Antibiotic Resistance in Bacteria: A Growing Global Health Threat

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Key points:

- Introduction
- Forms of antibiotic resistance
- Genetic basis of Bacterial Resistance
- Mechanism of Anti biotic resistance

Introduction

Bacterial resistance refers to the ability of bacteria to survive or neutralize the effects of antibiotics that would normally inhibit or kill them.[1] The excessive use of antibiotics contributes to resistance development in bacteria.[2] Overuse of antibiotics has accelerated the evolution of resistant microorganisms. As a result, treating certain infections has become increasingly difficult.[3] Nowadays, Antibiotic resistance is now a major obstacle in the development of new antimicrobial drugs, developing antibiotic resistance is a major public health problem worldwide.

Bacteria have a remarkable genetic flexibility that allows them to respond to a wide range of environmental threats, including the presence of antibiotic molecules that may jeopardize their existence. Bacteria sharing the same ecological niche with antimicrobial-producing organisms have evolved ancient mechanisms to withstand the effect of harmful antibiotic molecules, and consequently their intrinsic resistance permits them to thrive in its presence.

Figure 1*: Misusing and overusing ANTIBIOTICS puts us all at risk*. [5]

The four major forms of antibiotic resistance evolve as:

1. Natural Resistance

Refers to Bacterial species inherent ability to tolerate certain antibiotics, often due to structural or functional characteristics, independent of prior antibiotic exposure. [4]

2. Acquired Resistance

Occur when previously susceptible bacteria develop the ability to resist antimicrobial agents, either by mutations or by acquiring resistant genes from other bacteria. This form of resistance arises from mutations in chromosomal DNA or through acquisition via plasmids and other extrachromosomal elements.

3. Cross Resistance

Cross resistance occurs when bacteria become resistant to multiple antibiotics, typically those with similar mechanisms of action, due to a shared resistance trait.

4. Multidrug resistance

Multidrug resistance (MDR) refers to a microorganism's resistance to multiple antimicrobial drugs, making infections difficult or impossible to treat with standard antibiotics.

Genetic Basis of Antibiotic Resistance

Bacteria have several ways to fight off antibiotics. One method involves making enzymes that break down or change the antibiotic making it useless. For instance, β-lactamase enzymes break the β-lactam ring in penicillin and similar drugs, while other enzymes tweak the structure of aminoglycosides so they can't stick to their targets. Bacteria can also change the spots where antibiotics attach inside their cells. Through changes in their genes or by getting new ones, they can alter the structures antibiotics bind to, like the penicillin-binding proteins in MRSA or the ribosomal RNA that macrolides target. Some bacteria use pumps in their cell walls to push antibiotics out, lowering the amount inside and making the drugs less effective. Gram-negative bacteria can become more resistant by changing or losing certain proteins in their outer wall, which stops antibiotics from getting in. Some clever bacteria find new ways to do things that bypass the steps antibiotics try to block. Some bacteria, for instance, can form communities known as biofilms and produce a new enzyme that the drug cannot affect. These groups of cells make a protective layer around themselves that acts as a shield making it hard for antibiotics to reach them and helping the bacteria survive.

Mechanisms of Antibiotic Resistance

A - Target Modifications

Alterations occur in the drug-related receptors and the locations of the target regions regarding their interaction with antibiotics, which can involve complex enzymes and ribosomes. The most commonly recognized resistance associated with changes in the ribosomal target is seen in macrolide antibiotics. Notable examples include the development of penicillin resistance resulting from mutations in penicillin-binding proteins and the activity of beta-lactamase enzymes in strains of Staphylococcus aureus, Streptococcus pneumoniae, Neisseria meningitidis, and Enterococcus faecium.

B - Enzymatic Inactivation of Antibiotics

A majority of bacteria produce enzymes that degrade antibiotics, making the enzymatic inactivation mechanism one of the most important resistance mechanisms. This category includes widely recognized examples such as beta-lactamases, aminoglycosidases, and enzymes that modify chloramphenicol and erythromycin.

C. Reduced Membrane Permeability

This mechanism is characterized by alterations in the permeability of both the internal and external membranes, leading to a reduction in drug absorption into the cell or a swift expulsion via pump systems. Porin mutations that can occur in proteins of resistant strains can result in a decrease in membrane permeability. For example, the Pseudomonas

aeruginosa strain can become resistant to carbapenems due to a change in OprD porins. Resistance to quinolones and aminoglycosides can be significantly influenced by a decrease in the permeability of the outer membrane.

D. Efflux Pumps Activations

It is most frequently observed in the tetracycline antibiotic group due to active pumping systems. Through an energy-dependent active transport mechanism, tetracyclines are expelled from the cell and cannot accumulate inside. This resistance mechanism is regulated by plasmids and chromosomes. Active pumping systems, for instance, are effective against quinolones, 14-membered macrolides, chloramphenicol, and beta-lactams.

E. Metabolic Bypass Mechanisms

The newly susceptible metabolic pathway eliminates the need for objective development, which is in contrast to some target modifications that are observed in bacteria. Bacteria can obtain folic acid from their surroundings instead of synthesizing it, which leads to resistance against sulfonamides and trimethoprim.

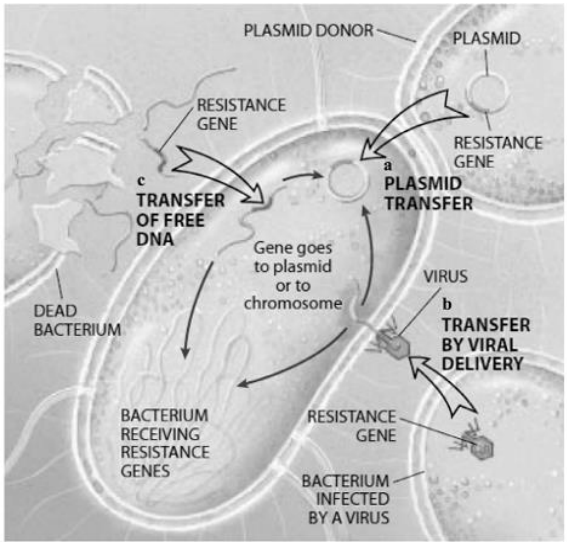

Figure 2: *Three main mechanisms of resistance gene transfer in a bacterium **a**, plasmid transfer; **b**, transfer by viral delivery; **c**, transfer of free DNA.* [6]

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