World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: http://www.wjpsonline.org/
Review Article

Antimicrobial Drug Resistance: A Review

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Received: 25-07-2020 / Revised Accepted: 27-08-2020 / Published: 30-08-2020

ABSTRACT

Problems of antimicrobial drug resistance are presently serious and desperate. The principal areas of concern are twofold: multiresistant opportunist bacteria that affect vulnerable patients in high dependency areas of hospitals major problem for developing countries like India. There is multidrug resistance among the classic pathogens. Almost 1/3rd population on the earth are infected by mycobacterium tuberculosis, salmonella typhi, Shigella spp., Neisseria gonorrhea and plasmodium falciparum. Number of drugs available for the treatment of viral, fungal and parasite infections is comparatively less; moreover very little is known about resistance. In recent years; concern has increased that the golden antibiotic era might be coming to an end. This is attributed to the rate of production of new antimicrobial agents has reduced. Moreover, different parasites are showing great inventiveness in devising mechanisms for overcoming the lethal activity of such agents. If antimicrobial chemotherapy is preserved for future; prescribers must learn to use these powerful tools with greater discretion and their use worldwide must be regulated effectively.

Keywords: Antimicrobial Drug; Drug Resistance; Parasites

INTRODUCTION

There should be awareness among the health professional and the public. They should be emphasis on infection and antimicrobial in medical curriculum. It is a need of time to discuss the issue at length to avoid mammoth problem of drug resistance. Drug resistance is a state of insensitivity or of decreased sensitivity to drugs that ordinarily cause growth inhibition or cell death.

Types of drug resistance: There are two types of bacterial resistance: Inherent and acquired.

1. Inherent: Gram negative bacteria as a group are inherently resistance to number of important antibiotics that are very effective against gram positive organism. Further, pseudomonas aeuruginosa presents high intrinsic resistance too many antibiotics among the gram negative organisms. This inherent resistance of gram negative organism is associated with the impermeability of the complex outer layers of the cell envelop to

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How to Cite this Article: Dr. Pravin J. Patil. Antimicrobial Drug Resistance: A Review. World J Pharm Sci 2020; 8(9): 169-174.

some drugs which prevents the attachment of an inhibitory concentration within the cell. Drugs with poor activity against gram negative bacteria because of permeability barriers are Benzylpenicillins, Fusidic acid, Macrolide, Bacitracin.etc.

2. Acquired resistance: The resistance is acquired by the microbes following the months or years of continuous use, to the new introduced drug. Despite common it is not necessarily predictable. Thus *streptococcus haemoliticus* has remained sensitive to benzylpenicillins after more than 40 years exposure to drugs. However, there is increasing occurrence of drug resistance. Penicillin resistant pneumococci, methicillin (and multidrug) resistant staphylococcus aureus (MRSA), vancomycin insensitive (VISA). The problem is undoubtedly increasing for example: Penicillin resistant meningococci are emerging and antiviral resistant HIV emerge even during treatment.

Mechanism of Development of Drug Resistance:

1. Resistance genes and mechanisms existed long before antibiotics were used. For example, antibiotic resistant bacteria have been isolated from deep within glaciers in Canada's high arctic regions, estimated at 2000 years old.
2. The microorganisms used to produce antibiotics must, by definition, be resistance and are thus a source of antibiotic resistance genes.
3. Antibiotics are given not for their direct effect on humans but to kill an infecting pathogen. Unfortunately they are not so namely targeted and will try to kill any bacterium they encounter.
4. The adult human composes some cells, but only 10% of these are human. The remainders are the bacteria, fungi, protozoa, worms and even insects that make up our normal flora. Each time an antibiotic is administered the normal flora are also exposed. In addition many antibiotics are excreted in an active form and thus environmental bacteria are exposed.
5. Bacteria thus have infinitely expandable and mutable populations to throw in waves at the barrier of antibiotics. Resistance can pass vertically from generation to generation and also horizontally gene transfer for example, plasmids have also evolved and resistance can passed to other species and genera.

Multiple drug resistance can be as assembled by sequential addition of other mobile genetic elements (integrons and transposons)

Example of resistance gene originating in environmental bacteria and transferring to pathogens includesTetracyclines resistance from enterococci to pneumococci and gonococci and erythromycin resistance from bacillus spaericus to bacteroids fragilis.

Genetic Basis of Acquired Antibiotic Resistance: This can be explained in two ways:

1. Spontaneous mutation: - Replica plating reveals that drug resistance cells appear in the absence of the antibiotic i.e. the drug does not induce the development of resistance.

The rate of occurrence of resistant cells can usually be increased by the exposure of bacterial cultures to mutagens usually, a single mutation at an appropriate genetic allows produces only a small increase in resistance and the level of resistance (as opposed to the frequency) gradually builds up with successive mutations at other sites each conferring a small increment in resistance.

2. Acquisition of antibiotic resistance by the transfer of genetic information

The ability to transfer genes that confer drug resistance by cellular conjugation is due to the presence of plasmid (extra chromosomal genetic DNA elements) in bacterial cell that replicate separately from but usually under the control of the bacterial chromosome.

The entire linked complex of resistance transfer factor (RTF) and resistance determinants is known as R- factor and takes the form of double stranded circular molecule of DNA, the size of which is determined by the number of resistance determinants attached to the RTF. The resistance determinants associated with R-factor confer resistance to many drugs, including the Tetracyclines, B-lactams, the Sulphonamides, the Aminoglycosides, Chloramphenicol and Trimethoprim.

The transfer of resistant genetic information takes place by three ways:

1. Conjugation: Transfer of genes between cells that are in physical contact with one another.
2. Transduction: Transfer of gene from one cell to another by a bacteriophage.
3. Transformation: Transfer of cell free or "naked" DNA from one cell to another. Before dealing with the first mechanism of resistance development i.e. due to reduction in permeability to antibiotics. We will see in brief the structure of bacterial cell wall.

Biochemical mechanisms of resistance:

The structure of bacterial cell and its role of outer membrane of gram negative organism in drug resistance.

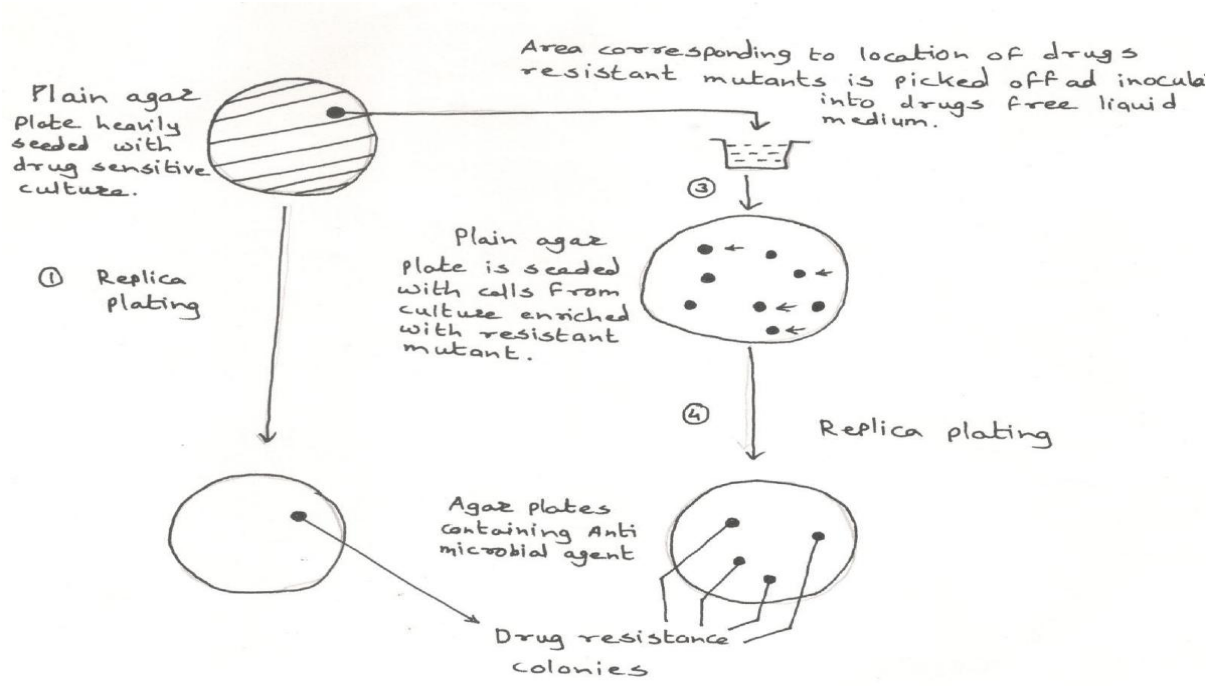

Figure No.1: The technique of replica plating reveals the existence of drug resistant cells in a population i.e. overall drug sensitive. The experiment indicates that drug resistance mutants occur in a bacterial population not previously exposed to the drug.

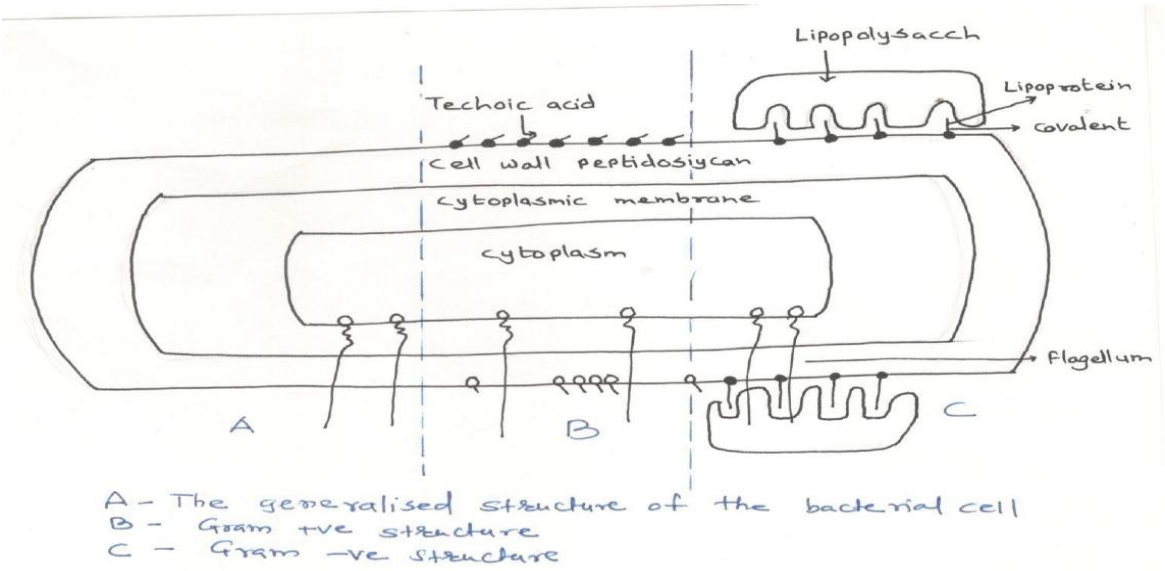

Figure No.2: Structure of bacterial cell

Three fundamental division of the bacterial cell occur in all species, cell wall, cell or cytoplasmic membrane and cytoplasm.

Cell wall- Extensive chemical studies have revealed a basic structure of alternating N-acetyl glucosamine and N-acetyl 3-o-l carboxy ethyl glucosamine molecules, giving a polysaccharide backbone. This is then cross linked by peptide chains the nature of which varies from species to species. This structure possesses good mechanical strength and is the target for the group of antibiotics which in different ways inhibit the biosynthesis occurring during cell growth and division.

The gram negative cell wall (in Fig.2) is even more complicated essentially, it contains lipoprotein molecules attached covalently to the oligosaccharide backbone and in addition on its outer side a layer of lipopolysaccharide (LPS) and protein attached by hydrophobic interactions and divalent metal cation Ca^{+2} and Mg^{+2} on the inner side is a layer of phospholipid (PL).

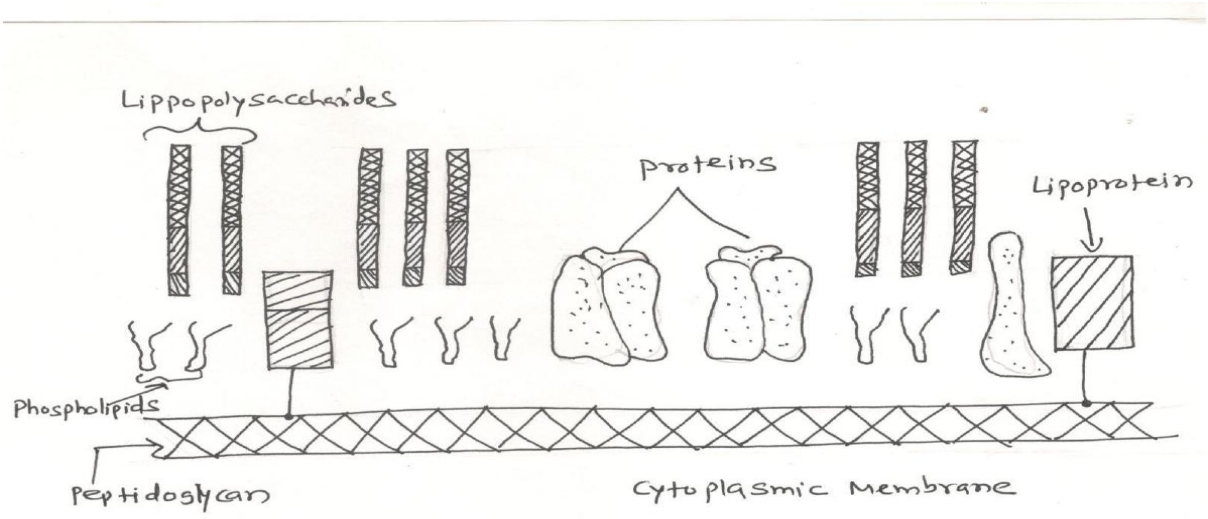

Figure No.3: Detail structure of the wall of Gram –ve bacteria

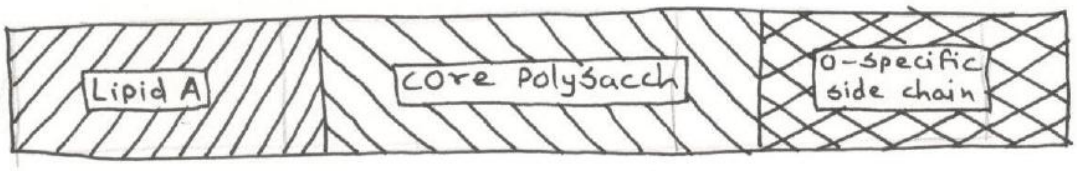

Figure No.4: Lipopolysaccharide structure in Gram –ve bacteria

The complex outer layers beyond the peptidoglycan in gram negative species protect organism against some of the antibiotics.

Some of the proteins consist of three subunits and these units with a central space or pore running through them are known as porins.

A. Reduction in cellular permeability to antibiotics:
I. Decreased in cellular permeability to the drug may therefore, depress the drug concentration at the target site below the inhibitory level. This reduction in permeability can arise in several ways.

a. As we have seen gram negative bacteria are intrinsically less sensitive than gram positive bacteria to a variety of antibiotics, some antibiotics active against gram negative bacteria may cross the outer lipoidal membrane of these organism via water filled channels that are created by the presence of pore forming proteins known as porins in the membrane. These pores permit the free diffusion of hydrophilic molecules of molecular weight up to 600-700. Mutation affecting the structure of the porins can adversely affect the uptake and therefore antibacterial action of antibiotics such as Chloramphenicol and Cephalosporin.

b. Antagonism of antibiotic transport process: The specific antibacterial effect of the Tetracyclines antibiotics is due to the ability of susceptible bacteria to accumulate these drugs within the cytoplasm by a transport process located in the cytoplasmic membrane there seems little doubt that resistance to the Tetracyclines is caused principally by a plasmid mediated specific antagonism of the Tetracyclines accumulation process. The antagonism of Tetracyclines accumulation is induced by sub inhibitory concentration of the Tetracyclines and is associated with synthesis of at least one protein associated with cytoplasmic (transport) membrane. There is evidence that some resistant bacteria can pump Tetracyclines out of the cells and reduce the intracellular concentration below the level required to inhibit protein synthesis. Semisynthetic Tetracyclines derivative Minocycline (7-dimethylamine-6-demethyl-6-deoxytetracycline) is active against several stains of staph. Aureus that are resistance to other Tetracyclines apparently because it can penetrate bacterial cells that that excludes the other Tetracyclines.

c. Loss of antibiotic transport process: The antibiotic Cycloserine, which has been used in the treatment of tuberculosis, is an analogue of the amino acid D-alanine. Cycloserine is concentrated in bacterial cells by the alanine transport system. Resistant mutants of E.coli are known that have partially or completely lost the ability to accumulate alanine and Cycloserine.

II. Conversion of an active drug to non-toxic derivative:
Example, inactivation of Penicillin resistant S. aureus isolated from proteins which failed to respond to therapy convert the drug to an inactive product penicilloic acid. This reaction is catalyzed by a family of related enzymes, the B-lactamases found in gram positive and gram negative bacteria.

Genetics and physiology of B-Lactamases synthesis

In many clinically important resistant strains of bacteria, the production of B-lactamase is controlled by extra chromosomal genetics elements. The R-factors in gram negative bacteria and transducible plasmids in gram positive bacteria such as s.aureus.

Table No.1: Differences in Gram Positive and Gram Negative B-lactamase

Sr. No.	Gram +ve B- lactamases	Gram –ve B- lactamases
1.	Molecular weight of enzymes around 28000	Molecular weight about 22000
2.	Synthesis is induced by antibiotics	Synthesis is constitutive i.e. continuously but smaller quantity than gram +ve
3.	Enzyme is released from the cell and destroyed the antibiotic in external environment	Enzyme is not released in to external environment
4.	These are more effective against penicillin than they are against the cephalosporin group	These are highly effective Cephalosporins and penicillinase

Because of the lower rate of access of B-lactam antibiotics to the target enzymes of gram –ve cells and because the B-lactamases are not subject to significant dilution there is no need for large scale B-Lactamase synthesis in these cells[1-3].

Newer Penicillins and Cephalosporins stable to B-lactamases are:
1. Cefotaxime a semisynthetic drug stable to B-Lactamases.
2. Thienamycin a naturally occurring drug stable to B-Lactamase.
3. Clavulanic acid, a naturally occurring
Inactivation of chloramphenicol by acetylation:
Chloramphenicol resistance mediated by R-factor in gram negative bacteria and by transducible plasmids in S. aureus is due to the presence of an enzyme, Chloramphenicol acetyl transferase (CAT) that acetylates the hydroxyl groups in the slide chain. The resulting 1,3-diacetoxy Chloramphenicol is inactive.

Table No.2: Inactivation of aminoglycoside antibiotics

Enzyme	Substrate
Streptomycin-spectinomycin adenyl transferase	Streptomycin-spectinomycin
Streptomycin phosphotransferase	Streptomycin
Kanamycin acetyl transferase	Kanamycins A and B neomycines

III. Changes in the target site resulting in resistance:
Example- Streptomycin
The ultimate target of Streptomycin in protein synthesis is protein S12 of the 30S subunit. In E. coli a single amino acids replacement in either one of two specific positions of S12 results in 30S ribosomes resistant to streptomycin; lysine 42 may be replaced by aspargin, threonine or arginine.
Streptococci facecalis and *staph.* aureus produces resistance, Streptomycin by enzyme inactivation.

IV. Increased production of a biochemical intermediate that is competitively antagonized by a drug
The sulphonamides antibacterial exert their antibacterial action by the competitive antagonism of an essential metabolic intermediate, p-amino benzoic acid.
Another mode of resistance has been identified in Staph. aureus that depends upon an unusually high level of synthesis of p-amino benzoic acid.
This results in competitive displacement of Sulphonamide from dihydropteroic acid synthetase and relief of the antibacterial action of the drug.

Recent Advances:

1. The study has been carried out to detect the heterogeneous location of the mupA high level mupirocin resistance gene in staphylococcus aureus. Mupirocin is a topical antibiotic used in the treatment of staphylococcal and streptococcal skin infection. The resistance gene has been cloned

sequenced and probes have been used to investigate its distribution. The present study was unable to detect a mupirocin resistance plasmid in control strain "STH 1" as probes appeared to hybridized with residual chromosomal DNA. In the present study the heterogeneous location of mupA was also indicated by HMC II digested DNA.

2. Antibiotic resistance pattern among blood culture isolates in a Danish country is determine. The aim of the present study was to examine the frequency of antibiotic resistance among blood culture isolates and analyze whether there have been any major changes in the patterns of resistance.

3. Million deaths occur each year due to TB so the technique is developed for the rapid diagnosis of isoniazid and rifampicin resistance in mycobacterium tuberculosis.

Genotypic methods

Mutation target in drug resistance of Isoniazide Gens – rpo B, kat G

Function: DNA dependent RNA polymerase catalyses peroxidase

DNA sequencing

Heteroduplex analysis[4-11]

By whom's mistakes drug resistance causes?

The report recognizes that antibiotics are overused and misused in 1. Human 2. Veterinary medicine 3. Farming (growth promoters) 4. Aquaculture 5. Plant culture.

Measures to prevent antimicrobial drug resistance:

1. Education: A thorough knowledge of antimicrobial drugs and the understanding what they will and will not do, is essential in the control of antimicrobial resistance.
2. The need of antibiotic should properly define i.e. use of antibiotic for treatment in which the bacteria are unlikely involve for example, viral respiratory infection. To avoid the antibiotic where there is little benefit of it for example, most diarroheal illness, acute recurrence of herpes simplex.
3. Emphasis in medical/pharmacy curriculum at UG and PG level.
4. In UK British society for antimicrobial chemotherapy initiates to formulate standard procedure that used to better information in future.
5. The WHO also attempting to coordinate information through its antimicrobial resistance monitoring program.
6. Non- human use of antimicrobial agents should be avoided.
7. There should be regulation for resistance as the global problem.
8. Encouraging program for development of new antibacterial agents. Many antibiotics developed during 1960 therefore derivatives only[12-13].

Acknowledgement:

Author is thankful to Dr. Manohar J. Patil, Principal, Marathwada Mitra Mandal's College of Pharmacy, Pune for providing the facility to generate this review.

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