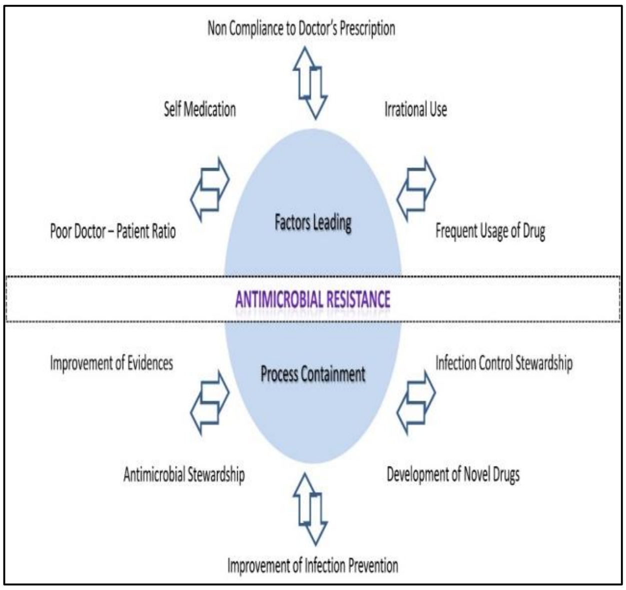

Figure 2: Factors leading to and remedies for AMR.

CONCLUSION

There has been a sharp rise in severe illnesses and the broad distribution of resistant microbes undoubtedly. The limits of already accessible antimicrobial medications necessitate the making of novel medications research for future use. In order to recover control over illnesses, it is also required to create numerous awareness initiatives to encourage their proper usage through various health education and promotion strategies. AMR is a normal, inescapable occurrence that seriously endangers public health across the world. In order to solve AMR and protect the future generations, concerted action must be taken on a worldwide scale. Pathogens frequently use a variety of resistance mechanisms to endure challenging circumstances. The creation of innovative treatments to fight these persistent infections should be made easier by a better strategy of health education and promotion to educate the population the drivers of AMR.

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