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The third world war: man versus drug resistant virus and bacteria.

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ABSTRACT

Unlimited commercial production of antibiotics and their ever increasing use in our day to day life has led to the evolution of a class of organism known as multi-drug resistance organisms (MDRO). Multi drug resistance (MDR) is a condition in which a particular disease causing microorganism (virus, bacteria, fungi and parasites) becomes resistant to antimicrobials (antivirals, antibiotics or antimicrobics). The present Chapter will focus on the cause and mechanism of MDR in bacteria and their prevention, if any, such as combination antibiotic therapy. These bacteria range from urgent threat level such as *Neisseria gonorrhoeae* to serious threat level such as *Streptococcus pneumoniae* and also includes microorganism with a concerning threat level such as Group A *Streptococcus*. The discussion also includes MDR in viruses (such as Hepatitis B) and their prevention, if any.

Keyword: Multi drug resistance; Antibiotics; Antiviral drugs; R plasmids; Efflux pumps; WHO.

INTRODUCTION

It was way back in 1928 when penicillin was discovered which paved the way for commercial production of many other antibiotics. The global annual antibiotic production stands at an estimated 1, 00,000 tons, reflecting the dependency of life on antibiotic therapy for the treatment of various infectious diseases. The extreme use of antibiotics has led to emergence of multi-drug resistance (MDR) in bacteria, virus and other pathogenic microbes.

Drug resistance in bacteria dates back to 1940's when certain strains of *Staphylococcus aureus* were

found to be resistant against treatment. Various biochemical mechanisms are responsible for the MDR in bacteria. The mechanisms include mutational alteration of the target protein of the antibiotics, enzymatic inactivation of the drug, preventing drug access to the target by means of drug specific efflux pump or by accumulation of resistance plasmids [1]. The various bacterial strains that are the pinnacle of drug resistance includes *Escherichia coli*, *Clostridium difficile*, *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*,

Salmonella typhi, *Acinetobacter*, *Campylobacter*, *Enterococcus* to name a few.

Multidrug resistant viruses have also been reported in patients who are subjected to sequential antiviral therapy like acyclovir resistance in Herpes Simplex Virus (HSV). Prolonged drug exposure and spontaneous viral replication has caused evolution of viruses to resist various drugs. These viruses include Human Immunodeficiency Virus (HIV), Cytomegalovirus, Influenza virus, Hepatitis B virus,

Herpes Simplex virus etc. Evidences of such drug resistant bacteria and viruses are based on reports from World Health Organization (WHO), U.S. Department of Health and Human Services, European Food Safety Authority (EFSA) and European Centre for Disease Prevention and Control (ECDC). Some important and major drug resistant bacteria and diseases caused by them are presented in Table 1 [2, 3, 4]; while major drug resistant viruses are depicted in Table 2 [3][5][6][7][8].

Table 1: Major drug resistant bacteria and the diseases caused by them

Name of the drug resistant bacteria	Resistance to drug(s)	Common diseases caused by the MDRO	Threat level
<i>Streptococcus pneumoniae</i>	Penicillin and Erythromycin	Community acquired pneumonia, acute otitis media, meningitis	Serious
<i>Staphylococcus aureus</i>	Methicillin and related antibiotics (Nafcillin and Oxacillin)	Pneumonia, skin, wound and blood stream infections	Concerning & Serious
<i>Kleibseilla pneumoniae</i>	Cotrimoxazole, Ciprofloxacin, Cephalosporin and Carbapenem	Urinary and Respiratory tract infection, Bloodstream infection, Hospital acquired Pneumonia	?
<i>Mycobacterium tuberculosis</i>	Rifampicin, Isoniazid, Fluoroquinolone, Capreomycin and Kanamycin	tuberculosis	Serious
<i>Escherichia coli</i>	Fluoroquinolone, Amoxicillin, Ampicillin and Cephalosporin	Peritonitis, bloodstream infections and urinary tract infections	?
Nontyphoidal <i>Salmonella</i>	Ceftriaxone and Ciprofloxacin	Fever, diarrhea, bloodstream infections	Serious
<i>Salmonella typhi</i>	Ceftriaxone, Azithromycin and Ciprofloxacin	Typhoid fever	Serious
<i>Clostridium difficile</i>	Fluoroquinolone	Life threatening diarrhea	Urgent
<i>Acinetobacter</i> species	carbapenem	Pneumonia, bloodstream infections	Serious
<i>Campylobacter</i> species	Ciprofloxacin and Azithromycin	Diarrhea, fever, temporary paralysis	Serious
<i>Enterobacteriaceae</i>	Carbapenem, Cephalosporin	Blood stream infections	Urgent & Serious
<i>Neisseria gonorrhoeae</i>	Cephalosporin, Tetracycline and Azithromycin	gonorrhea	Urgent
<i>Pseudomonas aeruginosa</i>	Cephalosporins, Fluoroquinolones and Carbapenem	Infection at surgical sites, blood stream infections and urinary tract infections	Serious
<i>Enterococcus</i>	Vancomycin	Infection at surgical sites, blood stream infections and urinary tract infections	Serious
Group A <i>Streptococcus</i>	Macrolides, Clindamycin, Tetracycline	Pharyngitis, rheumatic fever, skin infections, scarlet fever	Concerning
Group B <i>Streptococcus</i>	Clindamycin, Erythromycin	Sepsis, pneumonia	Concerning

Threat level ‘Urgent’ are those pathogens which requires highest attention from the public healthcare sector with decreasing order of attention for the threat level ‘ Serious’ and ‘Concerning’. Pathogens listed

under ‘Urgent’ show high antibiotic resistance while pathogens listed under ‘Serious’ & ‘Concerning’ shows significant and moderate antibiotic resistance respectively. (?) Not known

Table 2: Common drug resistant viruses and the diseases caused by them

Name of the drug resistant virus	Resistance to drug(s)	Common diseases caused by the MDRO
Human immunodeficiency virus (HIV)	Antiretroviral drug	Acquired immunodeficiency syndrome(AIDS)
Influenza Virus	Oseltamivir, Zanamivir and Adamantanes	Influenza
Hepatitis B virus	Lamivudine, Adefovir, Telbivudine and Entecavir	Hepatitis B
Herpes Simplex virus	Acyclovir and Famciclovir	Encephalitis, meningitis, cutaneous lesion of face, mouth and genitalia, infections of peripheral ganglia.
Varicella zoster virus	Acyclovir and Valacyclovir	Varicella (chicken pox)
Human Cytomegalovirus(HCMV)	Ganciclovir, Cidofovir and Foscarnet	Tissue invasive diseases, Congenital HCMV: mental disabilities, Chorioretinitis

Mechanism of multi drug resistance (MDR)

MDR can be broadly classified into primary and secondary resistance. Primary resistance occurs without any pre-exposure of the drug on the microbes within the host. Secondary resistance can be further subdivided into: intrinsic resistance and extensive resistance. In intrinsic resistance, microorganisms of a single species remain unaffected by the application of first line of drugs generally used for the treatment of the said microbes. On the other hand, extensive

resistance is observed in patients already treated with first line of drugs [5]. We will now consider how the pathogens have devised various strategies for their resistance against numerous antimicrobials. MDR has also been observed in fungi and parasite but is beyond the scope of this chapter due to space limitation and may be considered elsewhere. The various modes of MDR are diagrammatically illustrated in Figure 1

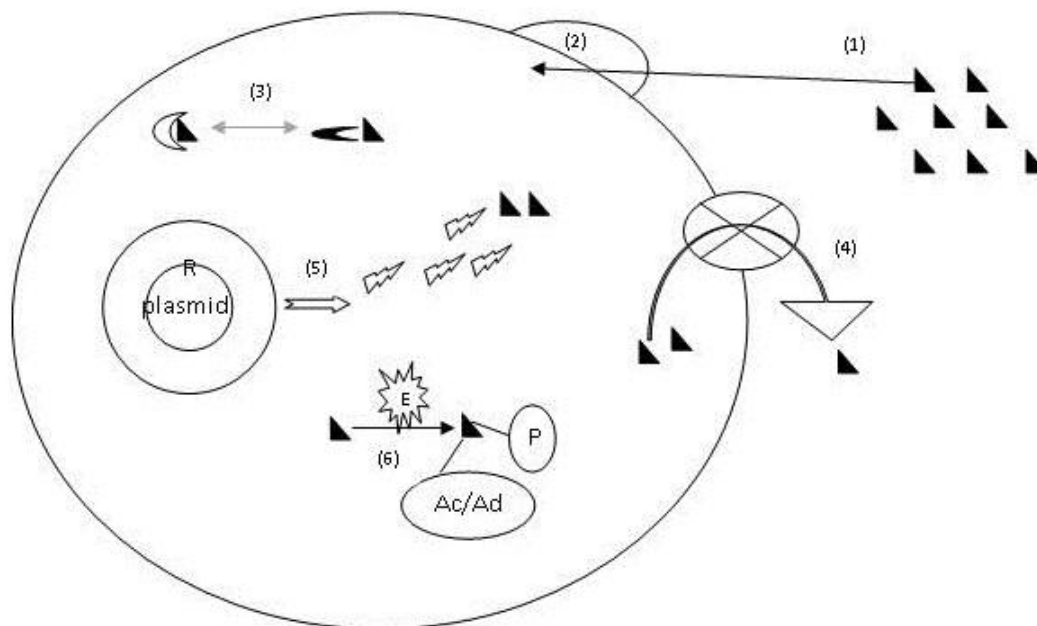


Figure 1: Various modes of multi drug resistance by drug resistant pathogens

- 1) Various drugs used in the treatment of MDRO.
- 2) Altered membrane permeability of MDRO which prevents the entry of drugs into the cell.
- 3) Mutation of the drug target prevents the drug-target interaction.
- 4) Efflux pumps which remove the antimicrobials from within the cell.
- 5) R plasmid contains genes which helps in combating drugs used against MDRO.
- 6) Enzymatic deactivation by acetylation (Ac), adenylation (Ad) or Phosphorylation (P).

Enzymatic deactivation of the antimicrobials is one of the effective measures taken up by the pathogens. Certain strains, for example, *E. coli* and *S. aureus* produces β -lactamase which resists the effect of β -lactam drugs by inactivating drugs like third generation Cephalosporins. Such enzymatic inactivation can also be done by phosphorylation, acetylation and adenylation. All these mechanism of resistance have been seen in strains of *Pseudomonas aeruginosa* which causes the inactivation of aminoglycoside [9].

Antimicrobials generally have a specific target, for example, a class of drugs may inhibit the nucleotide biosynthesis and this will in turn prevent the synthesis of proteins. However, in recent times, the drug resistant pathogens cause the mutation of the targets of the antimicrobials. Fluoroquinolone resistance partly is due to mutation in the DNA topoisomerase [1]. Again, altered mutations in the

reverse transcriptase domain of DNA polymerase minimize the action of antiviral drugs [7]. One such gene responsible for microbial resistance via altered mutation is the *erm* gene and causes resistance to Macrolides [1].

Sometimes, changes in the membrane composition prevent the entry of drug into the respective organism. Basically these changes causes modulation of the cell membrane permeability and this in turn reduces the uptake of drugs as in the case of *Enterobacter aerogenes* [10].

The hindered access of drug to the required target within the drug resistant organism is also seen. Certain proteins such as Tet (M) or Tet (S) brings about changes in the ribosomal conformation, thereby prevents the access of drugs like tetracycline to ribosome [1]. Access of the drug can also be inhibited by the presence of efflux pumps. Microorganisms use these efflux pumps to remove

antimicrobial agents and toxic substances from their internal environment to the outside. Bacterial efflux pumps can be divided into 6 families: major facilitator super family (MFS), small multidrug resistance (SMR) family, drug metabolite transporter (DMT) superfamily, multidrug and toxic compound extrusion (MATE), ATP binding cassette (ABP) superfamily and resistance-nodulation-division (RND) superfamily. The RND superfamily plays the preponderant influence within all the factors responsible for multidrug resistance in gram negative bacteria [11].

Multi drug resistance can also be due to R plasmids. A large number of resistance genes may be present in a single R plasmid. One unique characteristics of R plasmid is that it consists of genes which prevent the loss of R plasmid during multiplication of host cell unlike other recombinant plasmids [12]. They also code for an enzyme known as integrase whose main function is to insert the resistance genes (which are mostly transposons) in the downstream of a promoter. The main matter of concern is that these R plasmids have been found to be transferred by conjugation to susceptible species. Such conjugation has caused multi drug resistance in *S. aureus* [13][14].

Resistance of virus to antiviral drugs has been observed in various strains. Such resistance may be attributed to various causes. One such reason is Thymidine Kinase (TK) mutations in Herpes Simplex Virus (HSV) and Varicella zoster virus (VZV). Just like in bacteria, mutation in the DNA polymerase is responsible for antiviral drug resistance as is the case observed with Cytomegalovirus [7][8]. Again, mutation in the reverse transcriptase domain of the polymerase gene is responsible for ineffectiveness of various drugs used in the treatment of the Hepatitis B virus (HBV). Mutations in the catalytic domain (Domain C) of polymerase gene are also seen in HBV [6]. Resistance of Cytomegalovirus to Ganciclovir (GCV) or to Valganciclovir (VGCV) is due to mutation in *UL97* gene which encodes a protein kinase and this in turn phosphorylates GCV [7].

Some ray of hope: How we can resist the multi drug resistance..... New strategies

Recent reports have suggested the use of combination therapy as an effective therapeutic measure in treatment of MDR organisms. Extensive literature reviews have shown that combination of

Levofloxacin and Ceftriaxone or Ampicillin and Azithromycin is effective in down-regulating inflammation associated with *Streptococcus pneumoniae* in a mice model [15][16]. Available literature suggests that presently ten new or repurposed drugs are being used for clinical treatment of drug resistant *Mycobacterium tuberculosis*, including Gatifloxacin, Moxifloxacin, Rifapentine and Delamanid. Even combination of more than two antibiotics is helpful, e.g. NC001, a combination of Moxifloxacin, PA-824 and Pyrazinamide. Tuberculosis vaccines are also being employed for the treatment of infections associated with *Mycobacterium tuberculosis* [17]. Similarly, an oxazolidinone type antibiotic, known as Cadazolid is presently under clinical trial, which has been found to be effective against Linezolid and Fluoroquinolone resistant *Clostridium difficile* [18][19]. Like *Streptococcus pneumoniae*, combination therapy has also been found to be effective against *Pseudomonas aeruginosa*. Combination of Ceftolozane and Tazobactam has shown formidable anti-pseudomonal activity [20][21]. The same combination of Ceftolozane and Tazobactam has also been studied against *Pseudomonas aeruginosa* and *Enterobacteriaceae* [22]. In case of drug resistant *Neisseria gonorrhoeae* (*Ng*), oral formulation of DNA gyrase inhibitor (AZD0914) is found to be efficacious against MDR gonorrhea; while a combination of Fosfomycin with Azithromycin (AZT) or Ceftriaxone (CRO) is also effective in management of *Ng* [23, 24]. Thymidylate kinase (TMK) inhibitor, TK-666 as the name suggests inhibits TMK which is responsible for phosphorylation of deoxythymidine monophosphate to deoxythymidine diphosphate have potent antibacterial activity against Vancomycin resistant *Enterococcus* (VRE) and Methicillin resistant *Staphylococcus aureus* (MRSA) [25]. With the advancement of nanotechnology, nanoparticles are also considered as suitable candidates for antibacterial activity. Some studies have shown that silver nanoparticles functionalized with polyethylene glycol are effective in inhibiting *S. aureus* growth [26]. Methicillin resistant *S. aureus* can also be controlled with the application of ZnO NPs [27]. Cryptdin-2, an antimicrobial peptide, loaded nanoparticles have been partially successful in eradicating *Salmonella typhimurium* infection [28]. Even modification of active antibiotics where

lipophilic substitution of glycopeptides led to emergence of a new class of antibiotics known as lipoglycopeptides (e.g. Dalbavancin) which exhibited antibacterial activity against VRE [29][30]. Bacteriocins are low molecular weight proteins produced by various microorganisms are known to show antimicrobial activity. Review of pertinent literature reveals novel bacteriocins, known as Salivaricin SMXD5 (produced by *Lactobacillus salivarius* SMXD51) has anti-*Campylobacter* activity [31]. In contrary to the earlier statement, combination therapy is not always a success with MDR organisms, and combination therapy is not recommended for *Acinetobacter baumannii*, instead an antimicrobial peptide, known as Lycosin-I, isolated from the venom of the spider *Lycosa singoriensis*, have shown the potential to be developed as an antibiotic in treatment of MDR *Acinetobacter baumannii*. A change in the mode of delivery of antibiotics has also been proposed, and very recent a study showed that aerosolized administration of antibiotic have a greater chance of reducing ventilator-associated pneumonia (VAP) attributed to MDR *Acinetobacter baumannii* [32][33][34].

Various new treatment strategies are also being devised for the treatment of drug resistant viruses. Novel anti varicella zoster virus (VZV) drugs which are currently under clinical trial includes FV-100 (bicyclic nucleoside analogue), and ASP2151, a helicase primase inhibitor [35]. A recent WHO report recommends the use of Tenofovir, alone or in combination with Emtricitabine, for the treatment of hepatitis B virus infection [6]. Combination therapy has also found its application in drug resistant viruses like HCMV. Combination of two resistant antiviral drugs, Ganciclovir and Foscarnet, has been found to be effective based on a few case reports and *in vitro* data in earlier studies. Combination of two or more natural products lead to hybridization and formation of a hybrid molecule which shows enhanced biological activity. Such hybrid molecules, namely, 1, 2, 4-trioxane-ferrocene have shown activity against HCMV. Indeed, all recent report shows that combination therapy is the only possible way to combat HCMV. Again, in a recent study, combinations of Letemovir with other commonly used HCMV antivirals that target the viral DNA polymerase have shown strong antiviral activity [36][37][38]. Moreover, new compounds are being designed for treatment of viral infection. The

infections associated with HSV, can be treated with the compounds which are primarily immune response modifiers. It is known that the vaccines have long been recommended for the treatment of various infectious diseases. Nowadays, to combat drug resistance various new types of vaccines are being designed. Vaccines designed to eradicate HSV have recently been documented where a vaccine composed of HSV-1 glycoprotein C (gC1) and HSV-2 glycoprotein C (gC2) in combination with HSV-1 glycoprotein D (gD1) and HSV-2 glycoprotein D (gD2) prevents HSV infection by complement activation. Also topical treatment has been recommended for a long time. As a result, topical SMIP 7.7, a toll like receptor (TLR7) agonist showed promising activity against HSV diseases. Yet again, like bacteria, nanoparticles with surface modification find their application in antiviral treatment. For this, researchers have shown that mucus penetrating particles (MPPs) loaded with acyclovir monophosphate (ACVp) protected mice from vaginal HSV in a mice model [39][40][41][42][43]. In case of Influenza virus a compound known as UV-4 or N-(9-methoxynonyl)-1-deoxyojirimycin has been developed which is basically an imino-sugar analog, is found to be highly efficacious against influenza (H1N1) virus. In another report, Eritoran, a TLR4 antagonist, have shown anti-influenza activity in a mice model [44][45][46]. Though not curable, a sizable amount of research to find novel regimens for treatment against AIDS is going on. Recently, a group of researchers have shown that Dolutegravir, a new generation integrase strand transfer inhibitors (INSTIs) in HIV infected patients is active while another research group have shown that the combination of Elvitegravir, cobicistat, Emtricitabine and Tenofovir DF as the first line of treatment for AIDS. Recent findings also shown that vector mediated antibody expression can prevent HIV infections [47][48][49][50][51].

Most of the drugs mentioned above are going through any of the three phases as described in Figure 2, consists of Discovery, Preclinical development and Clinical development. While the discovery phase consists of lead optimization, phase 2 or preclinical development comprises of early stage development and Good laboratory practice toxicology study (GLPT), the clinical development includes phase 1, phase 2 and phase 3. This sequence forms the development pipeline of a new drug. A typical

example of this scheme is the development of a new tuberculosis drug where Nitroimidazoles are under lead optimization phase, and DC-159a (a fluoroquinolone) and BTZ043 (a benzothiazinone) are under the early development and GLPT phase,

respectively. In the clinical development phase drugs include AZD5847 (oxazolidinone), Pa-824 (nitroimidazole), Gatifloxacin (fluoroquinolone) are under phase 1, phase 2, and phase 3 clinical trials respectively [17].

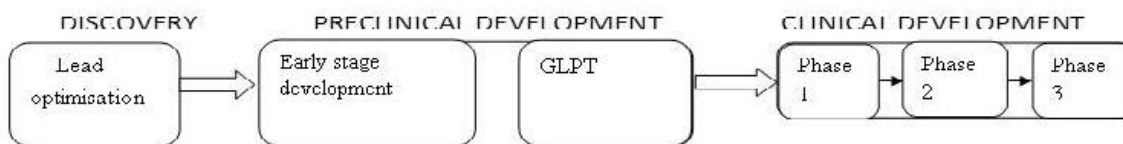


Figure 2: the pipeline for drug development against MDRO.

What the layman can do to contribute in prevention of MDR

Though a lot of emphasis in pursuing extended research on MDR organisms is presently taking place along with the additional responsibilities from the government organizations, common man also has to take some precautions in preventing further evolution of MDR microbes. Here are some preventive measures that can be taken up by layman for a better and safe future [2][5].

- Always use the drugs prescribed by qualified physician
- The schedule of prescribed drugs should strictly be followed.
- Scheduled medications should not be stopped even if they feel better.

- Patients should not ask for additional drugs when the physician thinks there is no necessity.
- Drugs should not be conserved for future illness.
- Alerting each other about infections caused by MDR organisms.
- Taking measures to prevent excessive use of antibiotics in animals, as this can prevent the transfer of any drug resistant zoonotic microbes from animals to human beings.
- Most importantly, self medications and chronic undesired use of antibiotics should strictly be avoided.

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