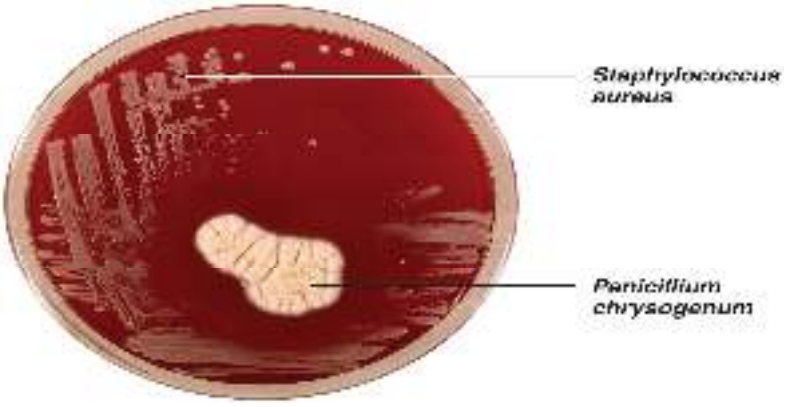
Antimicrobial Drugs and Resistance

Objective:

1- Recognize the meaning of antimicrobial, antibiotics, resistance and other terms.
2- Describe the mechanism of action of antibiotics.
3- Specify the general groups of antibiotics.
4- Identify the most common resistant pathogens.
5- Detect the ways for rising antimicrobial resistant.
6- Distinguish different mechanisms for antimicrobial resistant.

The History of Antimicrobial Agents

- Drugs have been used for the treatment of infectious diseases since the 17th century (eg, quinine for malaria)
- Paul Ehrlich
  -Arsenic compounds that killed microbes
- Alexander Fleming
  - Penicillin released from *Penicillium*
- Gerhard Domagk
  - Discovered sulfanilamide
- Selman Waksman
  - Antibiotics: Antimicrobial agents produced naturally by organisms



Terminology and features of antimicrobials

- **Chemotherapeutic agent:**

Any chemical used in treatment, relief or prophylaxis* of disease.

- **Antimicrobial drugs**:

Chemotherapeutic agents used to selectively interfere with the growth of microorganisms. The "ideal" antimicrobial drug kills the pathogenic microorganism without harming the host.

The antimicrobial drugs are (origin):

1- **Antibiotics** - Natural compounds produced by microorganisms that inhibit the growth or kill another microorganism.
2- **Semi-synthetics**: Chemically altered antibiotics that are more effective than naturally occurring ones.
3- **Synthetics**: Antimicrobials that are completely synthesized in a lab.

* prophylaxis: A process that prevent infection or disease in person at risk.

- **Selective Toxicity** :

Drugs cause greater harm to microorganisms than to host. It is the ability of a drug to target specific microbes without causing significant damage to other microbes or the patient. Selective toxicity relies upon differences between the structure and metabolism of the patient's cells and the structure of the microbe being targeted.

- **Antimicrobial Action**
  - **Bacteriostatic**: Inhibit growth of microorganisms. …e.g. **Tetracyclin**
  - **Bactericidal**: Kill microorganisms……e.g. **Aminoglycocides**

- **Antimicrobial drugs and scope of activity:**
  - **Narrow spectrum**: antimicrobial drugs are effective against a limited group of microbes and exhibit lower toxicity to the host. e.g. **Vancomycin, Griseoflavin.**
  - **Broad spectrum**: are effective against many types of microbes and tend to have higher toxicity to the host. e.g. **Tetracyclin**, **Ampicillin**

- **Effects of Combining Drugs**

Combinations are sometimes used to fight infections

- **Synergistic**: action of one drug enhances the activity of another or *vice versa*.
- **Antagonistic:** activity of one drug interferes with the action of another.

- **Types of Antimicrobial Drugs:**

There are many types: Antibacterial, Antiviral, Antifungal, Antiprotozoan and Antihelminthic drugs.

- **The feature of the ideal antimicrobial drugs:**

1- It is selectively toxic to the microbe.
2- Has low toxicity to the patient.
3- Does not cause drug allergies.
4- Does not disrupt the immune system or disrupt the normal protective microflora of the body.
5- Does not create drug resistance.

- **Adverse Effects**

1. Allergic Reactions
2. Toxic Effects
3. Suppression of normal flora

Mechanisms of action of Antibacterial Drugs

1. Inhibit cell wall synthesis.
2. Inhibit protein synthesis.
3. Inhibit nucleic acid synthesis.
4. Injury to plasma membrane.
5. Inhibit synthesis of essential metabolites.

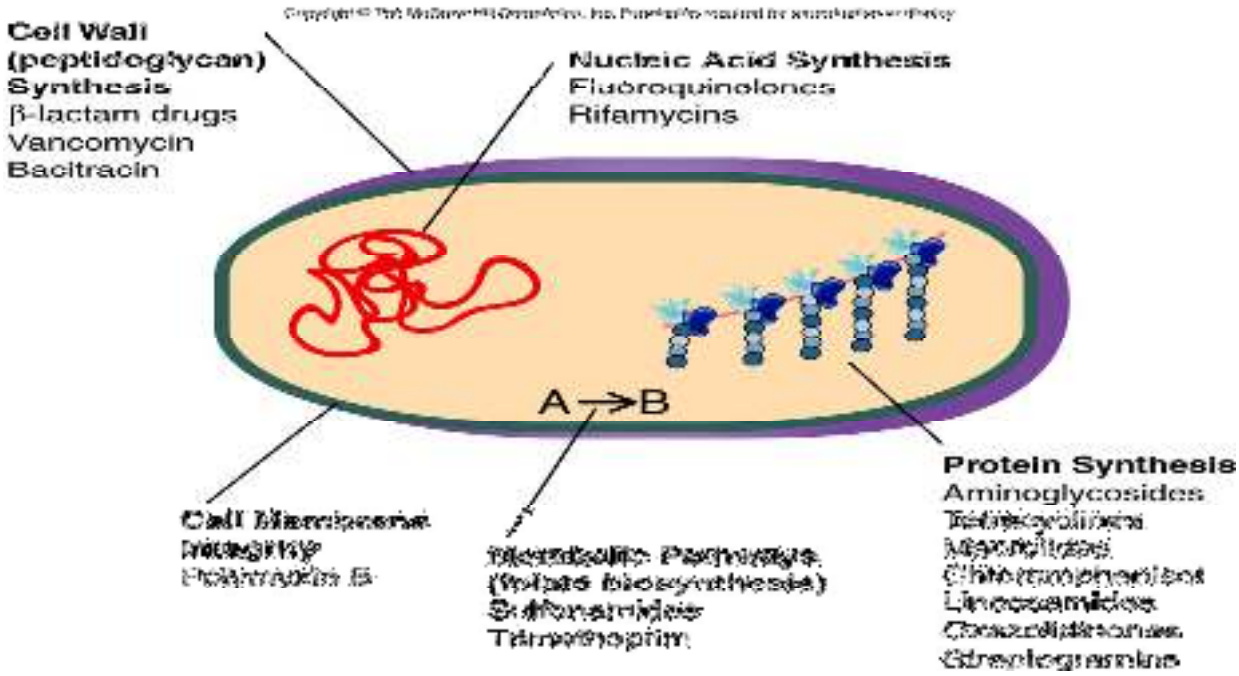


Fig-1-Targets of Antibacterial Drugs

1- Inhibition of Cell Wall Synthesis

By:

a- Inhibition of cross linking of peptidoglycan…….. Penicillins and cephalosporins (Beta-lactam group) and vancomycin.

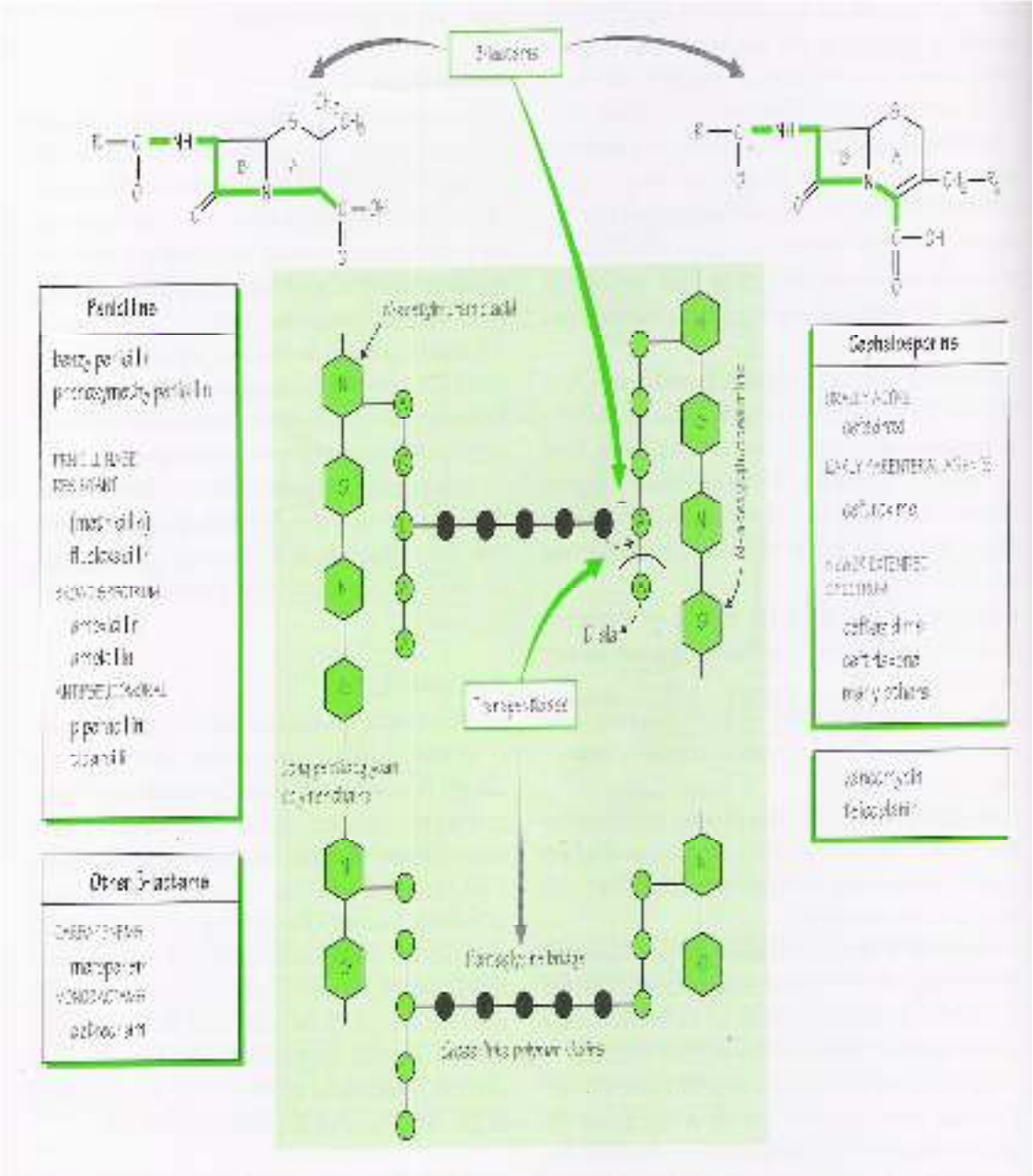
b- Inhibition of other steps in peptidoglycan synthesis…..Cycloserine

- Prevent bacteria from increasing amount of peptidoglycan.
- Have no effect on existing peptidoglycan layer
- Effective only for growing cells.

Penicillins and cephalosporin

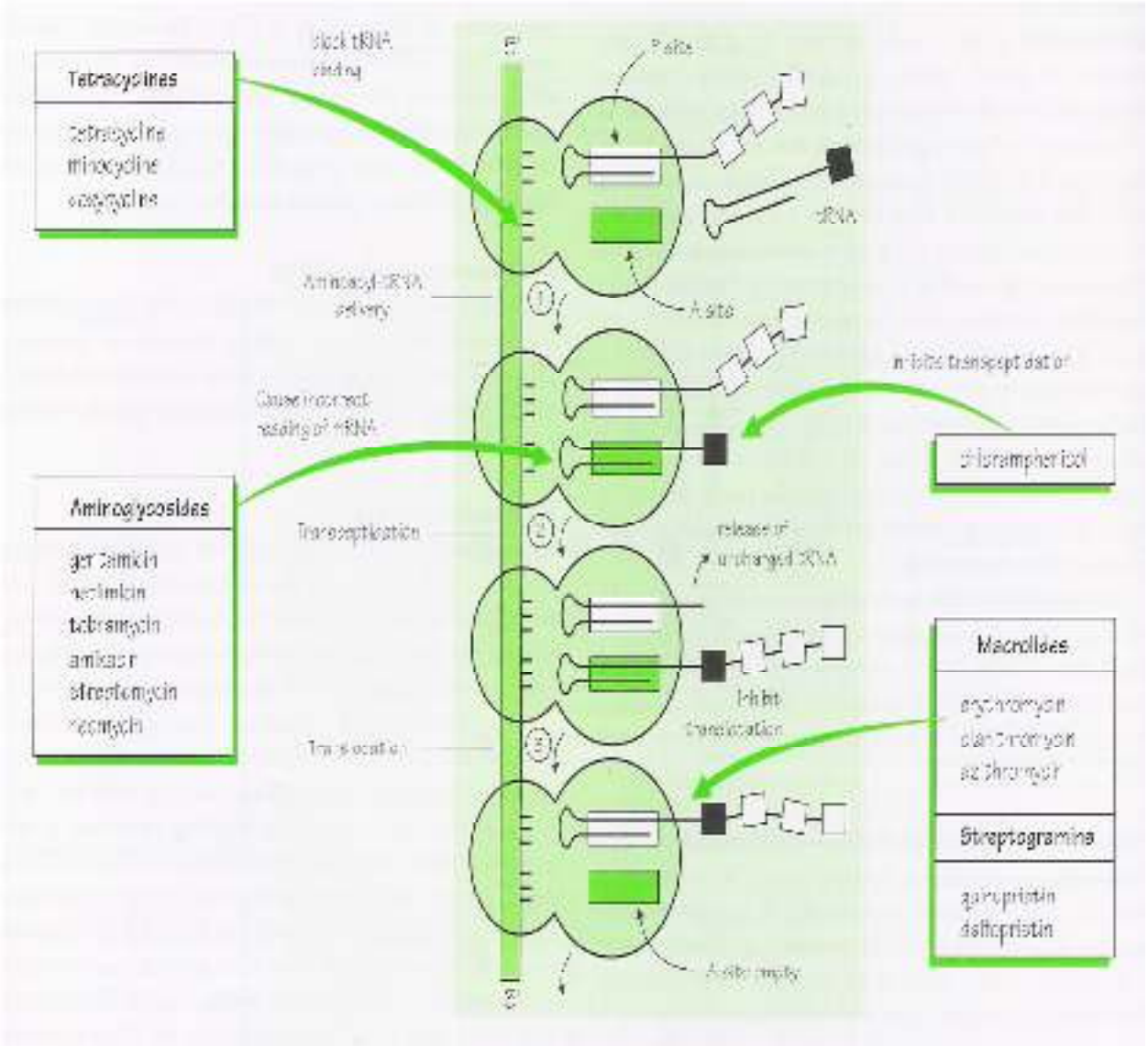
- Act by inhibiting **transpeptidase,** the enzyme that cross-link peptidoglycan.
- Transpeptidases are also penicillin-pinding protein.
- Exposure to penicillins activates **autolytic enzymes** that degrade the bacteria. If these autolytic enzymes are not activated e.g in certain strain of *Staph aureus*, the bacteria are not killed and the strain is said to be **tolerant.**

- **Hypersensitivity to** penicillin especially IgE mediated anaphylax is remains a significant problem.
- **Cephalosporins**: Effective against wide range of organisms. First generation is active primarily against Gram+ve cocci and the second, third and fourth generations have expanded coverage against Gram – ve rods.



2- Inhibition of Protein Synthesis

- Prokaryotic ribosomes are 70S (30S and 50S)
- Eukaryotic ribosomes are 80S (40S and 60S)
- Drugs can selectively target translation
- Chloramphenicole, erythromycin and clindamycin act on the 50S subunit, whereas tetracyclines and aminoglycosides act on the 30S subunits.



3- Disruption of Cytoplasmic Membranes

Some drugs form channel through cytoplasmic membrane and damage its integrity.

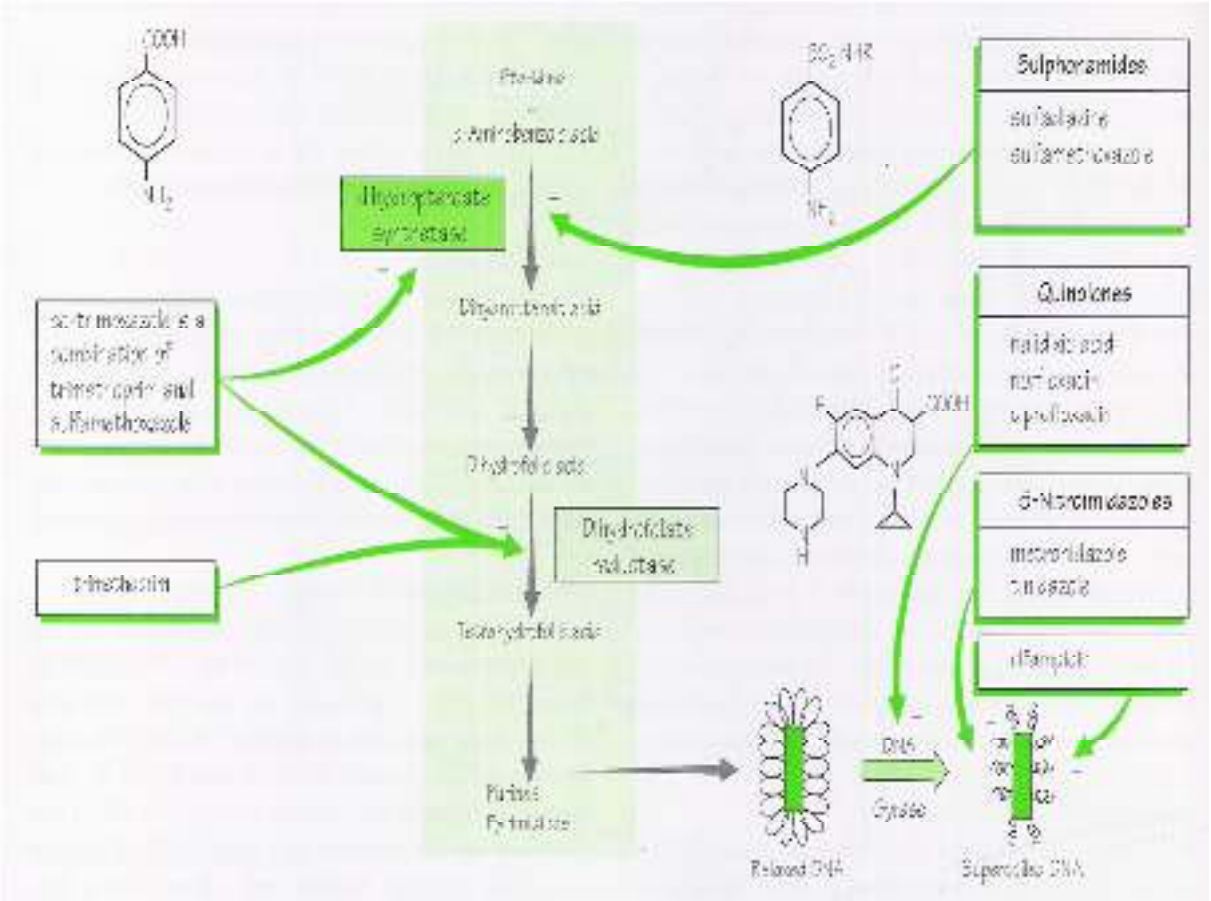
- Polymyxin disrupts cytoplasmic membranes of Gram-negatives.
- Amphotericin B attaches to ergosterol in fungal membranes.

4- Inhibition of Nucleic Acid Synthesis

1- Inhibition of nucleotide synthesis …..Sulfonamide,Trimethoprime
2- Inhibition of DNA synthesis….. Quinolones
3- Inhibition of mRNA synthesis….Rifampin

- Target enzymes required for nucleic acid synthesis e.g (Quinolones and fluoroquinolones)

1- Act against prokaryotic DNA gyrase.
2- RNA polymerase during transcription.
3- Reverse transcriptase inhibitors.

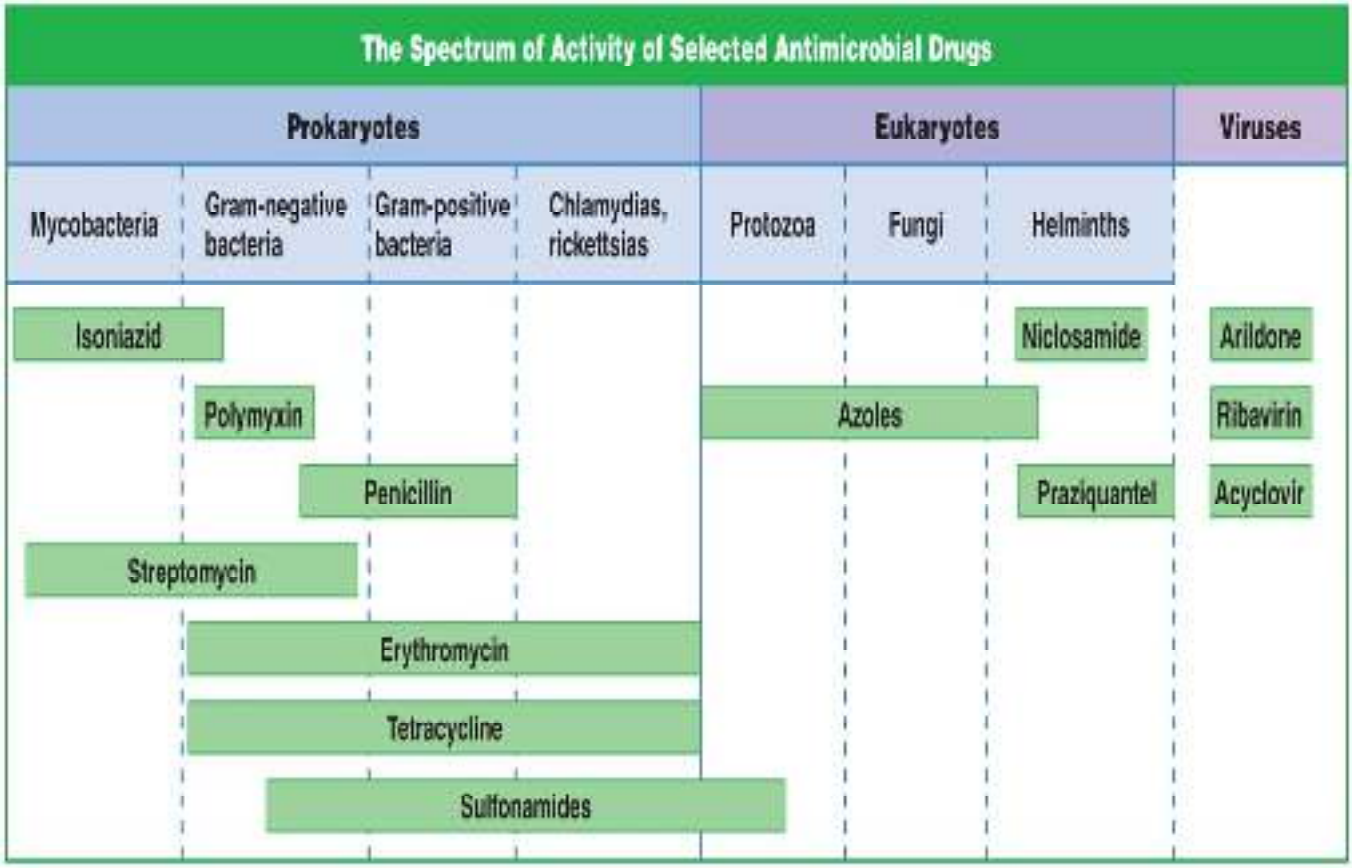


5- Inhibition of Metabolic Pathways

Antimetabolic agents can be effective when pathogen and host metabolic processes differ.

Sulfonamide and trimethoprime inhibit the synthesis of tetrahydrofolic acid the main donor of the methyl groups that are required to synthesis of nucleotides.

Spectrum of Activity of selected antimicrobial drugs



References

- Jawetz in medical microbiology
- Baily and Scott, Diagnostic microbiology
- Review of medical microbiology
- Web sites
- Note: All figures and pictures are available freely in web during preparation of this lecture.