Antimicrobial Chemotherapy

Lecture 16

Dr. Samer Y. Alqaraleh
PhD. Nanobiotechnology (Microbiology)

Faculty of Dentistry

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Antimicrobial chemotherapy

- Antimicrobial chemotherapy is the use of chemical substances, such as antibiotics and antiviral drugs, to treat infectious diseases by killing or inhibiting the growth of microorganisms like bacteria, viruses, fungi, or parasites.

The History of Chemotherapy

- **Selective toxicity:** selectively finding and destroying pathogens without damaging the host
- **Chemotherapy:** the use of chemicals to treat a disease
- **Antibiotic:** a substance produced by a microbe that, in small amounts, inhibits another microbe
- **Antimicrobial drugs:** synthetic substances that interfere with the growth of microbes

Fighting invaders by two root

infection كيف ينقل ال

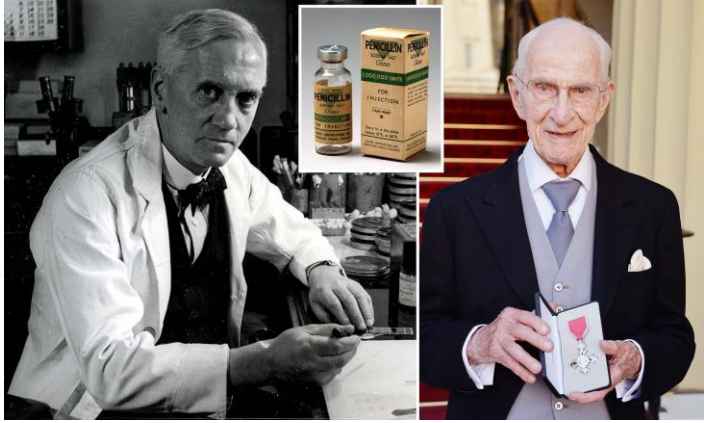
Inside
the body

Outside
the body

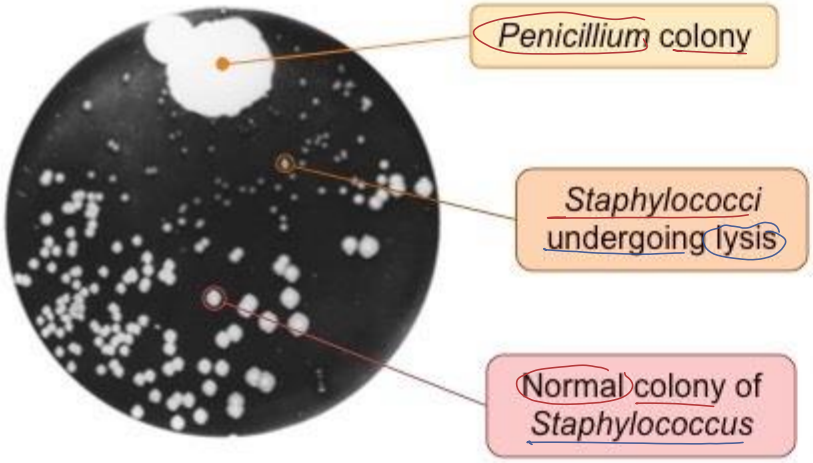
Antibiotics

Sterilization & Disinfection

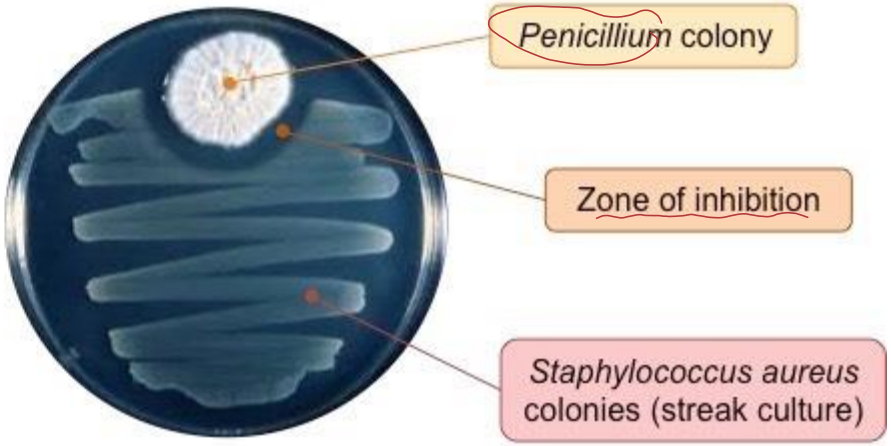
History of chemotherapy



Original Experiment (Fleming, 1928)



Modern Experiment (Streak Culture)



Classification of Antibiotics

1. Source

i) Antibiotic:-

- It is a chemical substance produced by one organism that kills or inhibits the growth of another pathogenic organism.
- Low Molecular weight.
- Antibiotics are called natural chemotherapeutic agents. (natural product)
- Penicillin, Streptomycin, Chloramphenicol, etc…

ii) Semi-synthetic antibiotics:

- These are modified natural products. e.g. Methicillin. Chemical modification in β lactam

β lactam present in penicillin
it modified because avoid of
bacterial resistance
some type of bacterial pathogenic microbes

iii) Synthetic chemotherapeutic agents:-

- These are the chemical drugs which are synthesized in the laboratory, e,g. Sulfonamides, etc.

(not natural)

Natural sources of Antibiotics

Microorganism	Antibiotic
Gram-positive Rods	
Bacillus subtilis	Bacitracin
Paenibacillus polymyxa	Polymyxin
Actinomycetes (Gram+)	
Streptomyces nodosus	Amphotericin B
Streptomyces venezuelae	Chloramphenicol
Streptomyces aureofaciens	Chlortetracycline and tetracycline
Saccharopolyspora erythraea	Erythromycin
Streptomyces fradiae	Neomycin
Streptomyces griseus	Streptomycin
Micromonospora purpurea	Gentamicin
Fungi	
Cephalosporium spp.	Cephalothin
Penicillium chrysogenum	Penicillin

Spectrum of Antimicrobial Activity

- **Narrow spectrum of microbial activity:** drugs that affect a narrow range of microbial types
  e.g. Vancomycin (staphylococci &Enterococci)
- **Broad-spectrum antibiotics:** affect a broad range of gram-positive or gram-negative bacteria
- **Limited spectrum antibiotics**

more specific
ممكن ان يوصفوه
one strain of bacteria → like isoniazed

- - Effective against certain organism
  - ISONIAZID (INH) Inhibit Mycolic acid in Mycobacterium (TB)

2. Mode of Action:

I. **Bactericidal:** agents kill bacteria (**Penicillin, Cephalosporines**) **attach cell wall.**

II. **Bacteriostatic:** agents that inhibit their growth. → so reduce cell division

(Sulphonamide, Tetracyclines, Chloramphenicol)

3. Mechanism of Action:

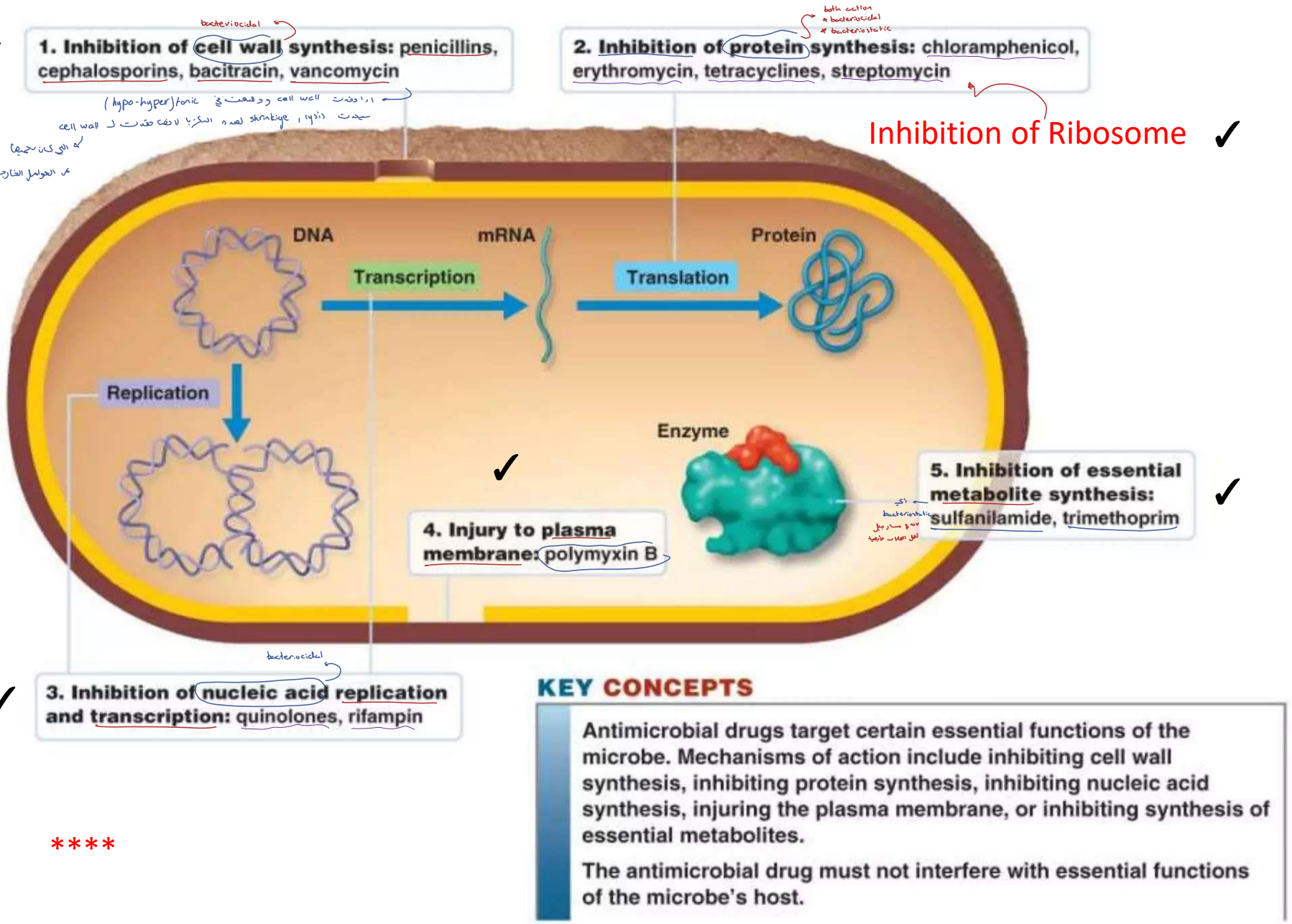
✓ Major mode of action by focused on five components of bacteria structure.

✓* Selectivity. → selectivity of toxicity

microorganism / pathogenic bacteria or microbe

host cells of humans

Figure 20.2 Major Action Modes of Antibacterial Drugs.



KEY CONCEPTS

Antimicrobial drugs target certain essential functions of the microbe. Mechanisms of action include inhibiting cell wall synthesis, inhibiting protein synthesis, inhibiting nucleic acid synthesis, injuring the plasma membrane, or inhibiting synthesis of essential metabolites.

The antimicrobial drug must not interfere with essential functions of the microbe's host.

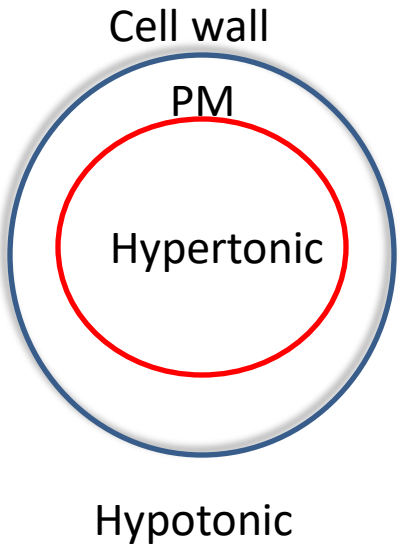
****

Inhibition of cell wall synthesis

- Destruction of cell wall.

L-wall bacterial
لـ فاقدة الجدار cell

← لا تتأثر لو كانت في حالة
isotonic مع انها فاقدة الجدار cell



Bactericidal with selective toxicity.

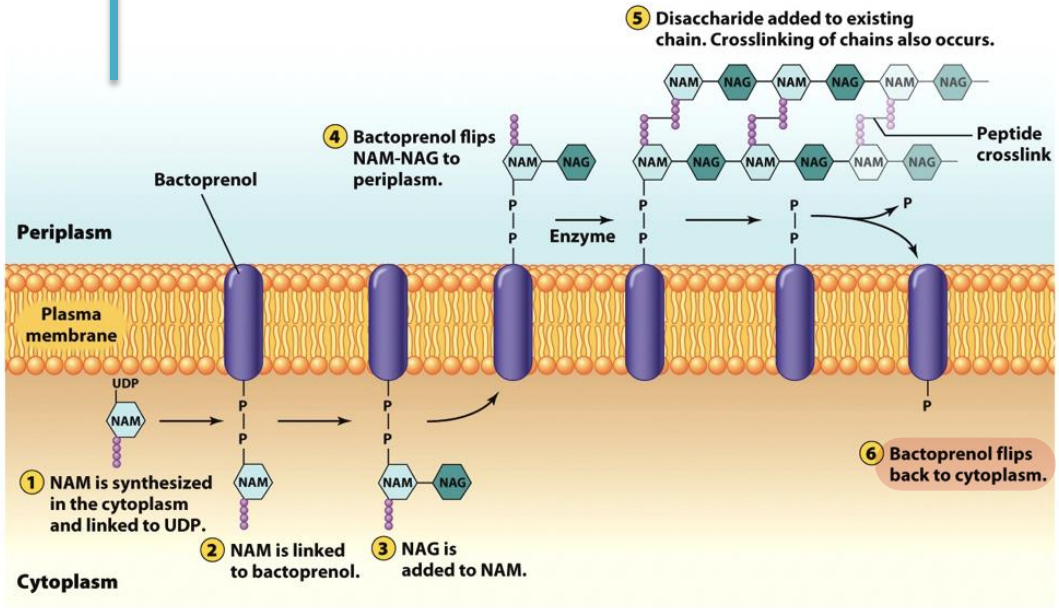
Types of cell wall Inhibitors

Early steps inhibitors of cell wall Synt

- Cycloserine: Block formation of NAM-peptide
- Bacitracin: Blocks Bactoprenol phosphate
- Glycopeptides, Vancomycin & Teicoplanin: Blocks Glycosidic bond (Glycopeptides)

Late steps inhibitors

- β-Lactam antibiotics.
- Penicillins, Cephalosporins: Blocks transpeptidase between NAM-NAM
- Carbapenems



Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis

- **Penicillin**
  - Contain a β-lactam ring
    - Types are differentiated by the chemical side chains attached to the ring
  - Prevent the cross-linking of peptidoglycans, interfering with cell wall construction (especially gram-positives)

Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis

- **Natural penicillins**
  - Extracted from *Penicillium* cultures
    - Penicillin G (injected) and Penicillin V (oral)
  - Narrow spectrum of activity
  - Susceptible to penicillinases (β-lactamases)
- **Semisynthetic penicillins**
  - Contain chemically added side chains, making them resistant to penicillinases

Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis

- Penicillinase-resistant penicillins
  - Methicillin and oxacillin
- Extended-spectrum penicillins
  - Effective against gram-negatives as well as gram-positives
    - Aminopenicillins: ampicillin, amoxicillin
- Penicillins plus β-lactamase inhibitors
  - Contain clavulanic acid, a noncompetitive inhibitor of penicillinase

Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis

- **Cephalosporins**
  - Work similar to penicillins
  - β-lactam ring differs from penicillin
  - Grouped according to their generation of development
- Polypeptide antibiotics
  - Bacitracin
    - Topical application; works against gram-positives
  - Vancomycin
    - Glycopeptide
    - Last line against antibiotic-resistant MRSA

Methicillin-resistant Staphylococcus aureus

The Action of Antimicrobial Drugs

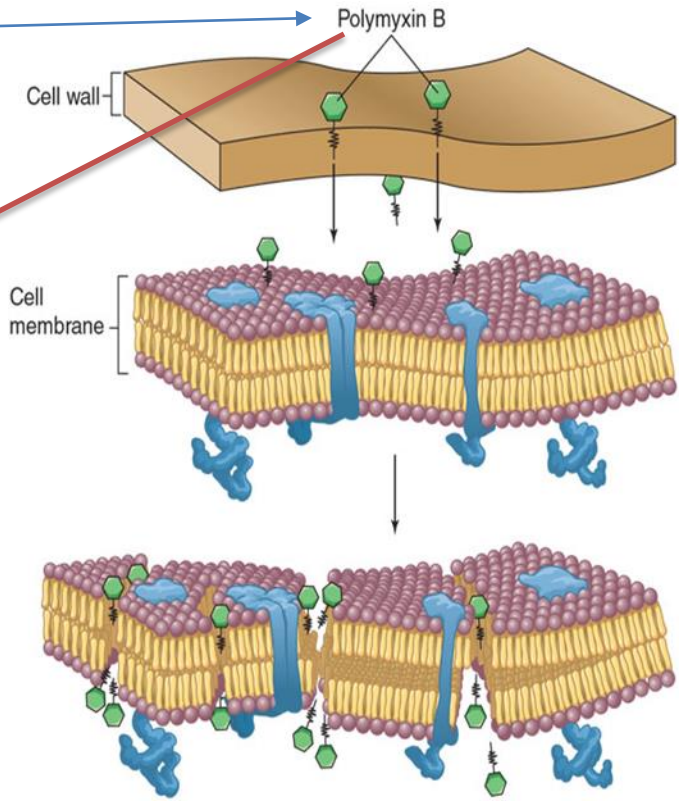
- Injuring the plasma membrane
  - Polypeptide antibiotics change membrane permeability
  - Antifungal drugs combine with membrane sterols

Bind to specific receptors

- **Polymyxin B**
- **Colistin**

Leakage of the essential component

coagulation of the cytoplasm



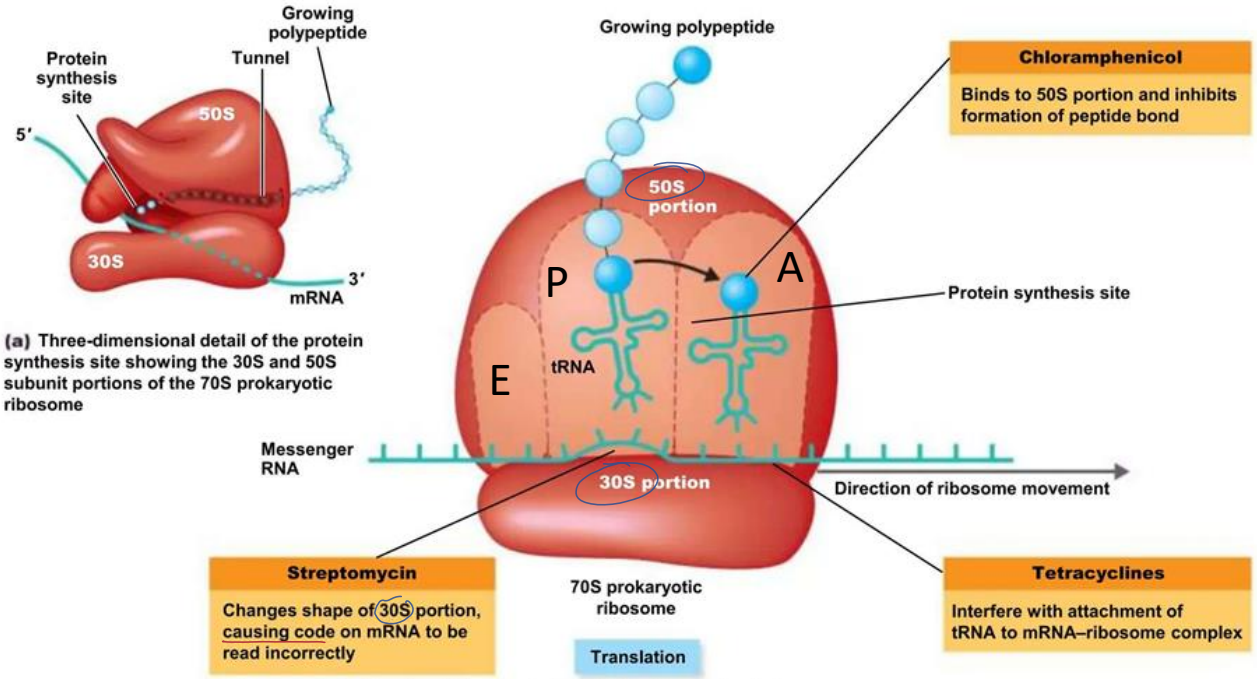
Injury to the Plasma Membrane

- Affects synthesis of bacterial plasma membranes
- **Lipopeptide**
  - Daptomycin
    - Produced by streptomycetes; used for skin infections
    - Attacks the bacterial cell membrane
  - Polymyxin B
    - Topical; bacteriocidal; effective against gram-negatives
    - Combined with bacitracin and neomycin in nonprescription ointments

The Action of Antimicrobial Drugs

- Inhibiting protein synthesis
  - Target bacterial 70S ribosomes
  - Chloramphenicol, erythromycin, streptomycin, tetracyclines

Figure 20.4 The inhibition of protein synthesis by antibiotics.



(a) Three-dimensional detail of the protein synthesis site showing the 30S and 50S subunit portions of the 70S prokaryotic ribosome

(b) Diagram indicating the different points at which chloramphenicol, the tetracyclines, and streptomycin exert their activities

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Chloramphenicol

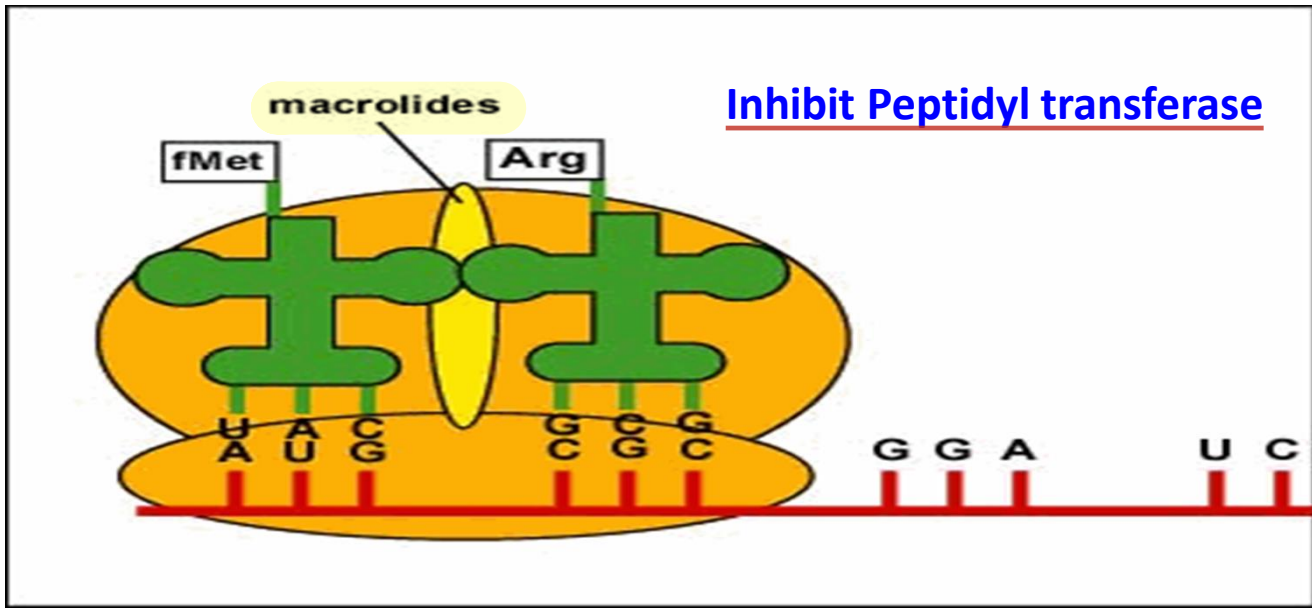
- Inhibits peptide bond formation
  - Binds to the 50S subunit of the 70S ribosome
- Synthesized chemically; broad spectrum
- Can suppress bone marrow and affect blood cell formation

e.g: Lincomycin

Linezolid

Streptogramins

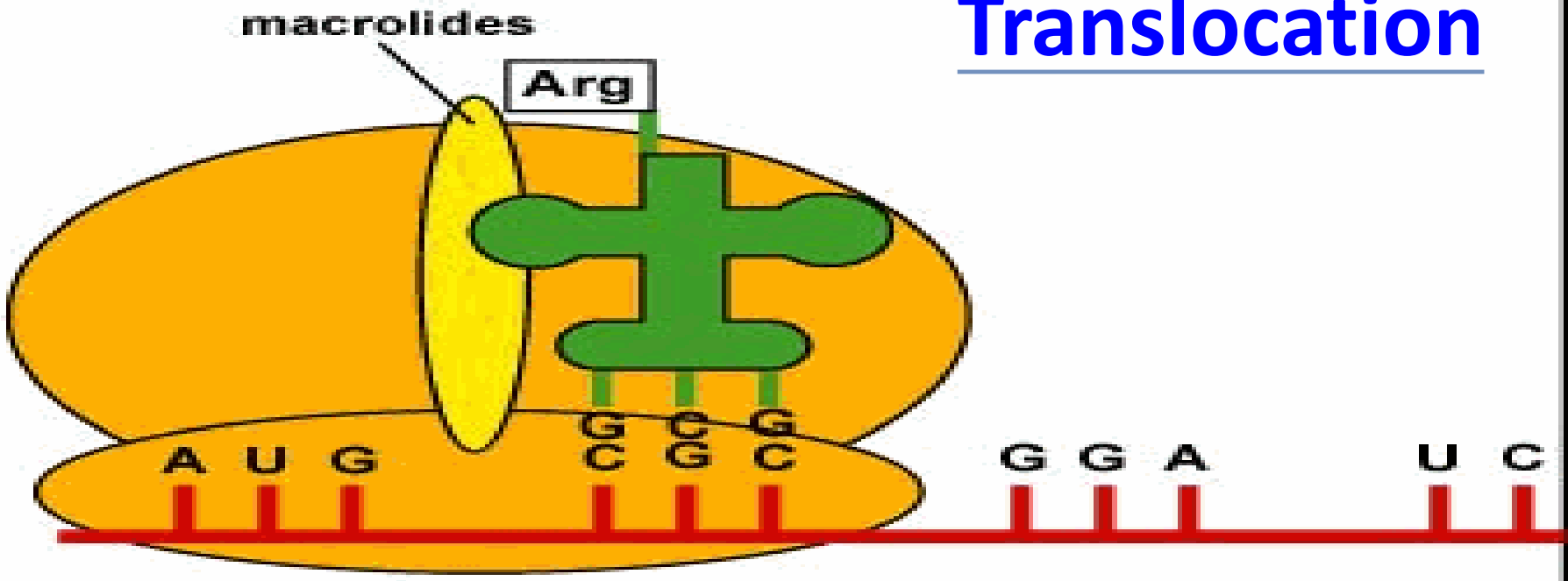
➢ Inhibit
✓ Peptidyl transferase
✓ Translocation



Inhibit Peptidyl transferase

Agents acting on the 50 S ribosomal subunit

Inhibit Translocation



Aminoglycosides

- Amino sugars linked by glycoside bonds
- Change the shape of the 30S subunit of the 70S ribosome
- Can cause auditory damage
- Streptomycin, neomycin, gentamicin

صعبت ارتباطهم

Tetracyclines

- Produced by *Streptomyces* spp.
- Interfere with the tRNA attachment to the ribosome
- Broad spectrum; penetrate tissues, making them valuable against rickettsias and chlamydias
- Can suppress normal intestinal microbiota

very small gram (-) bacteria

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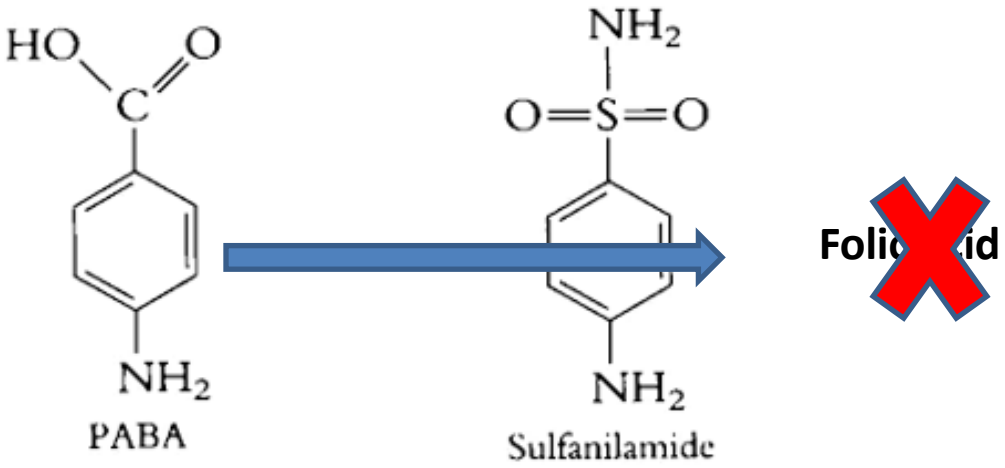
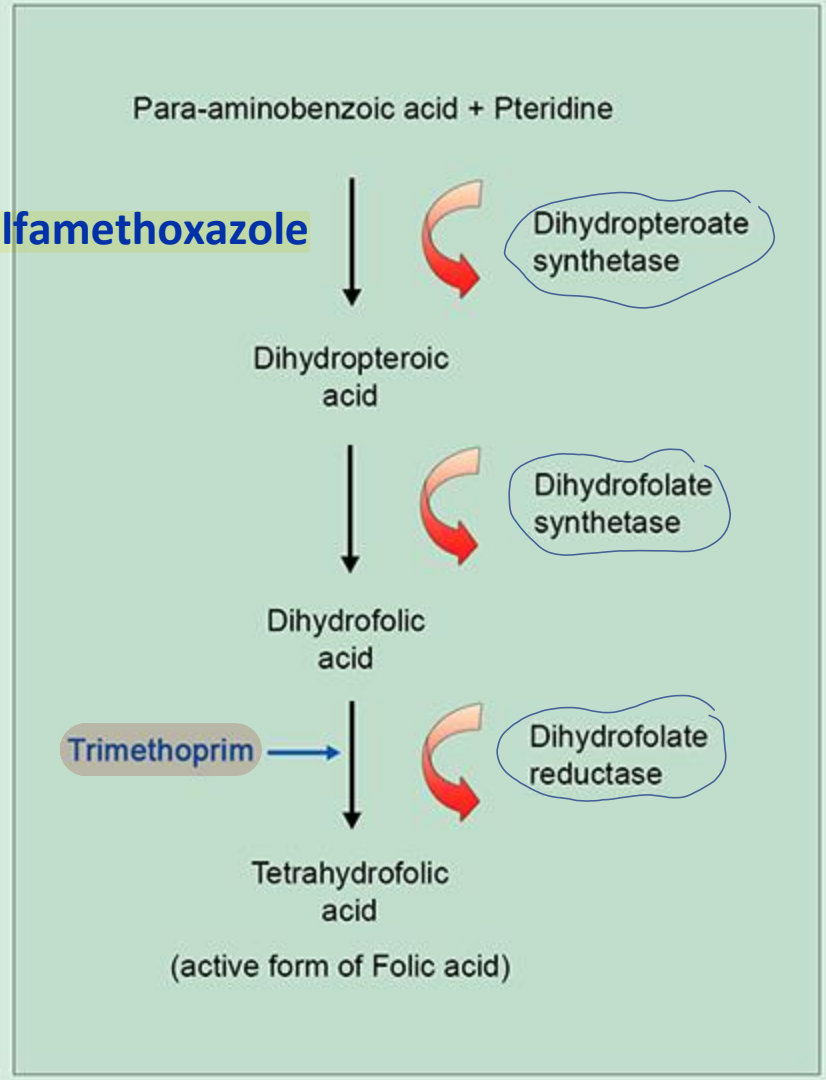
The Action of Antimicrobial Drugs

- Inhibiting nucleic acid synthesis
  - Interfere with DNA replication and transcription
- Inhibiting the synthesis of essential metabolites
  - Antimetabolites compete with normal substrates for an enzyme
    - Sulfanilamide competes with ***para*-aminobenzoic acid (PABA)**, stopping the synthesis of folic acid

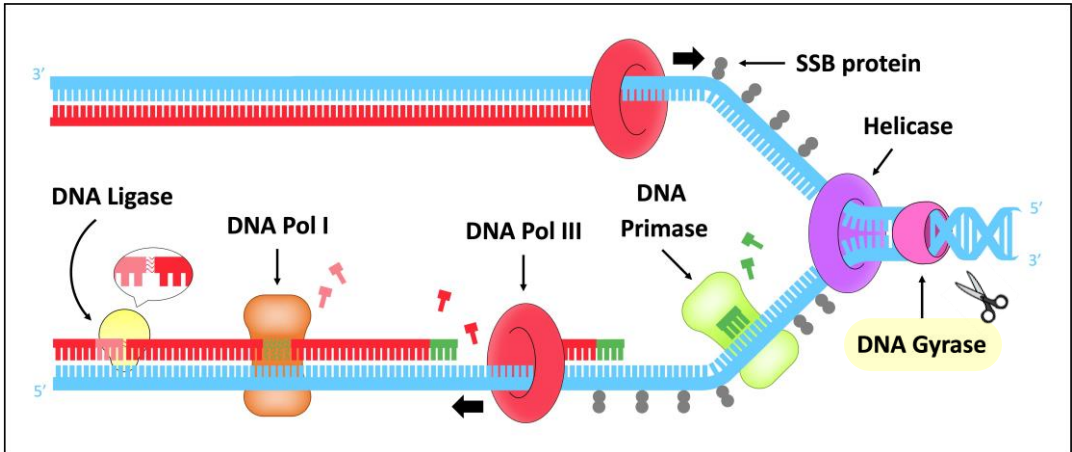


Competitive inhibition



Nucleic Acid Synthesis Inhibitors

- **Narrow margin of selective toxicity**
- **Rifamycin**
  - Inhibits mRNA synthesis **Block DNA dependent RNA Polymerase**
  - Penetrates tissues; antitubercular activity
- **Quinolone** and **fluoroquinolones**
  - Nalidixic acid
    - Synthetic; inhibits DNA gyrase (supercoiling)
  - Norfloxacin and ciprofloxacin **,Ofloxacin, Levofloxacin**
    - Broad spectrum; relatively nontoxic



Bacterial Resistant

Genetics

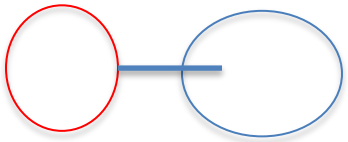
innate resistance

Mycobacterium (TB)

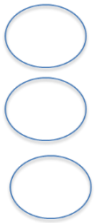
Pseudomonas

Acquired resistant

Horizontal



Vertical



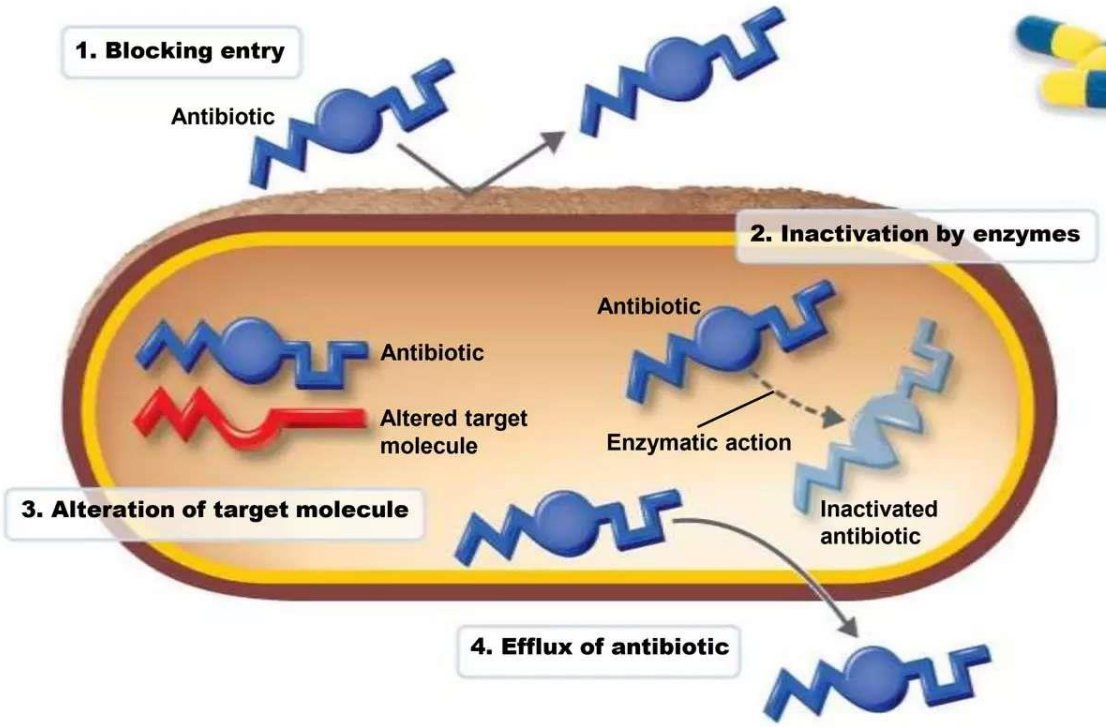
Function modification

e.g. 1. Normal bacteria not resistant, during the time modified some function by producing β lactamase. 2. porins. 3. alternative pathway of folic acid. 4. Mutation in Ribosome subunites

Mechanisms of Resistance

- Enzymatic destruction or inactivation of the drug
- Prevention of penetration to the target site within the microbe
- Alteration of the drug's target site
- Rapid efflux (ejection) of the antibiotic
- Variations of mechanisms of resistance

Figure 20.20 Bacterial Resistance to Antibiotics.



KEY CONCEPTS

- There are only a few mechanisms of microbial resistance to antimicrobial agents: blocking the drug's entry into the cell, inactivation of the drug by enzymes, alteration of the drug's target site, efflux of the drug from the cell, or alteration of the metabolic pathways of the host.
- The mechanisms of bacterial resistance to antibiotics are limited. Knowledge of these mechanisms is critical for understanding the limitations of antibiotic use.

Clinical approach to antimicrobial prescription

1. Patient:

Confirm infection by **fever** or Complete Blood test Count (**CBC**) test

2. Drug
3. Dose
4. Root
5. Duration

Table 11–2 COMPLETE BLOOD COUNT

Measurement	Normal Range*
Red blood cells	• 4.5–6.0 million/μL
Hemoglobin	• 12–18 grams/100 mL
Hematocrit	• 38%–48%
Reticulocytes	• 0%–1.5%
White blood cells (total)	• 5000–10,000/μL
Neutrophils	• 55%–70%
Eosinophils	• 1%–3%
Basophils	• 0.5%–1%
Lymphocytes	• 20%–35%
Monocytes	• 3%–8%
Platelets	• 150,000–300,000/μL

*The values on hospital lab slips may vary somewhat but will be very similar to the normal ranges given here.

- **Neutrophil** → fights bacterial infections.
- **Eosinophil** → fight parasites and is involved in allergic reactions.
- **Basophil** → involved in inflammatory and allergic responses.

Clinical approach to antimicrobial prescription

1. Patient
2. Drug selection
   - Identification Mo
   - Individual factor
   - Tissue penetration
3. Dose and frequency
4. Root (Injection, oral) based on severity of infection.
5. Duration

Clinical approach to antimicrobial prescription

1. Patient
2. Drug selection
3. Dose

- Minimum Inhibitory Concentration (MIC) is the lowest concentration of an antimicrobial agent that inhibits the visible growth of a microorganism after overnight incubation.
- A lower MIC is an indication of a better antimicrobial agent.

Minimum Inhibitory Concentration (MIC)

- A MIC is the most basic laboratory measurement of the activity of an antimicrobial agent against an organism.
- Clinically, the Minimum Inhibitory Concentration is used to determine the amount of antibiotics that patient will be given and also determines the type of antibiotic to be used.

Minimal Lethal Concentration (MLC)

- Another measure is the minimal lethal concentration (MLC) - it is the lowest concentration of antimicrobial agent required to kill 99.9% of the microorganisms within a specified period.

Ideal Characteristics of a chemotherapeutic agent

1. Antimicrobial spectrum:- The drug should be able to destroy or inhibit many kinds of pathogenic microorganisms.
2. No side effects:- The drug should not produce undesirable side effects.
3. No killing effect on normal flora: - The drug should not destroy the normal flora of the body.
4. No inactivation :- When the drug is given orally, it should not be inactivated by stomach acids.
5. Solubility in body fluids :- A drug must have solubility in body fluids.
6. Sufficient concentration of the drug in target tissues :- The drug must be able to reach sufficiently in high concentration in the tissues or the blood of the patient.
7. Low break down rate of drug :- Break down rate of drug must be low so that it will remain in the tissues long enough to exert its effects.
8. Availability :- Easily availability at affordable cost or prices.

Antibiotic Misuse

- **Misuse of antibiotics selects for resistance mutants**
- **Misuse includes:**
  1. Using outdated or weakened antibiotics
  2. Using antibiotics for the common cold and other inappropriate conditions
  3. Using antibiotics in animal feed
  4. Failing to complete the antibiotic course.
  5. Using someone else's leftover prescription

Effects of Combinations of Drugs

- **Synergism:** the effect of two drugs together is greater than the effect of either alone
- **Antagonism:** the effect of two drugs together is less than the effect of either alone