IMPACT OF MULTIDRUG RESISTANCE BACTERIA ON HUMAN HEALTH

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ABSTRACT

The increasing prevalence of infections caused by multi-drug resistant bacteria is a global health problem that is exacerbated by the dearth of novel classes of antibiotics entering the clinic over the past 40 years The resistance among various microbial species (infectious agents) to different antimicrobial drugs has emerged as a cause of public health threat all over the world at a terrifying rate. Due to the pacing advent of new resistance mechanisms and decrease in efficiency of treating common infectious diseases, it results in failure of microbial response to standard treatment, leading to prolonged illness, higher expenditures for health care, and an immense risk of death. Almost all the capable infecting agents (e.g., bacteria, fungi, virus, and parasite) have employed high levels of multidrug resistance (MDR) with enhanced morbidity and mortality; thus, they are referred to as "super bugs." Although the development of MDR is a natural phenomenon, the inappropriate use of antimicrobial drugs, inadequate sanitary conditions, inappropriate food-handling, and poor infection prevention and control practices contribute to emergence of and encourage the further spread of MDR. Considering the significance of MDR, emphasizes the problems associated with MDR and the need to of multidrug resistance understand its significance and mechanisms to combat microbial infections.

I. INTRODUCTION

During the last few decades, the incidence of microbial infections has increased dramatically. Continuous deployment of antimicrobial drugs in treating infections has led to the emergence of resistance among the various strains of microorganisms. Multidrug resistance (MDR) is defined as insensitivity or resistance of a microorganism to the administered antimicrobial medicines (which are structurally unrelated and have different molecular targets) despite earlier sensitivity to i. According to WHO, these resistant microorganisms (like bacteria, fungi, viruses, and parasites) are able to combat attack by antimicrobial drugs, which leads to ineffective treatment resulting in persistence and spreading of infections. Although the development of MDR is a natural phenomenon, extensive rise in the number of immunocompromised conditions, like HIV-infection, diabetic patients, individuals who have undergone organ transplantation, and severe burn patients, makes the body an easy target for hospital acquired infectious diseases, thereby contributing to further spread of MDR. Studies from WHO report have shown very high rates of resistance in bacteria such as Escherichia coli against antibiotics as cephalosporin and fluoroquinolones, Klebsiella pneumoniae against cephalosporin and carbapenems, Staphylococcus aureus against methicillin, Streptococcus pneumoniae against penicillin, Nontyphoidal Salmonella against fluoroquinolones, Shigella species against fluoroquinolones, Neisseria gonorrhoeae against cephalosporin, and Mycobacterium tuberculosis against rifampicin, isoniazid, and fluoroquinolone causing common infections (like urinary tract infections, pneumonia, and bloodstream infections) and high percentage of hospital-acquired infections. A limited number of antifungal drugs are available for the treatment of chronic fungal infections. Resistance to drugs such as polyene macrolides (amphotericin B), azole derivatives (ketoconazole, fluconazole, itraconazole, and voriconazole), DNA and RNA synthesis inhibitors (flucytosine), and 1,3-β-glucan synthase inhibitors exists in isolates of Candida spp., Aspergillus spp., Cryptococcus neoformans, Trichosporon beigelii, Scopulariopsis spp. Prolonged drug exposure and nonstop viral replication result in the advent of various resistant strains and persistence of infections despite therapy. This has made antiviral resistance a matter of concern in immunocompromised patients. Consequences of antiviral drug resistance were observed in immunosuppressed transplant recipients and oncology patients infected by either cytomegalovirus (CMV), herpes simplex virus (HSV), Varicella-zoster virus (VZV) , human immunodeficiency virus (HIV), analyzed in isolates of Plasmodia, Leishmania, During the last few decades, the incidence of microbial infections has increased dramatically. Continuous deployment of antimicrobial drugs in treating infections

has led to the emergence of resistance among the various strains of microorganisms. Multidrug resistance (MDR) is defined as insensitivity or resistance of a microorganism to the administered antimicrobial medicines (which are structurally unrelated and have different molecular targets) despite earlier sensitivity to it . According to WHO, these resistant microorganisms (like bacteria, fungi, viruses, and parasites) are able to combat attack by antimicrobial drugs, which leads to ineffective treatment resulting in persistence and spreading of infections. Although the development of MDR is a natural phenomenon, extensive rise in the number of immunocompromised conditions, like HIV-infection, diabetic patients, individuals who have undergone organ transplantation, and severe burn patients, makes the body high rates of resistance in bacteria such as Escherichia coli against antibiotics as cephalosporin and fluoroquinolones, Klebsiella pneumoniae against cephalosporin and carbapenems, Staphylococcus aureus against methicillin, Streptococcus pneumoniae against penicillin, Nontyphoidal Salmonella against fluoroquinolones, Shigella species against fluoroquinolones, Neisseria gonorrhoeae against cephalosporin, and Mycobacterium tuberculosis against rifampicin, isoniazid, and fluoroquinolone causing common infections (like urinary tract infections, pneumonia, and bloodstream infections) and high percentage of hospital-acquired infections. A limited number of antifungal drugs are available for the treatment of chronic fungal infections. Resistance to drugs such as polyene macrolides (amphotericin B), azole derivatives (ketoconazole, fluconazole, itraconazole, and voriconazole), DNA and RNA synthesis inhibitors (flucytosine), and 1,3-β-glucan synthase inhibitors (echinocandins) exists in isolates of Candida spp., Aspergillus spp., Cryptococcus neoformans, Trichosporon beigelii, Scopulariopsis spp., and Pseudallescheria boydii. Prolonged drug exposure and nonstop viral replication result in the advent of various resistant strains and persistence of infections despite therapy. This has made antiviral resistance a matter of concern in immunocompromised patients. Consequences of antiviral drug resistance were observed in immunosuppressed transplant recipients and oncology patients infected by either cytomegalovirus (CMV), herpes simplex virus (HSV), Varicella-zoster virus (VZV), human immunodeficiency virus (HIV), influenza A virus, hepatitis C (HCV), or hepatitis B virus (HBV) . Parasitic multidrug resistance has been analyzed in isolates of Plasmodia, Leishmania, Entamoeba, Trichomonas vaginalis, schistosomes , and Toxoplasma gondii against drugs such as, chloroquine, pyrimethamine, artemisinin, pentavalent antimonials, miltefosine, paromomycin, and amphotericin B as well as atovaquone and sulfadiazine. One of the most prime examples of disease prone to MDR is malaria, caused by Plasmodium falciparum . Another protozoan parasite, Entamoeba spp., causes amoebiasis which is also a major public health threat in many tropical and subtropical countries . A global health threat of schistosomiasis is also considered similar to that of malaria and other chronic diseases . This review article emphasizes the significance of MDR, various mechanisms contributing to its development, and problems associated with MDR and its possible remedies

II. ANTIMICROBIAL RESISTANCE

This is the ability of microbes to grow in the presence of a chemical (drug) that would normally restrict their growth or destroy them all. Microorganisms resistance to antimicrobial drug was basically effective for the treatment of infection caused by those microorganisms. Drug resistant microorganisms include (bacteria, fungi, viruses and parasite). These microorganisms are able to combat attack by antimicrobial drugs so that basic treatment becomes ineffective and infection prevails, raising the risk of spreading to others . Antimicrobial resistance makes it harder to eradicate infections from the body as current drugs become less effective. Consequently, some infection diseases today are more difficult to treat than they were just a few decades ago . As more microorganisms became resistant to antimicrobials, the protective value of these drugs is reduced due to the use and misuse of antimicrobial drugs and this is among the factors that have contributed to the development of drug resistant microbes. Resistance is the term referred to as the insensitivity of a microbe to an antimicrobial drug when compared with other isolates of the same species. Although several new drugs have been introduced commercially, this development of resistance among infectious microorganisms is increasing especially in patients under prolonged drug exposure . Antimicrobial drugs generally act on the microbes either by inhibiting a metabolic pathway like nucleotide synthesis which in turn leads to the inhibition of DNA/RNA synthesis and further protein synthesis and disruption of the cell membrane or by competing with the substrate of any enzyme involved in cell wall synthesis (e.g., chitin synthase) . Microorganisms have evolved a multitude of mechanisms to overcome the effectiveness of drugs, thereby surviving exposure to the drugs. This section will mainly describe the resistance mechanisms that the microbes develop to avoid getting killed by the drugs.

III. CLASSIFICATION OF MDR

Administration of appropriate doses of drugs for a particular duration of time, survival of different microbial strains suggests the high levels of resistance developed in them . This clinical failure is as a result of not only the antimicrobial resistance but also the suppressed immune function, deprived or poor drug bioavailability, or increased rate of drug metabolism. Multi drug resistance can be classified as primary or secondary resistance .

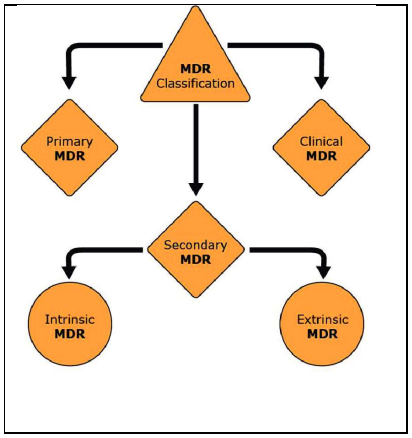


Figure:1.Classification of MDR

A. Primary resistance

Occurs when the organism has never confronted the drug of interest in a particular host i.e. it is a drug resistance in patient who has not received any previous antitubercular treatment . For example primary drug resistance tuberculosis, this occurs in patients who have not previously received tuberculosis treatment. Primary drug resistance is known to be caused by the dissemination of drug-resistant strains .

B. Secondary resistance

This is also known as "acquired resistance," this term is used to define the resistance that only occurs in an organism after an exposure to the drug . This can also be define as resistance that evolve in a patient who has previously received chemotherapy . For example acquired drug resistance expressed tuberculosis isolated from patients who currently are getting or until that time have received anti-tuberculosis drug treatment for at least one month.

It can further be classified as follows;

C. Intrinsic resistance

Intrinsic resistance is the innate ability of a microorganism to resist activity of a particular antimicrobial agent through its inherent structural or functional characteristics, which allow tolerance of a particular drug or antimicrobialss . This can also be called "insensitivity" since it occurs in organisms that have never been susceptible to that particular drug. Such natural insensitivity can be due to: • Lack of affinity of the drug for the bacterial target • Inaccessibility of the drug into the bacterial cell • Extrusion of the drug by chromosomally encoded active exporters • Innate production of enzymes that inactivate the drug . For example, Gram-positive bacteria to aztreonam (a betalactam), Gram-negative bacteria to vancomycin, anaerobic bacteria to aminoglycosides, aerobic bacteria to metronidazole .

D. Extensive resistance

It defines the ability of organisms to withstand the inhibitory effects of at least one or two most effective antimicrobial drugs (Loeffler and Stevens, 2003). Also termed as XDR, this seemed to arise in patients after they have undergone a treatment with first line drugs, for example, XDR-TB (extensive drug resistant tuberculosis) resistance against fluoroquinolone .

E.Clinical resistance

Clinical resistance is described by the situation in which the infecting organism is inhibited by a concentration of an antimicrobial agent that is linked with a high likelihood of therapeutic failure or reappearance of infections within an organism as a result of impaired host immune function especially the pathogen is inhibited by an antimicrobial concentration that is higher than could be carefully attained with normal dosing .

IV. MULTIDRUG RESISTANCE BACTERIA AND MODE OF ACTION

Multi drug resistance (MDR) bacteria are bacteria that have become resistant to certain commonly used antibiotics. There are many different types of MDR bacteria that can easily be found throughout the environment including water and soil . They cause the same type of infections as nonresistant bacteria . The difference is that when an infection with multi-drug resistant bacteria is developed, the choice of suitable antibiotic to treat the infection may be considerably more limited, example include Psuedomonas aeroginosa,

Staphylococcus aureus (MRSA), Esherichia coli, Acinetobacter baumannii, Klebsiella pneumoniae, Mycobacterium tuberculosis, Neisseria gonorrhoeae . Antibiotic resistance could occur in bacteria through four types of mechanisms:

A. Drug inactivation or modification

for example, enzymatic deactivation as in penicillin G in some penicillin-resistant bacteria through the production of β-lactamases . Protecting enzymes manufactured by the bacterial cell will add an acetyl or phosphate group to a specific site on the antibiotic, which will diminish its capacity to bind to the bacterial ribosomes and disrupt protein synthesis .

B. Modification of target- or binding site

for example, alteration of PBP-the binding target site of penicillin's-in MRSA and other penicillin-resistant bacteria, or modification in structure of ribosomal protection proteins . These proteins guard the bacterial cell from antibiotics through changes its conformational shape. Change of proteins conformational shape allows these proteins to loss their activity so, prevent inhibit protein synthesis, and this help in grow of bacteria and spread it .

C.Alteration of metabolic pathway

for example, absence of paraaminobenzoic acid (PABA), this is precursor for the synthesis of folic acid and nucleic acids .

D. Reduced drug accumulation

By decreasing drug permeability or increasing active pumping out of drugs through cell membrane . The balance of antibiotic uptake and elimination determines the susceptibility of bacteria to a particular drug. Thus, reducing the amount of antibiotic able to pass through the bacterial cell membrane is one strategy used by bacteria to develop antibiotic resistance .

V. MULTIDRUG RESISTANCE VIRUSES AND MODE OF ACTION

Viruses have developed numerous resistance mechanisms that enable them to evade the effect of antimicrobials and antivirals. As a result, many have become resistant to almost every available means of treatment .This problem, although not new, is becoming increasingly acute and it is now clear that a fundamental understanding of the mechanisms that microbes and viruses deploy in the development of resistance is essential if we are to gain new insights into ways to combat this problem . Antiviral drugs usually target viral DNA polymerase having the reverse transcriptase activity to inhibit the viral replication. Drug resistant mutant strains undergo mutations in the reverse transcriptase domains of the polymerase gene which affects the interaction between the drug and the enzyme. Resistance to the inhibitory effects of drug on the enzyme can also emerge due to any conformational changes or altered binding of substrate to the viral polymerase .

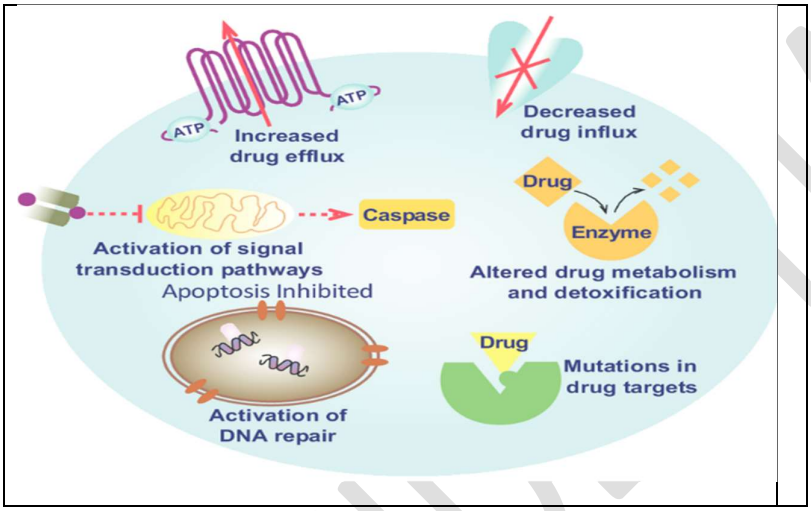
VI. MULTIDRUG RESISTANCE FUNGI AND MODE OF ACTION

Fungal cells have developed several strategies to deal with the antifungal. They have learnt to modify the antifungal drug targets or most commonly increase the efflux of the incoming drugs. Cell wall, in fungi plays a crucial role in their survival. Drugs affecting ergosterol synthesis (e.g polyenes) in fungi, thus, blocking the cell to grow then . Such as reduction in the ergosterol content in fungal plasma membrane) resulting in decreased permeability and uptake of drugs into the cell . Altered membrane composition (such as β-1, 3-glucan and lipid content in fungal cell membrane) also leads to lack of active target sites for the drugs (e.g., echinocandins in fungi to bind . Mutations in the genes encoding for the target cause modifications at the molecular level and retain cellular function by reducing susceptibility to inhibition . Another mechanism of MDR was found to be an over expression of drug target enzymes leading to target by pass due to modification in certain metabolic pathways (e.g., azoles and allylamines in fungi), which causes production of alternate target molecules and interference in some protein synthesis . Examples include yeast such as Candida species can become resistant under long time treatment with azoles preparations requiring treatment with a different drug class. Scedosporium proflificans infections are almost uniformly fatal because of their resistance to multiple antifungal agents .

VII. MECHANISMS AND THE EMERGENCE OF ANTIBIOTIC RESISTANCE

The long awaited “superbug” arrived in the summer of 2002 Staphylococcus aureus, a common but sometimes deadly bacterium, had acquired a new antibiotic resistance gene. This new strain was isolated from foot ulcers as diabetic patients in Detroit, Michigan, methicillin resistant (formally methicillinresistant) S. aureus (MRSA) had been well known as the bane of hospitals . The

newer strain had developed resistance to vancomycin, one of the few antibiotics that were still able to control S. aureus. This new vancomycin resistant S. aureus (VRSA) strain also resisted most other antibiotics including ciprofloxacin, methicillan and penicillin. Isolated from the same patient was dread of hospitals vancomycin-resistant Enterococci (VRE) . Genetics analysis reveal that the patient's own vancomycin sensitive S. aureus had acquired the vancomycin resistance gene VanA, from VRE through conjugation, so was born a new threat to the health of the human race Bacteria often become resistant in several ways. Unfortunately, a particular type of resistance mechanism is not confined to a single class of drugs. Two bacteria may use different resistant mechanisms to withstand the same chemotherapeutic agent. Susceptible bacteria can acquire resistance to antimicrobials by either genetic mutation or by accepting antimicrobial resistant genes from other bacteria. This could be through one of several biochemical mechanisms such as mutation, destruction or inactivation, efflux or genetic transfer of materials between bacteria by several means such as conjugation, transformation and transduction .



. Figure 2:Mechanism ofMDR

A.Mutation

This is a change in the DNA that can sometimes cause a change in the gene product, which is the target of the antimicrobial. When a susceptible bacterium comes in contact with a therapeutic concentration of antimicrobials, like fluroquinolones, the antimicrobial can bind to the specific enzymes, in this case, DNA gyrase . The DNA gyrase is an essential bacterial enzyme required for DNA replication. The end result is that fluroquninolones blocks bacterial DNA replication leading. However, when spontaneous mutations occur in specific areas of the genes encoding these enzymes, antimicrobials no longer bind efficiently. This allows the bacterium to continue DNA replication. Pathogens often become resistant simply by preventing entrance of the drug. Many gram negative bacteria are unaffected by penicillin G because it cannot penetrate the envelops outer membrane . Genetic mutations that lead to changes in penicillin binding proteins also render a cell resistant. A decrease in permeability can lead to sulfonamide resistance .

B. Destruction or Inactivation

Many bacteria possess genes which produce enzymes that chemically degrade or deactivate the antimicrobial rendering them ineffective against bacterium. Here the antimicrobial is either degraded or modified by enzymatic activity before it cn reach the target site and damage the bacterial cell (Bush, 2013).The best known example is the hydrolysis of the β - lactam ring of penicillin's by the enzymes penicillinase drugs are also inactive by the addition of chemical group (FDA, 2004). For example, chioramphenicol contains two hydroxyl groups that can be acetylated in a reaction catalyzed by the enzyme chioramphenicol acyltransferase with actyl CoA as the donor. Aminoglycosides can be modified and inactivated in several ways. Acetyltransferases catalyze the acetylation of amino groups. Some aminoglycoside modifying enzymes catalyze the addition of hydroxyl groups of either phosphat(phosphotransferasses) or adenyl groups (addenyltransferases) (FDA, 2004; Bush, 2013).

C.Efflux

One of the most common drug resistance mechanisms is active efflux of drugs from, the inside of the bacterial cells. Such drug resistant bacteria habour energy-driven drug efflux pumps which extrude antimicrobial agents thus reducing their intracellular

concentration to sub or non-inhibitory levels . Efflux pump is essentially a channel that actively exports antimicrobial and other compounds out of the cell. The antimicrobial enters the bacterium through a channel termed as porin and then is pumped back out of the bacterium by the efflux pump . Because they are relatively non-specific and can pump many different drugs, these transport proteins often are called multidrug resistant pumps. There are two main types of active efflux pumps; the first type called primary active transport the hydrolysis of ATP to actively efflux drugs from cells, while the second type, called secondary active transport, uses an iron gradient for actively efflux drugs from cells .The ATP driven transporters are also known as ABC (for ATP Binding Cassette) or P-glycoprotein transporters. Both active transport systems are used by bacteria to resistant the inhibitory effects of antimicrobial agents and are often referred to as efflux pumps . Many are drug/proton antiporters that are proton enters the cell that the drug leaves. Such systems are present in E. coil, P. aeruginosa and S. aureus etc .

D. Measures to Reverse Resistance

In main genetic processes, horizontal gene transfers, the resistant microbe is affected not only in its ability to withstand the antibiotic, but due to the fact that its interaction with the host and its ability to be transmitted between hosts. Usually, it is observed that most resistance mechanisms will confer a reduction in bacterial fitness, which might be expressed as reduced growth and survival inside and outside a host, and reduced virulence or transmission rate from environment to host or between host. Washing hands after seeing each patient is a major and obvious, but too often overlooked precaution . Two epidemiological studies, of erythromycin resistance in Streptococcus pyogenes and penicillin resistance in Streptococcus pneumonia, have been suggested as providing support for their versatility of resistance in community settings . Several laboratory and epidemiological studies indicate that various processes are predicted to cause long-term persistence of resistant bacteria. One process is compensatory evolution, where the costs of resistance are ameliorated by additional genetic changes, resulting in the stabilization of resistant bacteria in the population. Even though most resistance is associated with fitness cost, some resistance mutations appear to be gratuitous. The occurrence of such cost-free resistances will also cause irreversibility since the driving force for reversibility is absent. The public should wash raw fruit and vegetables thoroughly to clear off both resistant bacteria and possible antibiotic residues. When they receive prescriptions for antibiotics, they should complete the full course of therapy (to ensure that all the pathogenic bacteria die) and should not "save" any pills for later use . Consumers also should refrain from demanding antibiotics for colds and other viral infections and might consider seeking non antibiotic therapies for minor conditions, such as certain cases of acne. They can continue to put antibiotic ointments on small cuts but they should think twice about routinely using hand lotions and a proliferation of other products now imbued with antibacterial agents. New laboratory findings indicate that certain of the bacteria-fighting chemicals being incorporated into consumer products can select for bacteria resistant both to the antibacterial preparations and to antibiotic

VIII. THE PROBLEM OF MULTI DRUG-RESISTANT BACTERIA

The emergence of resistance to multiple antimicrobial agents in pathogenic bacteria has become a significant global public health threat. Drug resistant bacterial infections cause considerable patient mortality and morbidity, and rising antibiotic resistance is seriously threatening the vast medical advancements made possible by antibiotics over the past 70 years. For example, in 2020 almost 95,000 people acquired methicillin-resistant Staphylococcus aureus (MRSA) infections in the United States and 19,000 people died from MRSA infections – more than die annually from HIV/AIDS, emphysema, Parkinson’s disease, and homicide combined. Without developing innovative approaches to combat multi-drug resistant (MDR) pathogens, many fields of medicine will be severely affected, including surgery, premature infant care, cancer chemotherapy, care of the critically ill, and transplantation medicine, all of which are feasible only with the existence of effective antibiotic therapy. Compounding the problem of rising bacterial resistance to currently approved antibiotics is a lack of investment in antibiotic discovery by the pharmaceutical industry due to the inherently low rate of return for antibiotics compared to drugs targeted at chronic diseases. This situation is so dire that the World Health Organization has identified MDR bacteria as one of the top three threats to human health,4 while the Infectious Disease Society of America has issued a call to action from the biomedical community to deal with the MDR bacteria.

While the development of new antibiotics is one approach for the treatment of MDR bacterial infections, the fact remains that only two new classes of antibiotics have been introduced into the clinic over the last two decades, neither of which are significantly active against Gram-negative bacteria invariably develop resistance to any introduced therapy that relies solely upon a bacteriostatic/bactericidal mechanism and clinically significant resistance can appear in a period of just months to years following introduction of a new antibiotic into the clinic. For example, daptomycin was introduced into the clinic in 2003, and less than a year later the emergence of resistance in patients with Enterococcus faecium and MRSA infections was observed. As a result, alternative approaches to controlling bacterial infections are sorely needed.

Figure 3. :MDR prevention

Bacteria and antibiotics :Bacteria have a remarkable ability to adapt to adverse environmental conditions, which is an example of the ancient law of nature of 'survival of the fittest'. It appears that the emergence of antimicrobial resistant bacteria is inevitable to most every new drug and it is recognized as a major problem in the treatment of microbial infections in hospitals and in the community .

Combinations of two or more antibiotics :One approach to combating MDR infections is combination of two or more antimicrobial drugs during a treatment regimen. Although the possibility of drug-drug interactions is a possible pitfall to this approach, and must be taken into consideration during the drug development process, combination therapy is common and critical in many areas of medicine. For example, drug combinations are key to most cancer treatments, combination therapy regimens have long been used to treat HIV infected patients,and artemisinin-based combination treatments are now generally accepted as the most effective treatments for malaria. Combination therapies are also important for the treatment of bacterial infections, and are used almost exclusively for the treatment of Mycobacterium tuberculosis infections, with combinations of up to four drugs typical. The rise in occurrence of other MDR bacteria, particularly MDMDR.

IX. SIGNIFICANCE OF MDR

Antimicrobial drugs have been used for several decades across the world. Surveillance in different regions of the world such as Africa, some parts of America, Eastern Mediterranean Region, Europe, South-East Asia, and Western Pacific Region has shown that many infectious microorganisms have evolved over the years and there is an alarming high number of antibiotic-resistant species enabling themselves to resist the inhibitory effects of these drugs. Not only a single but almost all the capable infecting agents (e.g., bacteria, fungi, virus, and parasite) have employed high levels of MDR with enhanced morbidity and mortality and, thus, are referred to as "super bugs." Tuberculosis, pneumonia, HIV, influenza, malaria, yeast infections, and many other deadly diseases are major causes of deaths in modern era, therefore, indicating MDR as a serious worldwide threat to public health. The chances of controlling tuberculosis have decreased due to resistance of MTB to respective antibiotics, thus, making it a global concern. A 2012 survey suggests that an overall 6% of recent TB cases and 20% of formerly treated TB cases are likely to possess MDR, while 92 countries were found to have extensively drug resistant TB (XDR-TB). Another bacterial infection, pneumonia, has become untreatable because its causative agent has been found to be resistant to cephalosporin as well as carbapenems due to extended spectrum β-lactamases (ESBL) mediated mechanism [30], thereby rendering all available treatment using β-lactam antibiotics. In recent years, HIV drug resistance has driven the antiretroviral therapy failure to such an extent that it is charging exorbitant rates along with a number of side effects. The protozoan parasite responsible for malaria had embarked on showing resistance to some of its most effective drugs, chloroquine, artemisinin, and pyrimethamine . This has resulted in replacement of these old ineffective drugs by novel drugs, which has increased the health care expenses. The emergence of resistance to antifungal drugs in invasive yeast infections, for example, Candidiasis, has led to worldwide morbidity and mortality, contributing to global economic burden. Antimicrobial resistance (AMR) or MDR is the reason why microbes fail to respond to standard drugs, thus, extending the duration of course of treatment further increasing the health care costs which tend to worsen the situation of people who are not capable of such expenses.

X. PROBLEMS ASSOCIATED WITH MDR

Antimicrobial resistance is associated with high mortality rates and high medical costs and has a significant impact on the effectiveness of antimicrobial agents . MDR provokes obstruction in disease control by intensifying the possibility of spreading of

resistant pathogens, thus, declining efficacy of treatment and, hence, resulting in prolonged time of infection in patient. The cost of treatment is also increased due to MDR as the pathogens have become resistant to commercially available drugs, which has triggered the use of more expensive therapies. The rate of success of present-day medical applications like organ transplantation and cancer chemotherapy has contributed immensely towards development of MDR. Differences in the resistance profiles of bacterial and fungal pathogens as well as the quality of public hygiene also have a considerable impact on the effectiveness of antimicrobial agents. Expansion of global trade and tourism lead to increased potential of MDR to spread all over the world and decrease in export and import of various products affecting the economy of developing countries .

XI. REMEDIES FOR MDR

The development of MDR is a complicated issue which has become an international dreadful concern. To decrease the rise and spread of MDR, cooperative efforts are requisite because diseases which were curable earlier are becomry[pulling major causes of deaths in this era . Moreover, focusing on areas which are susceptible to inappropriate use of antimicrobials by implementation of antibiotic stewardship (defined as coordinated interventions designed to improve and measure the appropriate use of antimicrobials) is the need of the hour . In fact, various antimicrobial stewardship programs (ASPs) are conducted nowadays to optimize antimicrobial therapy, reduce treatment-related cost, improve clinical outcomes and safety, and minimize or stabilize MDR . Interventions through ASPs are either by restricting the availability of selected antimicrobial agents, known as “front-end,” or by examining broad spectrum use of antibiotics and then streamlining or discontinuing it, known as “back-end” . Therefore, there is an urgent need of support and coordination at the global, regional, subregional, and national level to serve in future progress .

XII. CONCLUSION

Rapid increase of severe systemic infections and the spread of resistant microorganisms are indisputable facts. Inadequacy of available antimicrobial drugs compels continuous development newer drugs. Moreover, various awareness programmes which should facilitate their appropriate use to reestablish dominance over diseases must be implemented. MDR is an unavoidable natural phenomenon, posing a serious worldwide menace to public health. A cooperative action at global level is a must to combat the MDR. Pathogens tend to adopt various resistance mechanisms to survive the un favorable conditions. Improved knowledge of molecular mechanisms controlling MDR should facilitate the development of novel therapies to combat these intransigent infections and will help cultivate a deeper understanding of the pathobiology of microbial organisms. Inadequacy of available antimicrobial drugs compels continuous development of newer drugs.

REFERENCES

1.V Singh "Antimicrobial resistance," in Microbial Pathogens and Strategies for Combating Them: Science, Technology and Education, vol. 1, pp. 291–296, Formatex Research Center, 2013.

2., E. Płuciennik, and A. K. Bednarek, "Proteins in cancer resistance," Postępy Higieny I Medycyny Doświadczalnej, vol. 68, pp. 616–632, 20 Google Scholar

3.H. Nikaido, "Multidrug resistance in bacteria," Annual Review of Biochemistry, vol. 78, pp. 119–146, 2009. Google Scholar

4.Antimicrobial Resistance Global Report on Surveillance, World Health Organization, Geneva, Switzerland, 2014.

5. Loeffler and D. A. Stevens, "Antifungal drug resistance," Clinical Infectious Diseases, vol. 36, no. 1, pp. S31–S41, 2003.Publisher Site | Google Scholar

6.L. Strasfeld and S. Chou, "Antiviral drug resistance: mechanisms and clinical implications," Infectious Disease Clinics of North America, vol. 24, no. 2, pp. 413–437, 2010.Publisher Site | Google Scholar

7. Margeridon-Thermet and R. W. Shafer, "Comparison of the mechanisms of drug resistance among HIV, hepatitis B, and hepatitis C," Viruses, vol. 2, no. 12, pp. 2696–2739, 2010. Google Scholar

8.B. Ullman, "Multidrug resistance and P-glycoproteins in parasitic protozoa," Journal of Bioenergetics and Biomembranes, vol. 27, no. 1, pp. 77–84, 1995. View at: Publisher Site | Google Scholar

9.R. M. Greenberg, "New approaches for understanding mechanisms of drug resistance in schistosomes," Parasitology, vol. 140, no. 12, pp. 1534–1546, 2013.

10. Google Scholar

11.D. C. McFadden, S. Tomavo, E. A. Berry, and J. C. Boothroyd, "Characterization of cytochrome b from Toxoplasma gondii and Q(o) domain mutations as a mechanism of atovaquone-resistance," Molecular and Biochemical Parasitology, vol. 108, no. 1, pp. 1–12, 2000. | Google Scholar.

12.K. Nagamune, S. N. J. Moreno, and L. D. Sibley, "Artemisinin-resistant mutants of Toxoplasma gondii have altered calcium homeostasis," Antimicrobial Agents and Chemotherapy, vol. 51, no. 11, pp. 3816–3823, 2007. Google Scholar

13.C. Doliwa, S. Escotte-Binet, D. Aubert et al., "Sulfadiazine resistance in Toxoplasma gondii: no involvement of overexpression or polymorphisms in genes of therapeutic targets and ABC transporters," Parasite, vol. 20, no. 19, pp. 1–6, 2013. Google Scholar

14.M. Vanaerschot, F. Dumetz, S. Roy, A. Ponte-Sucre, J. Arevalo, and J. C. Dujardin, "Treatment failure in leishmaniasis: drug-resistance or another (epi-) phenotype?" Expert Review of Anti-Infective Therapy, vol. 12, no. 8, pp. 937–946, 2014.: Google Scholar

15.S. Mohapatra, "Drug resistance in leishmaniasis: newer developments," Tropical Parasitology, vol. 4, no. 1, pp. 4–9, 2014. Google Scholar

16.Z. Yang, C. Li, M. Miao et al., "Multidrug- resistant genotypes of plasmodium falciparum, Myanmar," Emerging Infectious Diseases, vol. 17, no. 3, pp. 498–501, 2011. | Google Scholar

17.D. Bansal, R. Sehgal, Y. Chawla, N. Malla, and R. C. Mahajan, "Multidrug resistance in amoebiasis patients," Indian Journal of Medical Research, vol. 124, no. 2, pp. 189–194, 2006.Google Scholar

18.L. Rodero, E. Mellado, A. C. Rodriguez et al., "G484S amino acid substitution in lanosterol 14-α demethylase (ERG11) is related to fluconazole resistance in a recurrent Cryptococcus neoformans clinical isolate," Antimicrobial Agents and Chemotherapy, vol. 47, no. 11, pp. 3653–3656, 2003. | Google Scholar

19.S. J. Howard and M. C. Arendrup, "Acquired antifungal drug resistance in Aspergillus fumigatus: epidemiology and detection," Medical Mycology, vol. 49, no.1, pp. S90–S95, 2011 | Google 20.P. Wutzler, "Antiviral therapy of herpes simplex and varicella-zoster virus infections," Intervirology, vol. 40, no. 5-6, pp. 343–356, 1997. Google Scholar

21.K. J. Cortez and F. Maldarelli, "Clinical management of HIV drug resistance," Viruses, vol. 3, no. 4, pp. 347–378, 2011.: | Google Scholar

22.J. Suppiah, R. M. Zain, S. H. Nawi, N. Bahari, and Z. Saat, "Drug-resistance associated mutations in polymerase (p) gene of hepatitis B virus isolated from malaysian HBV carriers," Hepatitis Monthly, vol. 14, no. 1, Article ID e13173, 7 pages, 2014. | Google Scholar

23,.P. B. Bloland, Drug Resistance in Malaria, World Health Organization, 2001.

24.P. G. Fallon and M. J. Doenhoff, "Drug-resistant schistosomiasis: resistance to praziquantel and oxamniquine induced in Schistosoma mansoni in mice is drug specific," The American Journal of Tropical Medicine and Hygiene, vol. 51, no. 1, pp. 83–88, 1994.

25.D. Bansal, N. Malla, and R. C. Mahajan, "Drug resistance in amoebiasis," Indian Journal of Medical Research, vol. 123, no. 2, pp. 115–118, 2006.

: Google Scholar

26.A. Muzny and J. R. Schwebke, "The clinical spectrum of Trichomonas vaginalis infection and challenges to management," Sexually Transmitted Infections, vol. 89, no. 6, pp. 423–425, 2013. | Google Scholar

27.J. W. Bennett, J. L. Robertson, D. R. Hospenthal et al., "Impact of extended spectrum beta-lactamase producing Klebsiella pneumoniae infections in severely burned patients," Journal of the American College of Surgeons, vol. 211, no. 3, pp. 391–399, 2010. Google Scholar.

28.G. I. Olasehinde, O. Ojurongbe, A. O. Adeyeba et al., "In vitro studies on the sensitivity pattern of Plasmodium falciparum to anti-malarial drugs and local herbal extracts," Malaria Journal, vol. 13, article 63, 2014. | Google Scholar

29.J. Fishbain and A. Y. Peleg, “Treatment of Acinetobacter infections,” Clinical Infectious Diseases, vol. 51, no. 1, pp. 79–84, 2010. | Google Scholar

30 S. Khalilzadeh, M. R. Boloorsaz, A. Safavi, P. Farnia, and A. A. Velayati, “Primary and acquired drug resistance in childhood tuberculosis,” Eastern Mediterranean health Journal, vol. 12, no. 6, pp. 909–914, 2006. Google Scholar

31 A R. Lee, I. H. Cho, B. C. Jeong, and S. H. Lee, “Strategies to minimize antibiotic resistance,” International Journal of Environmental Research and Public Health, vol. 10, no. 9, pp. 4274–4304, 2013. Google Scholar

32.S. M. Marks, J. Flood, B. Seaworth et al., “Treatment practices, outcomes, and costs of multidrug-resistant and extensively drug-resistant tuberculosis, United States, 2005–2007,” Emerging Infectious Diseases, vol. 20, no. 5, pp. 812–821, 2014. Google Scholar

33.M. Popęda, E. Płuciennik, and A. K. Bednarek, “Proteins in cancer resistance,” Postępy Higieny I Medycyny Doświadczalnej, vol. 68, pp. 616–632,

2014.Google Scholar

34.H. Nikaido, “Multidrug resistance in bacteria,” Annual Review of Biochemistry, vol. 78, pp. 119–146, 2009. Google Scholar

35.Antimicrobial Resistance Global Report on Surveillance, World Health Organization, Geneva, Switzerland, 2014.

36.J. Loeffler and D. A. Stevens, “Antifungal drug resistance,” Clinical Infectious Diseases, vol. 36, no. 1, pp. S31–S41, 2003. | Google Scholar

37.L. Strasfeld and S. Chou, “Antiviral drug resistance: mechanisms and clinical implications,” Infectious Disease Clinics of North America, vol. 24, no. 2, pp. 413–437, 2010: Google

38.Z. Yang, C. Li, M. Miao et al., “Multidrug- resistant genotypes of plasmodium falciparum, Myanmar,” Emerging Infectious Diseases, vol. 17, no. 3, pp. 498–501, 2011.| Google Scholar

39.D. Bansal, R. Sehgal, Y. Chawla, N. Malla, and R. C. Mahajan, “Multidrug resistance in amoebiasis patients,” Indian Journal of Medical Research, vol. 124, no. 2, pp. 189–194, 2004: Google Scholar.

40.D. Bansal, N. Malla, and R. C. Mahajan, “Drug resistance in amoebiasis,” Indian Journal of Medical Research, vol. 123, no. 2, pp. 115–118, 2006.: Google Scholar

41.J. W. Bennett, J. L. Robertson, D. R. Hospenthal et al., “Impact of extended spectrum beta-lactamase producing Klebsiella pneumoniae infections in severely burned patients,” Journal of the American College of Surgey.