

REVIEW ARTICLE**Mechanisms of Bacterial Resistance****Muhammad Ali Sheraz¹, Sofia Ahmed¹, Iqbal Ahmad¹ and Saif ur Rehman Khattak²****ABSTRACT**

The antibiotic resistance in microorganisms is a worldwide problem that results due to chemotherapy of microbial diseases. The appearance of gradual resistance shows that a single antibiotic loses its effectiveness with the laps of time against microorganisms. Bacteria may develop resistance intrinsically or acquire it either vertically or horizontally. This review highlights the mechanisms involved in the resistance development of bacterial species against different classes of widely used antibiotics.

KEYWORDS:

Antibiotics, bacteria, resistance, vertical evolution, horizontal evolution.

INTRODUCTION

Since the discovery of antimicrobial drugs, they have proved remarkably effective for the control of bacterial infections and have saved the lives of millions of people. However, it soon became evident that bacterial pathogens were unlikely to surrender unconditionally, because of the development of resistance to many of the first effective drugs including the recently developed ones, soon after they were marketed¹⁻⁴. It is important to distinguish the several ways in which an organism may demonstrate resistance. The antibiotic resistance may be intrinsic or acquired.

Intrinsic Resistance

Intrinsic resistance (also called innate or natural resistance) to an antimicrobial agent characterizes resistance that is inherently or naturally possessed by bacteria. These organisms may lack the appropriate drug-susceptible targets or possess natural barriers that prevent the agent from reaching the target, e.g. *Streptomyces* possess some genes that are responsible for resistance to its own antibiotic. Gram-negative bacteria have an outer membrane that establishes a permeability barrier against the antibiotics. An organism may lack a transport system, or the target, or receptor for the antibiotic⁵⁻⁹.

Acquired Resistance

Acquired resistance is developed due to the changes in the genetic composition of a bacterium so that a

drug that once was effective, fails to be active. Tolerance to the previously lethal bactericidal actions is also considered as a type of acquired resistance, even if the organisms remain susceptible to the drugs⁵⁻⁹. Tolerance is the ability of bacteria to survive in the presence of antibiotics, but fail to continue cell division i.e. action of the antibiotic is converted from bactericidal to bacteriostatic. Resistance, on the other hand, is continuation of both survival and duplication of bacteria in the presence of antibiotics⁵. Novak et al.¹⁰ observed the emergence of vancomycin tolerant strains of *Streptococcus pneumoniae* in community. They concluded that the appearance of tolerance in *S. pneumoniae* might be a serious concern, as it could be a direct precursor to resistance.

When a new antibiotic is introduced, many bacteria are susceptible to it. Hughes and Datta¹¹ noted that bacteria preserved from 1917–1954 (the “pre-antibiotic” era) had very little antibiotic resistance (i.e. acquired resistance) except intrinsic resistance. However, since the dawn of the antibiotic era, acquired resistance to every known antibiotic has been observed in one or more bacterial strains. The resistance sometimes arises in an individual patient during the course of treatment, but more often people are infected by resistant bacteria that are acquired from the community or the hospital environment¹².

Davis and Smith¹³ reported that microorganisms have

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gained resistance to most antibiotics through a variety of biochemical mechanisms, which may be classified as follows:

1. Limiting the intracellular concentration of the antimicrobial agent by decreased influx or increased efflux.
2. Enzymatic inactivation of antimicrobial agent.
3. Decreased conversion of drug to active growth inhibitory compounds.
4. Increased concentration of metabolites antagonizing the drug.
5. Altered amount of drug receptor.
6. Decreased affinity of receptor for the drug.
7. Decreased activity of an enzyme required to express the drug effect.

Antibiotic resistant bacteria are associated with failure to respond to antibiotics, which consequently results in increased mortality and morbidity¹⁴. Studies conducted by McGowan¹⁵, Moller¹⁶, Ringertz and Kronvall¹⁷ and Mouton et al.¹⁸ have indicated a direct relationship between the use of antibiotics and the spread of antibiotic resistance among bacteria, while Ballou and Schentag¹⁹ and McGowan¹⁵ reported that the reduction in the use of antibiotics, could lower the frequency of antibiotic-resistant bacteria.

It is known that organisms that were resistant to several different groups of antimicrobials are now becoming more prevalent in recent years²⁰. The extent to which bacteria develop resistance to antimicrobial drugs and the speed, with which they do so, vary with different types of drugs⁴.

Bacterial Genome

The bacterial genome consists of a single, circular chromosome that carries all of the essential genes and also the non-essential genes, and one or more varieties of small DNA circles called plasmid that generally carries non-essential gene (Fig.1). Plasmids replicate independently of the chromosome, and can exist in the cell as one copy or as many copies. Many plasmids contain mobile DNA elements or sequences called as transposons (jumping genes)²¹.

The transposons are very often on plasmids but have the ability to jump from plasmid to plasmid or from plasmid to chromosome. They carry single or multiple

resistance. The transposons can enter and remain stable in different species even if its entry vector (e.g. plasmid or phage) is lost as it can be incorporated into the resident plasmid or the chromosome of the new host. The discovery of transposons has helped in understanding that why different genera evolve similar genes of resistance²¹.

Mechanisms of Resistance in Bacteria

Bacteria acquire resistance through two genetic processes:

- 1) Vertical evolution or vertical gene transfer.
- 2) Horizontal evolution or horizontal gene transfer.

1) Vertical gene transfer

In vertical genetic exchange, genetic information is passed down to daughter cells through cell division. This resistance may be acquired by mutation and selection^{5-8, 21}.

Mutation and Selection

Any change in the structure of the genetic material or more specifically, any change in the base sequence of the DNA is called Mutation (Fig. 2). It occurs spontaneously in bacterial DNA that:

- Modify or eliminate a target for an antibiotic's action, or
- Cause changes in the bacterial surface so that the antibiotic is not taken up, or
- Cause the production of an enzyme that inactivates the antibiotic, or
- Cause the antibiotic to be excreted from the bacterial cell.

If a mutation for an antibiotic resistance does occur, and the person is being treated with that antibiotic, it will kill or inhibit the non-resistant or susceptible bacteria, leaving the antibiotic-resistant bacteria to multiply and flourish. This is the process of Selection (Fig. 3).

Some important examples of mutational resistance include:

- Resistance to streptomycin (ribosomal mutation),
- Quinolones (gyrase gene mutation),
- Rifampin (RNA polymerase gene mutation), etc.

2) Horizontal gene transfer

Horizontal evolution is the acquisition of genes for resistance from another organism. Horizontal genetic exchange is the primary mechanism of the evolution of antibiotic resistance. Some bacterium develops genetic resistance through the process of mutation and selection and then donates these genes to some other bacterium through one of several processes for genetic exchange that exists in bacteria i.e. through conjugation, transduction, or transformation (Fig. 4). For example, *Streptomyces* has a gene for resistance to its own antibiotic i.e. streptomycin, but due to horizontal evolution that gene enters into *E. coli* or *Shigella*^{5-8, 21}.

Transduction

In transduction the gene for determining drug resistance are located in a plasmid and this extra chromosomal DNA is transferred from one bacterium to another by a phage. This mechanism of transferring antibiotic resistance has clinical importance. The penicillin resistant *Staphylococci* have plasmid containing genes for beta-lactamases, which confer resistance to Penicillin.

Transformation

This method of transferring genetic information involves uptake and incorporation of DNA that is free in the environment into the bacterial genome leading to the emergence of a new genotype (recombinant). It is common for DNA to be transferred as plasmids between mating bacteria. Since bacteria usually develop their genes for drug resistance on plasmids (called Resistance Transfer Factors or RTF), they are able to spread drug resistance to other strains and species during genetic exchange processes. Although some bacterial cells are capable of excreting transforming DNA during certain phases of growth, the importance of this method of transfer remains unknown.

Conjugation

The passage of genes from cell to cell by direct contact through a sex pilus or bridge is termed as conjugation. This is now recognized as an extremely important mechanism for spread of antibiotic resistance, since DNA that codes for resistance to multiple drugs may be so transferred. Conjugation was first recognized in

Japan in 1959 after an outbreak of bacillary dysentery caused by *Shigella flexneri* that was resistant to four different classes of antibiotics.

CONCLUSION

Drug resistance is one of the most important problems in present day antimicrobial chemotherapy. In the recent past, high level resistance to multiple antibiotics has been reported. With the emergence of multidrug-resistant organisms, physicians are now faced with the challenge of treating infections that have no established therapeutic guidelines. Bacteria may acquire resistance vertically through mutation and selection or horizontally through transduction, transformation or conjugation. Acquired resistance is the major pathway of spreading single or multiple drug resistance among the bacterial isolates.

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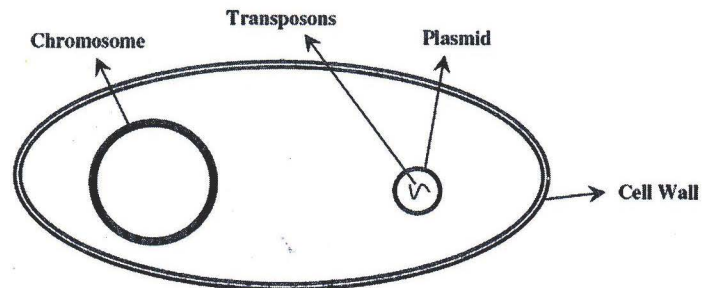


Fig. 1: Bacterial genome

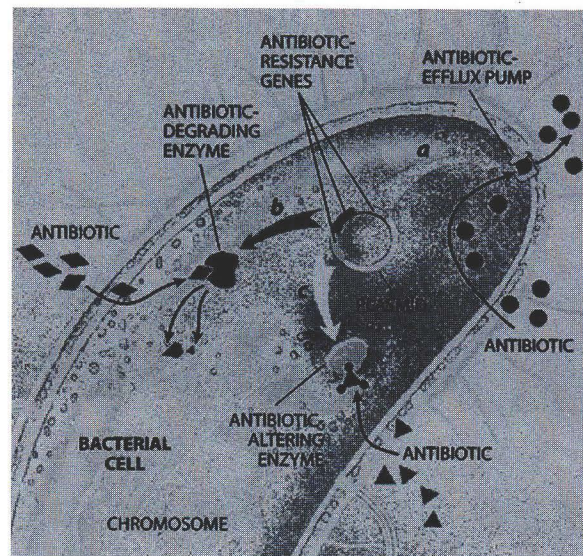


Fig. 2: Transfer of genetic material through transformation, transduction, and conjugation

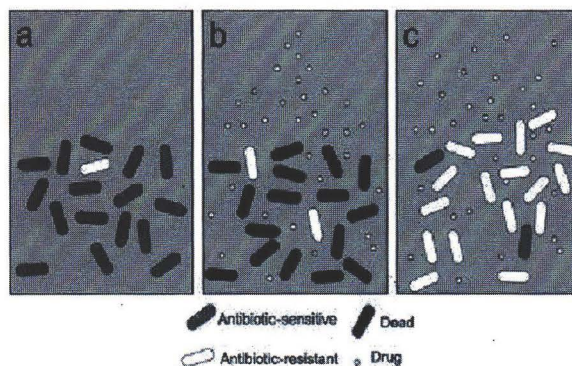


Fig. 3: Mutation and selection of an antibiotic resistant colony

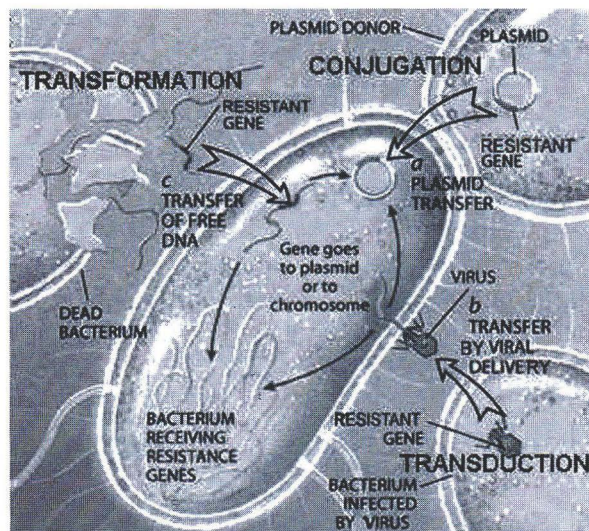


Fig. 4: Mutation in bacterial cell