

Chapter 3

Drug Resistance

Section 1

Drug resistance of bacteria

Antibacterial agents

Mechanism

1. Inhibition of cell wall synthesis

penicillins, cephalosporins, vancomycin

2. Alteration of cell membrane function

polymyxin, amphotericin B.....

3. Inhibition of protein synthesis

chloramphenicol, erythromycin, tetracyclines

4. Inhibition of nucleic acid synthesis

sulfonamides, rifampin, quinolones.....

Bacterial Targets for Current Antibiotics Used in the Clinic

Cell wall synthesis

- Cycloserine
- Vancomycin, Teichoplanin
- Bacitracin
- Penicillins
- Cephalosporins
- Monobactams
- Carbapenems

Folic acid metabolism

- Trimethoprim
- Sulfonamides

Cell Membrane

Polymyxins

PABA

THFA

DHFA

DNA

mRNA

Ribosomes



Chloramphenicol
Transacetylase

Cell wall

DNA Gyrase Quinolones
DNA-directed RNA polymerase

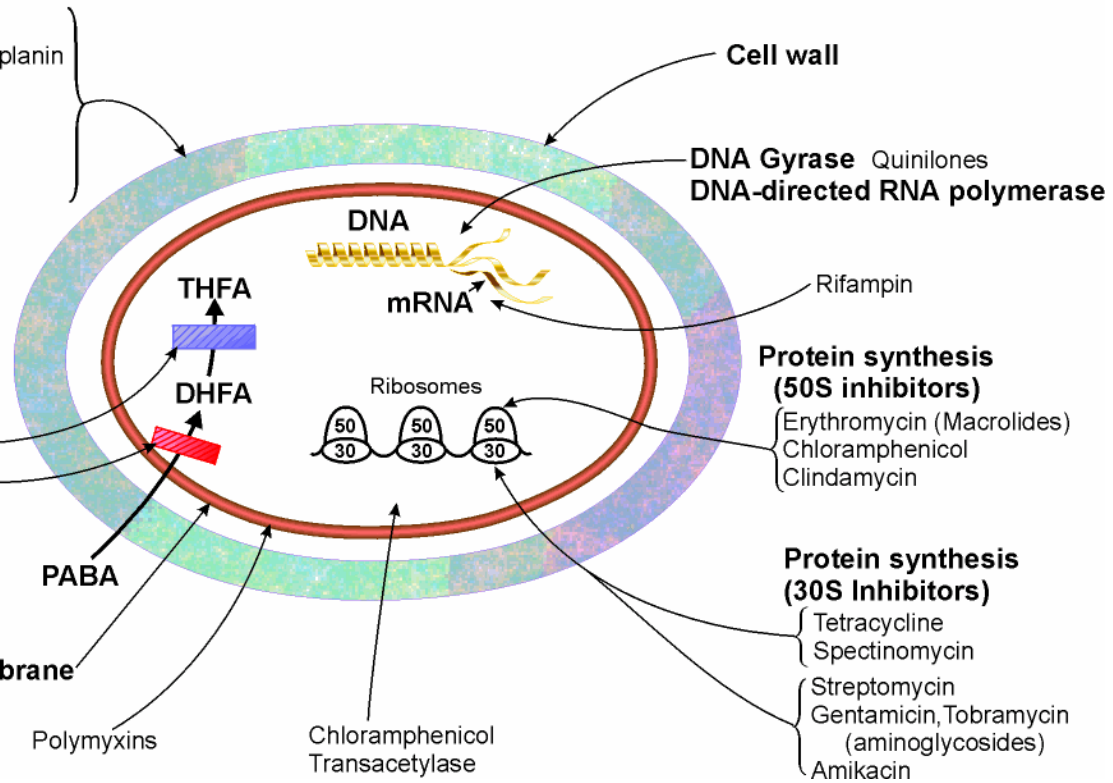
Rifampin

Protein synthesis (50S inhibitors)

- Erythromycin (Macrolides)
- Chloramphenicol
- Clindamycin

Protein synthesis (30S inhibitors)

- Tetracycline
- Spectinomycin
- Streptomycin
- Gentamicin, Tobramycin (aminoglycosides)
- Amikacin



Section 2

The Mechanism of Drug Resistance

genetic mechanism

Intrinsic resistance:

Bacteria absence of **the target** for the action of the drug *or* presence of a **permeability barrier**

Acquired resistance:

- *Chromosome mediated resistance
- *Plasmid mediated resistance
- *Transposon mediated resistance

Chromosome mediated resistance

Chromosomal resistance is due to a mutation in the gene that codes for either the target of the drug or the transport system in the membrane that controls the uptake of the drug.

Plasmid mediated resistance

R plasmid

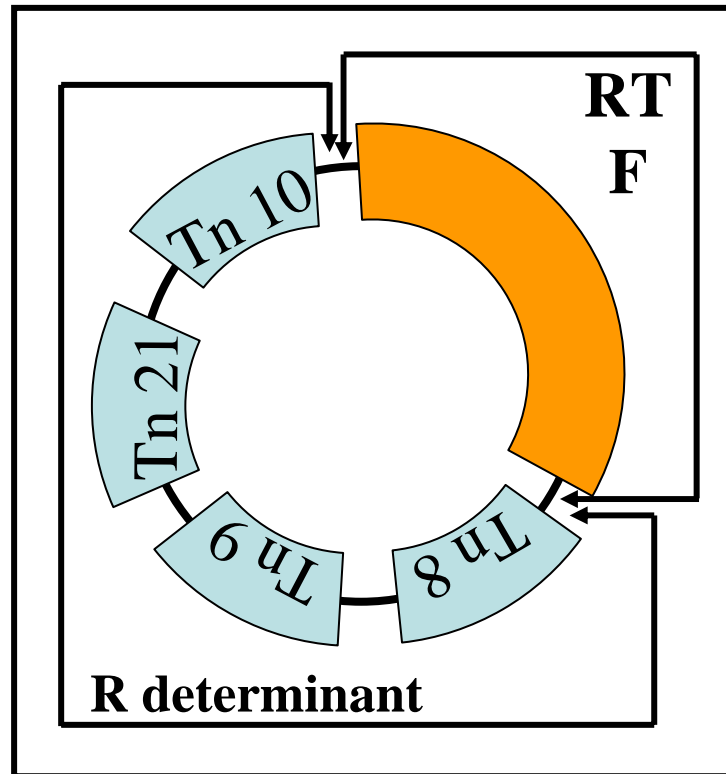
RTF

- Conjugative plasmid
- Transfer genes

R determinant

Resistance genes

Transposons



Multiple resistance

Transposon mediated resistance



T_n

biochemica mechanism

1. Bacteria produce enzymes that inactivate the drugs

β -lactamase \rightarrow cleaving the β -lactam ring of drug
 \rightarrow inactivate *penicillin*,
cephalosporins

2. Bacteria develop an altered structural target for the antibacterial drug

30S ribosomal subunit → mutant protein

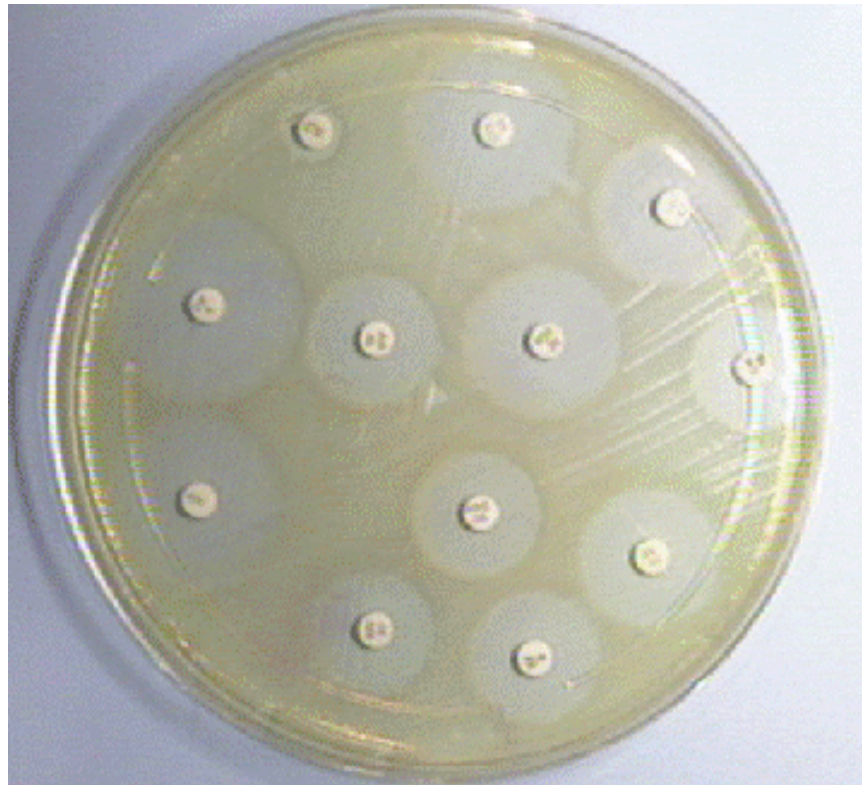
→ resistance to ***streptomycin***

23S rRNA → methylated → resistance to ***erythromycin***

3. Bacteria decrease their permeability and efflux pump system

change porin → reduce the amount of drug entering the bacterium. ***penicillin***

multidrug resistance pump → exports a variety of foreign molecules including certain antibiotics
quinolones



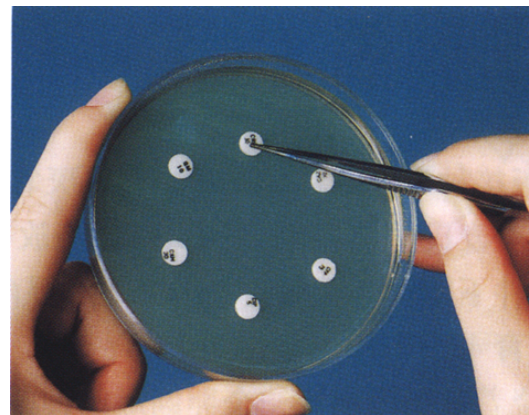
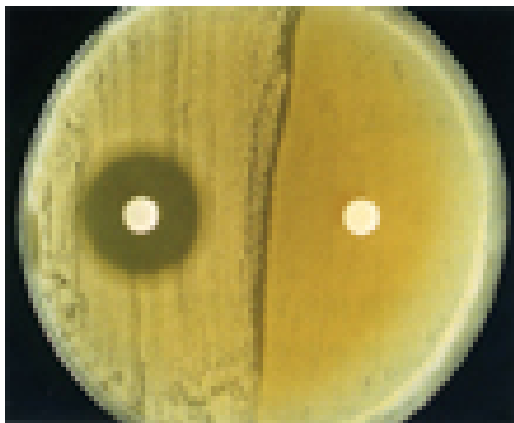
***Controlling Strategy against
Drug Resistance***

1. correct usage of antibiotics

drug dosages and delivery routes

Selection of drugs

Monitoring for resistance and early treatment



- 2. Disinfection and isolation**
- 3. Clear policy of using antibiotics**
- 4. get rid of the plasmid.**
- 5. Studies of new antibiotics**
- 6. Evaluation of drug rotation strategies**