MULTI DRUG RESISTANCE

INTRODUCTION

The resistance among various bacteria (infectious agents) to various antimicrobial drugs has led to multiple drug resistance phenomenons in the society at an increasing rate. Due to the increased resistance mechanisms of bacterial species against the frequent use of antibiotics and decrease in the efficiency of treatment of infections, results in the failure of microbial response to standard treatment, leads to severe illness, higher expenditures for health care, and an immense risk of death. All the pathogenic agents (e.g., bacteria, fungi, virus, and parasite) have employed high levels of multidrug resistance (MDR) with enhanced morbidity and mortality leading to 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.

CAUSES

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 immune compromised 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

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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.

CLASSIFICATION

Despite of administration of appropriate doses of drugs for a specific duration of time, survival of various microbial strains recommends the high levels of resistance developed in them. This clinical failure is due to not only the antimicrobial resistance but also the suppressed immune function, poor/deprived drug bioavailability, or increased rate of drug metabolism. Persistence of

microbes after conventional/standard treatments points out different types of antimicrobial drug resistance which is an expanding problem in medical world. MDR can be classified as primary or secondary resistance.
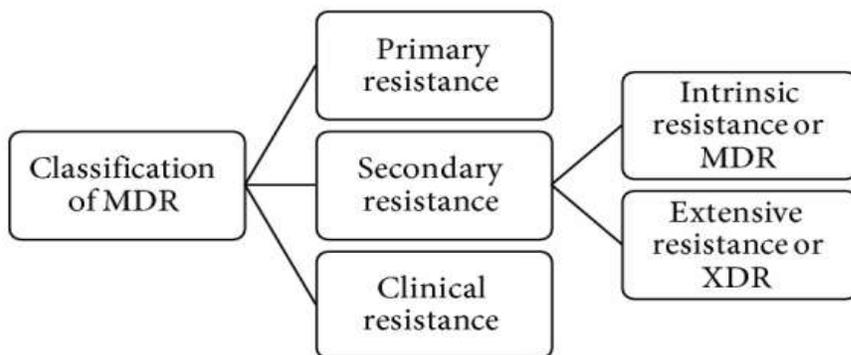
1. **Primary Resistance**

It occurs when the organism has never encountered the drug of interest in a particular host.

2. **Secondary Resistance (Acquired Resistance)**

It occurs when the organism has previously encountered the drug of interest in a particular host. It is further classified as Intrinsic Resistance and Extensive Resistance**.**

i.   **Intrinsic Resistance:** The insensitivity of all microorganisms of a single species to certain common first-line drugs, which are used to treat diseases based on the clinical evidence of the patient. It is also known as multidrug resistance (MDR), for example, *Mycobacterium tuberculosis* to rifampicin and isoniazid or *Candida spp.* to fluconazole.

ii. **Extensive Resistance:** The ability of organisms to withstand the inhibitory effects of at least one or two most effective antimicrobial drugs. Also known as extensive drug resistance arises in patients after they have undergone a treatment with first line drugs, for example, XDR-TB resistance against fluoroquinolone.

3. **Clinical resistance:** Clinical resistance is defined by the situation in which the infecting organism is inhibited by a concentration of an antimicrobial agent that is associated with a high likelihood of therapeutic failure or reappearance of infections within an organism

due to impaired host immune function. In other words, the pathogen is inhibited by an antimicrobial concentration that is higher than could be safely achieved with normal dosing.

Mechanism of Multi Drug Resistance

Resistance means 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.
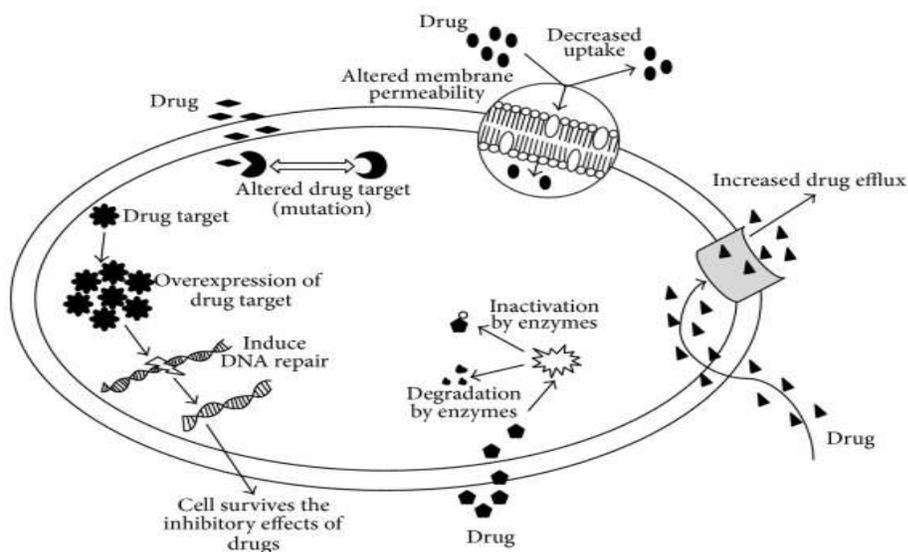
Mechanism of Multi Drug Resistance

1. Alteration in membrane permeability:

Cell wall, in both bacteria and fungi, plays a crucial role in their survival. As we all know, drugs inhibit the cell wall synthesis by binding with the peptidoglycan layer in bacteria or affecting

ergosterol synthesis (e.g., polyenes) in fungi, thus, blocking the cell growth and division. These organisms undergo certain chromosomal mutations or exchange of extrachromosomal DNA elements through conjugation or transformation (horizontal gene transfer) such as in K. pneumonia, which can cause alteration in the cell membrane composition (e.g., a reduction in the ergosterol content in fungal plasma membrane) resulting in decreased permeability and uptake of drugs into the cell. Altered membrane composition (such asβ-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.

2. Modifications in metabolic pathways:

Another mechanism of MDR was found to be an over expression of drug target enzymes leading to target bypass 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. This can influence the access of drugs to the target sites.

3. Inactivation or enzymatic degradation:

Inactivation or enzymatic degradation of antimicrobials by hydrolysis of ester or amide bonds (such as resistance to β-lactams due to β-lactamases, etc.) and chemical transformation of these compounds by acetylation, phosphorylation, adenylation, glycosylation, and hydroxylation have also become increasingly apparent as causes of MDR. The resistant strains of clinical isolates of different microorganisms have developed the ability to oxidize or reduce the antimicrobial compounds to prevent their interaction with the respective targets. 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. With the lack of effective antiparasitic vaccines yet in sight and new drugs developing slowly, MDR in parasites is emerging as a global public health threat. These parasites such as Plasmodia spp. and Toxoplasma gondii, like bacteria or fungi, also undergo certain point mutations/substitutions resulting in altered drug targets, alter

calcium homeostasis in endoplasmic reticulum, and expel drugs (e.g., chloroquine, atovaquone, antifolate combination drugs, and artemisinin) out of the cells.

4. Increased Drug efflux:

MDR mediated by drug efflux pumps remains the predominant mechanism of MDR. The overexpression of genes encoding for ATP-binding cassette (ABC) transporter membrane proteins (e.g., P-glycoprotein (Pgp)), also known as the multidrug efflux pumps which are responsible for the export or expulsion of drugs out of the cell, usually generates MDR and continues cellular functions without any interference. Over expression of P-glycoprotein, in Entamoeba spp. and Leishmania spp. membrane or multidrug resistant proteins (MRP), affects the fluidity and permeability, leading to an ATP-dependent efflux of the antimicrobials and decreasing their intracellular concentration. MDR is also employed by cancer cells, which limits the long-term use of chemotherapy. An insight into the mechanisms involved in the chemo resistance, which can occur either at the beginning of the therapy (innate) or during the course of treatment, reveals that the cancer cells exhibit over expression of certain multidrug resistance proteins (e.g., MRP and Pgp) which induce DNA repair mechanism, inhibit apoptosis, alter drug targets, and modify cell membrane composition as well as promoting an increased efflux of drugs preventing proper diffusion into the cells.

Preventing the emergence of multi drug Resistance

To limit the development of antimicrobial resistance, it has been suggested to:

- Usage of the appropriate antimicrobial drug for the treatment of an infection; e.g. no antibiotics for viral infections.
- Identification of the etiologic agent whenever possible
- Selection of an antimicrobial which specifically targets the pathogen, instead relying on broad-spectrum antimicrobial drugs.
- Complete an appropriate duration of antimicrobial treatment (not too short and not too long)
- Usage of the correct dose for eradication; sub therapeutic dosage is associated with resistance, as demonstrated in food animals.

Infection prevention is the most efficient strategy of prevention of an infection with a MDR organism within a hospital, because there are few alternatives to antibiotics in the case of an extensively resistant or pan resistant infection; if an infection is localized, removal or excision can be attempted (with MDR-TB the lung for example), but in the case of a systemic infection only generic measures like boosting the immune system with immunoglobulins may be possible.

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