Antimicrobial drugs: Resistance

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Lecture No. 7

Contents

Introduction

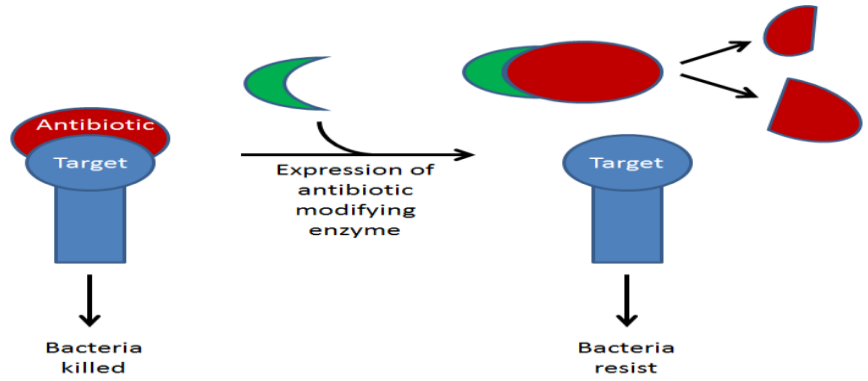
- Antibiotics are medicines used to prevent and treat bacterial infections. Antibiotic resistance occurs when bacteria change in response to the use of these medicines.
- Bacteria, not humans or animals, become antibiotic-resistant.
- Antibiotic resistance leads to higher medical costs, prolonged hospital stays, and increased mortality.
- The world urgently needs to change the way it prescribes and uses antibiotics (reduce the spread of infections through vaccination, hand washing, and good food hygiene).

Principles of antibiotic resistance

There are four major mechanisms that mediate bacterial resistance to drugs :

(1) **Bacteria produce enzymes that inactivate the drug,** e.g., β-lactamases can inactivate penicillins by cleaving the β-lactam ring of the drug.

β-Lactamase: An enzyme that hydrolyzes the β-lactam ring in the β-lactam class of antibiotics, inactivating the antibiotic. The enzymes specific for penicillins, cephalosporins, and carbapenems are the **penicillinases, cephalosporinases,** and **carbapenemases,** respectively.



(2) Bacteria synthesize modified targets against which the drug has a reduced effect

- e.g., a mutant protein in the 30S ribosomal subunit can result in resistance to streptomycin

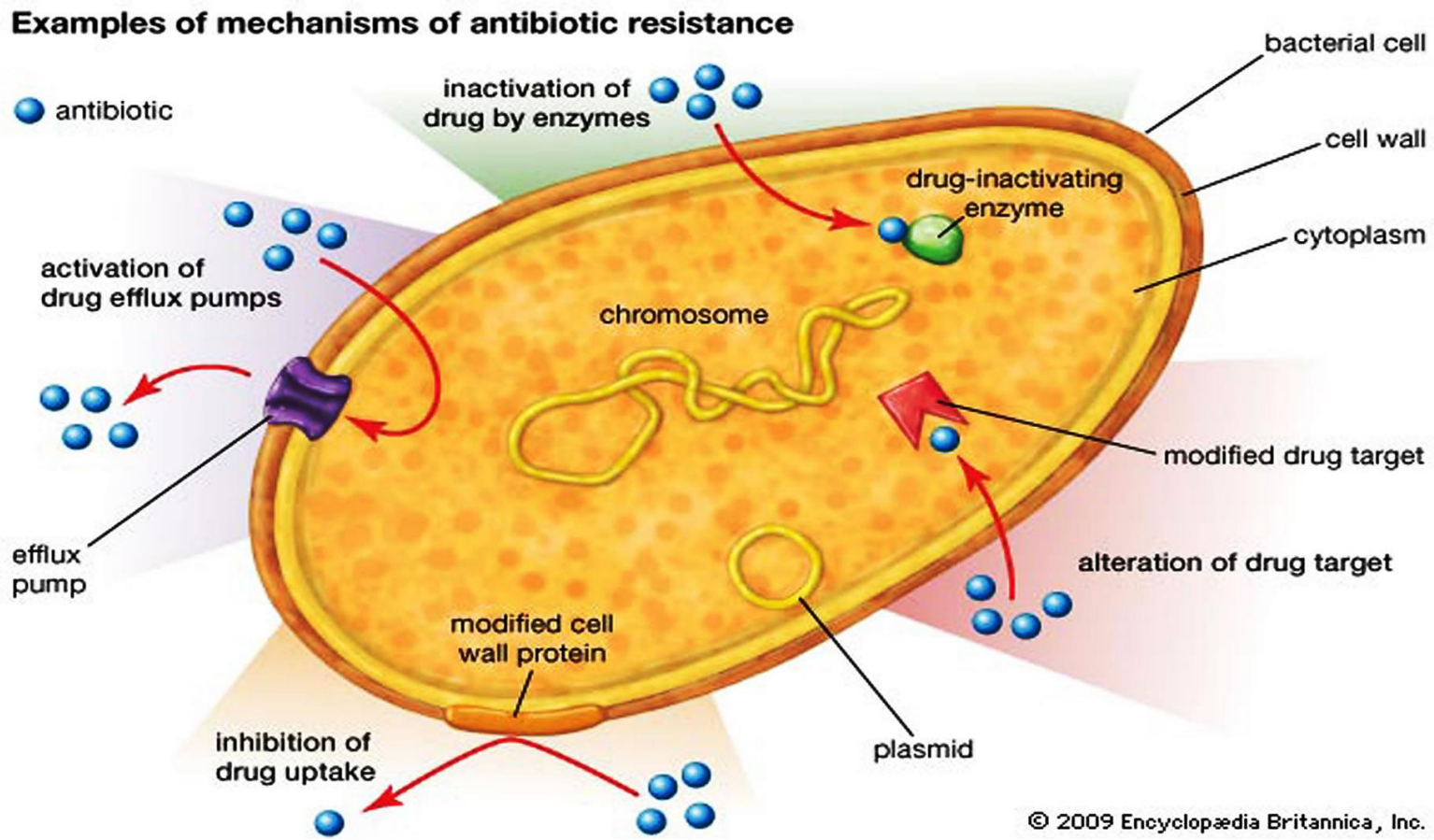
(3) Bacteria reduce permeability to the drug such that an effective intracellular concentration of the drug is not achieved

- e.g., Changes in porins can reduce the amount of penicillin entering the bacterium.

(4) Bacteria actively export drugs using a “multidrug-resistance pump” (MDR pump).

- The MDR pump imports protons and exports a variety of foreign molecules including certain antibiotics, such as tetracyclines.

Mechanisms of antibiotic drug resistance among bacteria



Most drug resistance is due to:

1- Genetic change in the organism

- Chromosomal mutation
- Acquisition of a plasmid or transposon

2- Nongenetic changes:

such as bacteria within an abscess being more difficult to reach with the antibiotic are less importance.

Genetic Basis of Resistance

1- Chromosome-Mediated Resistance

- **Change the target of the drug** so that the drug does not bind
- **Change the membrane** so that the drug does not penetrate well into the cell.
- **Chromosomal mutations occur at a low frequency** (perhaps 1 in 10 million organisms) and often affect only one drug or one family of drugs.
- **Chromosomal resistance is less of a clinical problem than is plasmid mediated resistance.**

2- Plasmid-Mediated Resistance

- **Plasmids cause drug resistance by encoding enzymes that degrade or modify drugs.**

- **Plasmid-mediated resistance occurs at a higher frequency than chromosomal mutations**, often affecting multiple drugs or families of drugs.

- **Plasmid-mediated resistance is very important from a clinical point of view**

(1) Occurs in many different species, especially gram-negative rods.

(2) Frequently mediate resistance to multiple drugs.

(3) Have a high rate of transfer from one cell to another, usually by conjugation.

3- Transposon-Mediated Resistance

- Transposons are genes that are transferred either within or between larger pieces of DNA such as the bacterial chromosome and plasmids.

  A typical drug resistance transposon is composed of three genes which code for:

(1) **Transposase,** the enzyme that catalyzes excision and reintegration of the transposon

(2) **A repressor** that regulates synthesis of the transposase

(3) **The drug resistance gene**.

Non-genetic basis of resistance

- There are several nongenetic reasons for the failure of drugs to inhibit the growth of bacteria:

1) **Bacteria can be walled off within an abscess cavity that the drug cannot penetrate effectively**. Surgical drainage is therefore a necessary adjunct to chemotherapy.
2) **Bacteria can be in a resting state (i.e., not growing);** they are therefore insensitive to cell wall inhibitors such as penicillins and cephalosporins.
3) **Under certain circumstances**, organisms that would ordinarily be killed by penicillin can lose their cell walls, survive as protoplasts. Later, if such organisms resynthesize their cell walls, they are fully susceptible to these drugs.

(4) The presence of foreign bodies makes successful antibiotic treatment more difficult. This applies to foreign bodies such as surgical implants and catheters.

(5) Several artifacts can make it appear that the organisms are resistant.

- e.g., administration of the wrong drug or the wrong dose or failure of the drug to reach the appropriate site in the body
- e.g. the poor penetration into spinal fluid by several early-generation cephalosporins.

Selection of resistant bacteria by overuse & misuse of antibiotics

(1) **Some physicians use multiple antibiotics when one would be sufficient**, prescribe unnecessarily long courses of antibiotic therapy, use antibiotics in selflimited infections for which they are not needed, and overuse antibiotics for prophylaxis before and after surgery.

(2) **In many countries, antibiotics are sold over the counter to the general public**.

(3) **Antibiotics are used in animal feed to prevent infections and promote growth**.

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