MULTIDRUG RESISTANCE BY MICROORGANISMS: A REVIEW

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ABSTRACT
Multiple drug resistance (MDR) is the ability of some microorganisms to resist the actions of multiple antimicrobial agents. MDR include those resistant to multiple antibacterial, antifungal, antiviral, and anti-parasitic drugs. Similar activities of some microorganisms to certain chemical (drug) that would normally kill them or limit their growth is called antimicrobial resistance (AMR). Multi drug resistance can be classified as primary resistance, secondary resistance, intrinsic resistance, extensive resistance and clinical resistance. The classes of antibiotics that fall victim of resistance include beta-lactams, glycopeptide, aminoglycosides, sulphonamides, cephalosporins etc. The mode of action of antimicrobial drug includes cell wall synthesis inhibitors, protein synthesis inhibitor, blockage of key metabolic pathways, nucleic acid synthesis inhibitors etc. Bacteria often become resistant and this could be through one of several biochemical mechanisms such as mutation, destruction or inactivation and efflux or genetic transfer of materials between bacteria by several means such as conjugation, transformation and transduction. The mode of action of MDR protozoa occurs through decrease of drug uptake, the export of drugs from the parasite by P-glycoproteins and other traffic ATPases etc. The mode of action of MDR helminths occurs through genetic changes in the drug target, changes in drug transport, drug metabolism etc. The mode of action of antiviral drugs usually target viral DNA polymerase having the reverse transcriptase activity to inhibit the viral replication. The mode of action of MDR fungi occurs as they have learnt to modify the antifungal drug targets or most commonly increase the efflux of the incoming drugs. There are various ways to reverse this resistance such as washing hands after seeing each patient, the public should wash raw fruit and vegetables thoroughly to clear off both resistant bacteria and possible antibiotic residues, avoid the misuse of antibiotics, etc.

Keywords: Microorganism, Multiple drug resistance (MDR)

INTRODUCTION
Multiple drug resistance (MDR) is an antimicrobial resistance exhibited by some microorganisms to multiple antimicrobial drugs. MDR microorganisms are mostly threatening to public health because they resist multiple antibiotics. Other MDR include those that are resistant to multiple antifungal, antiviral, and anti-parasitic drugs (Magiorakos, 2014; WHO, 2018).

A broad range of biochemical and physiological mechanism may be culpable for resistance (Liu and Pop, 2009; WHO, 2014). In the specific case of antimicrobial agents, the complexity of the processes that contribute to emergence and propagation of resistance cannot be overestimated, and due to the lack of elemental knowledge on these topics is one of the major reasons that there has been so limited significant fulfillment in the effective prevention and control of resistance development (Liu and Pop, 2009; WHO, 2014).

There are specific classes of compounds of antimicrobial that are capable of destroying or inhibiting microorganisms even in high dilutions. (Laxminarayan et al., 2013). Antibiotics are substances that are produced by the natural metabolic processes of some microorganisms which can either inhibit or destroy other microorganisms (Talaro and Talaro, 2002; Nester et al., 2004). The current root of antimicrobial drugs is diverse (Rudramurthy, 2016). The Synthetic antimicrobial drugs in the laboratory are derived from dyes or other organic compounds through chemical reactions (Laxminarayan et al., 2013). For more than 60 years, antibiotics have been critical in the fight against infectious diseases which are caused by bacteria and other microorganism (Laxminarayan and Heymann, 2012). Nevertheless disease-causing microbes that have come to be resistant to antibiotic drug treatment such as pneumonia, septicemia, gonorrhea, tuberculosis, wound infections, and diseases that have become difficult to treat with antibiotics remains an increasing public health problem (WHO, 2013). One side of the issue is that bacteria and other microbes that cause infections are exceptionally volatile and have developed various ways to resist antibiotics and other form of antimicrobial drug (Boucher et al., 2013). Another side of the issue is as a result of increasing use and misuse of current antibiotics in human, veterinary medicine and in agriculture (Todar, 2012). Microbes developing resistance, as well as due to economic reasons have arisen in the research and development in the search for novel antibiotics in order to provide a wide range of effective drugs at all times (WHO, 2014).

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 (Hutner et al., 2013). 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 (Roca et al., 2015). 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 (NIH, 2009). 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 (NIH, 2009). Examples of these microbes include Drug resistant

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Mycobacterium tuberculosis (TB), Methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin-resistant Enterococci (VRE), and Multidrug-resistant Neisseria gonorrhoeae (Gonorrhea), Gram-negative bacteria (NIAID, 2009; Arumugam, 2016; Swamy and Sinniah, 2016).

Classification of Multi Drug Resistance

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 (Tanwar et al., 2014). 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. Multidrug resistance can be classified as primary or secondary resistance (Tanwar et al., 2014).

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 anti-tubercular treatment (Mathur et al., 2000; Paramasivan et al., 2000 Hemvani et al., 2001). 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 (Jassal and Bishai, 2009).

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 (Loeffler and Stevens, 2003; Khalilzadeh et al., 2006). This can also be define as resistance that evolve in a patient who has previously received chemotherapy (Mathur et al., 2000; Paramasivan et al., 2000; Hemvani et al., 2001). 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 (Van Rie et al., 2000).

It can further be classified as follows;

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 antimicrobial class (Chuanchuen et al., 2003). This can also be called “insensitivity” since it occurs in organisms that have never been susceptible to that particular drug (Alekhshun and Levy, 2007). 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 (Alekhshun and Levy, 2007).

For example, Gram-positive bacteria to aztreonam (a beta-lactam), Gram-negative bacteria to vancomycin, anaerobic bacteria to aminoglycosides, aerobic bacteria to metronidazole etc (Forbes and Sahm, 1998; Giguere et al., 2006).

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 (Gandhi et al., 2003; Loeffler and Stevens, 2003).

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 (Loeffler and Stevens, 2003)

Common Drugs: Victim of Resistance

Table 1: Microorganisms and their resistance mechanism to various antibiotics

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Natural resistance against:</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaerobic bacteria</td>
<td>Aminoglycosides</td>
<td>Lack of oxidative metabolism to drive uptake of aminoglycosides.</td>
</tr>
<tr>
<td>Aerobic bacteria</td>
<td>Metronidazole</td>
<td>Inability to anaerobically reduce drug to its active form.</td>
</tr>
<tr>
<td>Gram positive bacteria</td>
<td>Aztreonam (a beta-lactam)</td>
<td>Lack of penicillin binding proteins (PBPs) that bind and are inhibited by beta lactam antibiotic.</td>
</tr>
<tr>
<td>Gram negative bacteria</td>
<td>Vancomycin</td>
<td>Lack of uptake resulting from inability of vancomycin to penetrate outer membrane.</td>
</tr>
<tr>
<td>Klebsiella sp.</td>
<td>Ampicillin (a beta lactam)</td>
<td>Production of enzymes (beta lactamases) that destroy ampicillin before the drug can reach the PBP targets.</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>Imipenem (a beta-lactam)</td>
<td>Production of enzymes (beta lactamases) that destroy imipenem before the drug can reach the PBP targets.</td>
</tr>
<tr>
<td>Lactobacilli and Leuconostoc</td>
<td>Vancomycin</td>
<td>Lack of appropriate cell wall precursor target to allow vancomycin to bind and inhibit cell wall synthesis.</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Sulfonamides, trimethoprim, tetracycline, or chloramphenicol</td>
<td>Lack of uptake resulting from inability of antibiotics to achieve effective intracellular concentrations.</td>
</tr>
<tr>
<td>Enterococci</td>
<td>All cephalosporins</td>
<td>Lack of PBPs that effectively bind and are inhibited by these beta lactam antibiotics.</td>
</tr>
</tbody>
</table>

(Forbes and Sahm, 1998; Giguere et al., 2006)
Multidrug Resistance Protozoa and Mode of Action

Parasitic protozoa are responsible for some of the most devastating and prevalent diseases of humans and domestic animals. Even though protozoa are eukaryotes and usually contain many of the organelles and metabolic pathways of their hosts, the differences in biochemistry between parasite and host are great enough to leave a large window for the development of parasite-specific drugs (Brianti et al., 2016). For example, Malaria (Plasmodium sp.), the various forms of (muco) cutaneous and visceral leishmaniasis (Leishmania sp.), African sleeping sickness (Trypanosoma brucei gambiense, Trypanosoma brucei rhodesiense), Toxoplasma gondii etc (Doliwa et al., 2013; Oliva et al., 2014). Drug resistance mechanisms here in certain protozoans could be described as follows:

- Decrease of drug uptake because of the loss of a transporter required for uptake. This decrease contributes to resistance to arsenicals and diamidines in African trypanosomes (Borst and Ouellette, 1995; Upcroft and Upcroft, 2001). The export of drugs from the parasite by P-glycoproteins and other traffic ATPases. This export could potentially be an important mechanism of resistance, as these proteins are richly represented in the few protozoa. There are indications that such transmembrane transporters can be involved in resistance to emetine in Entamoeba sp., to mefloquine in Plasmodium sp., and to antimonials in Leishmania sp (Borst and Ouellette, 1995; Upcroft and Upcroft, 2001).

- Loss of drug activation as the main mechanism of metronidazole resistance in Trichomonas and Giardia sp. Recent evidence indicates that a decrease of the proximal cellular electron donor for metronidazole activation, ferredoxin, is the main cause of resistance in Trichomonas (Borst and Ouellette, 1995; Upcroft and Upcroft, 2001).

- Resistance arising through alteration of drug targets. The amino acid substitutions in the dihydrofolic reductase-thymidylate synthase of Plasmodium sp. are good examples of this mechanism (Borst and Ouellette, 1995; Upcroft and Upcroft, 2001).

Multidrug Resistance Helminth and Mode of Action

Helminths are a diverse group of parasitic worms, encompassing nematodes, cestodes and trematodes are a major health problem for human and animals in many part of the world (Kaplan, 2004; Hotez et al., 2008).

Genetic changes in the drug target

Most efforts to identify drug resistance in helminths have concentrated on alteration of the drug’s cellular target, identified by changes in the genome sequence. Several single-nucleotide polymorphisms (SNPs) have been associated with resistance (Gilleard, 2006). SNPs are unique genetic differences between individuals and are the basis of genetic differences in a population. SNPs can also arise by gene mutation after drug treatment (Voicey and Morris, 2008).
Changes in drug transport

Although genetic selection contributes to anthelmintic resistance, other mechanisms also contribute. Early studies in cancer cells showed that some tissues were inherently resistant to treatment, whereas other tumours acquired resistance after treatment (Zhou, 2008). This resistance was to a variety of drugs and was mediated by the expression of a membrane protein known as P-glycoprotein (Zhou, 2008). The transport of several anthelmintics (including ivermectin, benzimidazoles and imidazothiazole derivatives) by human P-glycoprotein in cells expressing the transport protein has been reported (Nare et al., 1994; Brayden and Griffin, 2008). This suggests that drug efflux mechanisms might function in drug resistance in Helminths that contain functionally related transport proteins.

Drug metabolism

There is also evidence for increased drug metabolism as a mechanism for drug resistance in parasites, but this is mainly substantiated for protozoa. However, many anthelmintics currently in use cause increased free radical production as part of their cytotoxic activity – for example, praziquantel and artemisinin used to treat Schistosoma sp (El-Bassiouni et al., 2007).

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 (McKeegan et al., 2002). 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 (McKeegan et al., 2002). 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 (Strasfeld and Chou, 2010).

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 (He et al., 2013). Such as reduction in the ergosterol content in fungal plasma membrane) resulting in decreased permeability and uptake of drugs into the cell (Loeffler and Stevens, 2003; Singh, 2013). 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 (He et al., 2013). Mutations in the genes encoding for the target cause modifications at the molecular level and retain cellular function by reducing susceptibility to inhibition (Loeffler and Stevens, 2003; Singh, 2013). 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 (He et al., 2013). 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 prolificans infections are almost uniformly fatal because of their resistance to multiple antifungal agents (Howden et al., 2003).

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 methicillin-resistant) S. aureus (MRSA) had been well known as the bane of hospitals (Deurenberg et al., 2007; Willey et al., 2008; Paterson et al., 2014). 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, methicillin and penicillin. Isolated from the same patient was dread of hospitals vancomycin-resistant Enterococci (VRE) (CDC, 2004). 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 (Willey et al., 2008; Paterson et al., 2014).

Fig. 2: Biochemical and genetic aspects of antibiotic resistance mechanisms in bacteria (Dzidic et al., 2008).

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 (Willey et al., 2008). Susceptible bacteria can acquire resistance to antimicrobials by either genetic mutation or by accepting antimicrobial resistant genes from other bacteria (Martinez et al., 2009). This could be through one of several biochemical mechanisms such as mutation, destruction or inactivation, efflux or genetic transfer of

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materials between bacteria by several means such as conjugation, transformation and transduction (Wiley et al., 2008; Munita and Arias, 2016).

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 fluoroquinolones, the antimicrobial can bind to the specific enzymes, in this case, DNA gyrase (Cattore et al., 2007). The DNA gyrase is an essential bacterial enzyme required for DNA replication. The end result is that fluoroquinolones blocks bacterial DNA replication leading to cell death (FDA, 2004; Cattore et al., 2007). 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 envelopes outer membrane (Delcour, 2009). Genetic mutations that lead to changes in penicillin binding proteins also render a cell resistant. A decrease in permeability can lead to sulfonamide resistance (FDA, 2004).

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 can 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, chloramphenicol contains two hydroxyl groups that can be acetylated in a reaction catalyzed by the enzyme chloramphenicol acetyltransferase with acetyl 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 phosphates (phosphotransferases) or adenyl groups (adenyltransferases) (FDA, 2004; Bush, 2013).

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 harbour energy-driven drug efflux pumps which extrude antimicrobial agents thus reducing their intracellular concentration to sub or non-inhibitory levels (Piddock, 2006). 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 (FDA, 2004). 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 uses the hydrolysis of ATP to actively efflux drugs from cells, while the second type, called secondary active transport, uses an ion gradient for actively efflux drugs from cells (Poole, 2005). 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 (Sanath and Manuel, 2013). Many are drug/proton antporters that are proton enters the cell that the drug leaves. Such systems are present in E. coli, P. aeruginosa and S. aureus etc (Willey et al., 2008).

Fig 3: Showing Efflux and Enzymatic degradation (Todar, 2012).

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 hosts (Todar, 2002; Laxminarayan, 2003; Dromigny and Perrier-Gros-Claude, 2003). Washing hands after seeing each patient is a major and obvious, but too often overlooked precaution (Okeke et al., 2001). 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 (Masters et al., 2003; Szczepanowski et al., 2009).

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 (Woodhead and Blasi, 2005). 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 (Stephen and Kennedy, 2011).
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 drugs (Stephen and Kennedy, 2011).

Conclusion

Inadequacy of available antimicrobial drugs compels continuous development of newer drugs. 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 unfavourable conditions. Improved knowledge of molecular mechanisms controlling MDR should facilitate the development of novel therapies to combat these intrinsignificant infections and will help cultivate a deeper understanding of the pathobiology of microbial organisms.

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