Antimicrobial resistance

Antimicrobial resistance (AMR) is one of the most significant public health challenges of the twenty-first century. It threatens the effective prevention and treatment of a growing number of infections caused by bacteria, parasites, viruses, and fungi that are no longer responsive to conventional medications.

Antimicrobial resistance refers to the capacity of microorganisms to survive and reproduce even in the presence of drugs that would typically kill them or suppress their growth. For treatment to be effective, the drug concentration at the site of infection must be sufficient to inhibit the pathogen while remaining at levels that are not harmful to human cells.

Antimicrobial resistance is a serious concern for several reasons. It can lead to treatment failure, making infections harder or sometimes impossible to cure, and it is associated with increased mortality rates. Resistant organisms can also spread within the community, posing a wider public health risk. In addition, resistance places a significant financial burden on healthcare systems due to longer hospital stays and the need for more expensive treatments. It also raises the alarming possibility of a return to the pre-antibiotic era, when even minor infections could be life-threatening. Furthermore, the use of antimicrobial agents creates selection pressure that encourages the survival of resistant strains. Not only bacteria, but also viruses, fungi, and even cancer cells can develop resistance, complicating treatment across multiple fields of medicine.

Mechanisms of antibiotic resistance (rephrased):

1. Production of enzymes that inactivate or destroy the antibiotic.
2. Formation of modified enzymes with reduced susceptibility to the antibiotic.
3. Development of altered target sites that prevent antibiotic binding.
4. Changes in cell wall permeability that limit antibiotic entry.
5. Alteration of metabolic pathways to bypass the antibiotic's effect.
6. Activation of efflux pumps to expel the antibiotic from the cell.

Antibiotic resistance is classified primarily by its origin (intrinsic vs. acquired)
Antibiotic resistance can arise through several natural and acquired mechanisms

Intrinsic resistance might include:

Some microorganisms lack the specific target of the drug; for example, *Mycoplasma* does not have a cell wall, making it inherently resistant to penicillin.
In other cases, bacteria possess innate efflux pumps that either prevent the drug from entering the cell or actively expel it, so it cannot reach an effective internal concentration. This is seen in organisms such as *Escherichia coli* and *Pseudomonas aeruginosa*.
Another mechanism involves enzymatic inactivation or modification of antibiotics. For instance, Cephalosporinase produced by *Klebsiella* species can break down cephalosporin antibiotics.
Additionally, Gram-negative bacteria have a highly effective permeability barrier due to their cell envelope. For example, the outer structure of Pseudomonas aeruginosa enables it to resist many chemicals, dyes, disinfectants, and antibiotics.

Acquired antibiotic resistance can occur through mechanisms involving extrachromosomal elements or chromosomal changes.

One major pathway is through **extrachromosomal genetic elements**, particularly plasmids. Plasmids are small, double-stranded DNA molecules found in the cytoplasm that can replicate independently of the bacterial chromosome or integrate into it and replicate along with it. These plasmids often carry antibiotic resistance genes (R-genes) and are therefore known as R-plasmids. Importantly, these resistance genes can be easily transferred between plasmids or even incorporated into the bacterial chromosome. A significant proportion of antibiotic resistance observed in clinical settings is mediated by such plasmids.

Another mechanism involves **mutations within the bacterial chromosome**, which refer to changes in the DNA structure of genes. These mutations occur at a rate typically ranging from one in 10 million to one in a billion base substitutions per nucleotide per generation. Such mutations often lead to alterations in the target sites of antibiotics, resulting in reduced susceptibility to multiple drugs. Examples of bacteria where this occurs include Mycobacterium tuberculosis, *Mycobacterium leprae*, and methicillin-resistant *Staphylococcus aureus*.

Mechanisms of Resistance Gene Transfer

The transfer of resistance genes (R-genes) between bacteria can occur through several mechanisms:

Conjugation is the most important and common method for spreading resistance. In this process, conjugative plasmids form a connecting bridge between two bacterial cells, allowing the plasmid DNA to pass directly from one bacterium to another.

Transduction is a less common mechanism. It involves the transfer of plasmid DNA via bacteriophages (viruses that infect bacteria), which carry the genetic material from one bacterium to another of the same species. This process is observed in organisms such as *Staphylococcus* and *Streptococcus*.

Transformation is another less frequent method, where bacteria take up free DNA fragments from their surrounding environment. These DNA fragments usually originate from closely related or the same bacterial strains.

The transfer of resistance genes (R-genes) can also occur within the same bacterium, moving between plasmids or between plasmids and the chromosome:

Transposons are segments of DNA that can move from one location to another within the genome. They can transfer resistance genes between plasmids or between a plasmid and the bacterial chromosome through a process known as transposition.

Integrons are mobile genetic elements capable of capturing and carrying genes, especially those related to antibiotic resistance. They contain multiple gene cassettes, each made up of a resistance gene linked to a specific recognition site, allowing bacteria to accumulate and express several resistance traits simultaneously.