Lecture 6 **Dr. Basim Mohammed Hanon**

Antimicrobial Agents or Antibiotics and Chemotherapeutics Agents

The current era of antimicrobial chemotherapy began in 1935 with the discovery of the sulfonamides. In 1940, it was demonstrated that penicillin, discovered in 1929, could be an effective therapeutic substance. During the next 25 years, research on chemotherapeutic agents centered largely on substances of microbial origin called antibiotics

- An antibiotic is a **selective poison**. It has been chosen so that it will **kill the desired bacteria**, but **not the cells in your body.**
- Each **different type of antibiotic** affects **different bacteria** in **different ways**. For example, an antibiotic might inhibit a bacteria's ability to turn glucose into energy, or the bacteria's ability to construct its cell wall. Therefore the bacteria dies instead of reproducing.
- Antibiotics substances produced by various species of microorganisms: **bacteria, fungi,** to suppress the growth of other microorganisms and to destroy them.
- Today the term antibiotics extends to include **synthetic antibacterial** agents: ex. sulfonamides and quinolones.

Source of antibiotics?

- Several species of fungi including *Penicillium* and *Cephalosporium* E.g. penicillin, cephalosporin
- Species of Actinomycetes, Gram positive filamentous bacteria. Many from species of *Streptomyces*. Also from *Bacillus*, Gram positive spore formers. A few from Myxobacteria, Gram negative bacteria.
- New sources explored: plants, herbs, fish.

Selective toxicity

Antimicrobial drugs act in one of several ways: by selective toxicity, by inhibition of cell membrane synthesis and function, by inhibition of protein synthesis, or by inhibition of nucleic acid synthesis.

Basic principles of antimicrobial therapy

- **Chemotherapy** = the use of chemicals against invading organisms (ie bacteria).The term is used for both treatment of cancer and treatment of infection.
- **Antibiotic** = a chemical that is produced by one microorganism and has the ability to harm other microbes.
- **Selective toxicity** = the ability of a drug to injure a target cell or organism without injuring other cells or organisms that are in intimate contact.

Classification of antimicrobial drugs by susceptible organisms

- **Antibacterial drugs** (narrow and broad spectrum).Examples: Penicillin G, erythromycin, cephalosporins, sulfonamides.
- **Antiviral drugs** (examples : acyclovir, amantadine)
- **Antifungal drugs (**examples: amphotericin, ketoconazole)

Classification by mechanism of action

- Drugs that **inhibit bacterial wall synthesis** or activate enzymes that disrupt the cell wall.
- Drugs that **increase cell membrane permeability** (causing leakage of intracellular material)
- Drugs that cause **lethal inhibition of bacterial protein synthesis**.
- Drugs that cause **nonlethal inhibition of protein synthesis** (bacteriostatics).
- Drugs that inhibit **bacterial synthesis of nucleic acids**.
- Antimetabolites (**disruption of specific biochemichal reactions**-->decrease in the synthesis of essential cell constituents).
- Inhibitors of **viral enzymes**.

Acquired resistance to Antimicrobial drugs.

Mechanisms:

- Microbes may elaborate **drug-metabolizing enzymes (ie penicillinase).**
- Microbes may **cease active uptake of certain drugs.**

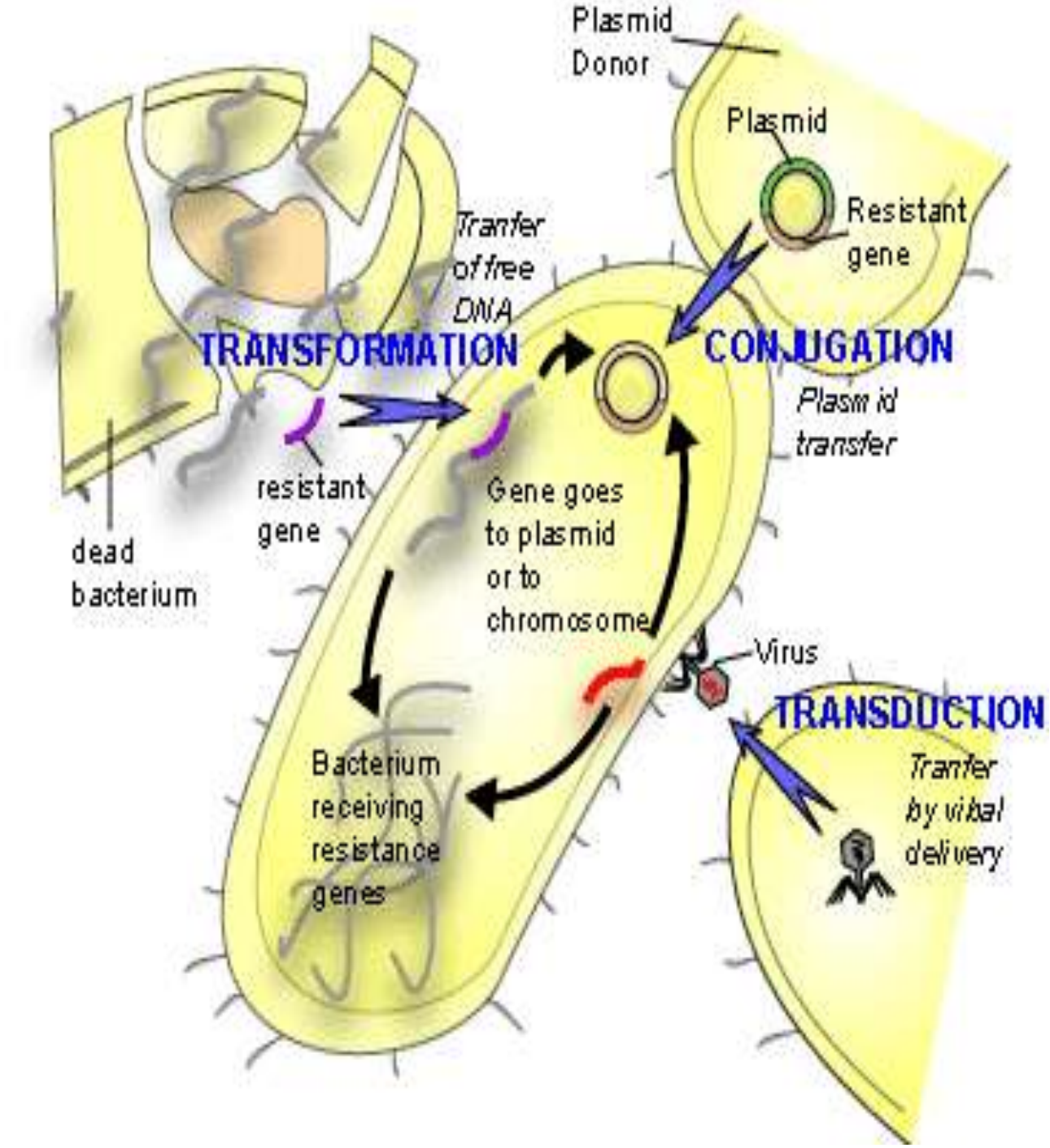
- ❒ Microbial drug receptors may undergo **change resulting in decreased antibiotic binding and action.**
- ❒ Microbes may synthesize compounds that **antagonize drug actions**.

How is resistance acquired?

A) Spontaneous mutation

B) Acquired Mutation

- Vertical
- Horizontal
    - Transformation
    - Transduction
    - Conjugation



Use of antibiotics PROMOTES the emergence of drug-resistant microbes.

Suprainfection (or supeinfection): a new infection that appears through the course of treatment for a primary infection

Delaying the emergence of resistance

1) Use antimicrobial agents only when needed.

2) Use narrow-spectrum antibiotics whenever possible.

3) Newer antibiotics should be reserved for situations in which older drugs are dangerous or no longer effective.

SELECTION OF ANTIBIOTICS

Factors to take into consideration:

1) The identity of the **infecting organism**.
2) **Drug sensitivity** of the infecting organism.
3) **Host factors** (ie site of the infection, status of host defenses).

Empiric therapy prior to completion of lab tests:

It may be necessary to begin treatment in patients with serious infections BEFORE the lab results.

Take samples for culture PRIOR TO INITIATION of treatment.

Host factors

- **Host defenses** (immune system and phagocytic cells).
- **Site of infection** .To be effective an antibiotic must be present in the site of infection in a concentration greater than MIC (endocarditis, meningitis, abscesses)
- **Age** (infants and elderly highly vulnerable to drug toxicity).
- Pregnancy and lactation
- Previous allergic reactions
- **Genetic factors** (ie hemolysis in patients with G-6PD deficiency if given sulfonamides).

Antibiotic combinations:

The result may be additive, potentiative or antagonistic.

Additive response: one in which the antimicrobial effect of the combination is equal to the sum of the effects of the two drugs alone.

Potentiative interaction: one in which the effect of the combination is GREATER than the sum of the effects of the individual agents.

Antagonistic response: in certain cases the combination of two antibiotics may be less effective than one of the agents by itself (ie combination of a bacteriostatic with a bactericidal drug).

PENICILLINS

Mechanism of action: the drugs weaken the cell wall, causing the bacterium to take up excessive amounts of water and then rupture.

Penicillinases (Beta-lactamases):

Enzymes that cleave the beta-lactam ring and thereby render penicillin and other beta-lactam antibiotics inactive.

Classification:

- ❒ Narrow-spectrum (penicillinase sensitive)
- ❒ Narrow-spectrum that are penicillinase resistant (antistaphylococcal)
- ❒ Broad-spectrum penicillins (aminopenicillins).
- ❒ Extended-spectrum penicillins (antipseudomonal)

Antimicrobial spectrum: active against most gram-positive bacteria, gram-negative cocci (ie neisseria meningitis) and spirochetes. With few exceptions gram-negative bacteria are resistant.

Therapeutic uses:

- ❒ Pneumonia and meningitis caused by Streptococcus pneumonia
- ❒ Pharyngitis caused by Streptococcus Pyogenes
- ❒ Infectious endocarditisis (Streptococcus viridans)
- ❒ Gangrene ,tetanus
- ❒ Syphilis (treponema pallidum).

Side Effects and toxicities:

- ❒ Pain at the site of injection, neurotoxicity with too high plasma levels. Inadvertent intra-arterial injection can produce severe reactions (gangrene, necrosis) and must be avoided
- ❒ Penicillin are the most common cause of drug allergy (1-10% of the patients will experience an allergic response).There is no direct relationship between the size of the dose and the intensity of allergic response.

Cross-sensitivity:

- 5-10% of patients allergic to penicillins are also allergic to cephalosporins.
- Penicillinase-resistant penicillins (Antistaphococcal).
- Resistant to beta-lactamases. Examples: Methicillin, Nafcillin.

- Broad-spectrum penicillins. (Aminopenicillins)
    - ❒ Ampicillin (Bordetella pertussis, E. Coli, Salmonella, Shigella).
    - ❒ Most common adverse effects : rash and diarrhea.

Cephalosporins

The drugs are beta-lactamic antibiotics similar in structure and actions with penicillins. Broadspectrum antibiotics with low toxicity.

Mechanism of action: disruption of cell wall synthesis and consequent lysis of the cell.

Classification:

- ❒ **First generation**: highly active against gram-positive bacteria (staphylococci).
- ❒ **Second-generation:** enhanced activity against gram-negative bacteria.
- ❒ **Third-generation:** more active against gram negative aerobes (important activity against Pseudomonas Aeruginosa).
- ❒ **Fourth generation:** highly resistant to betalactamases. Broad spectrum antibiotics.

Therapeutic uses: first and second generation are rarely drugs of choice for active infections. Third generation agents have qualities that make them the preferred agents for several infections (Pseudomonas aeruginosa, nosocomial infections, gonorrhea, proteus).

Other inhibitors of cell wall synthesis

Imipenem

Relatively new beta-lactam antibiotic with very broad spectrum.

Antimiocrobial spectrum: highly active against gram-positive and gram-negative cocci. It is also the most effective beta-lactam antibiotic against anaerobic bacteria.

Vancomycin

It is used only for serious infections due to toxicity

Principal indications: antibiotic-associated pseudomembranous colitis (Clostridium difficile), infection with methicillin-resistant Staphylococcus aureus.

Bacteriostatic inhibitors of protein synthesis

TETRACYCLIN

- ❒ Broad specterium antibiotics.
- ❒ Mechanism of action supression of bacterial growth by inhibiting protein synthesis.

Therapeutic uses.

- ❒ Treatment of infectious diseases (rickettsial diseases--> Rocky mountain spotty fever, typhus fever, Q fever, infections caused by chlamydia trachomatis, brucellosis, cholera, pneumonia caused by Mucoplasma pneumonia, gastric infections with Helicobacter Pylori).
- ❒ Treatment of Acne (orally and topically for severe acne vulgaris).
- ❒ Peptic ulcer disease (combination of tetracyclines, metronidazole and bismuth salicylate against Helicobacter Pylori).

Absorption: the drugs should NOT be administered together with calcium supplements, milk products, iron supplements,

MACROLIDES

Erythromycin

Mechanism of action: inhibition of protein synthesis.

Antimicrobial spectrum: (similar to penicillins) effective against most gram-positive bacteria and against some gram-negative.

Therapeutic uses

1) Legionella pneumophila pneumonia (legionnaires' disease).
2) Whooping cough (Bordetella Pertussis)
3) Corynebacterium diptheriae (Diptheria)
4) Chlamydial infections
5) Mucoplasma pneumoniae pneumonia.
6) Alternative to Penicillin G in patients with penicillin allergy.

CLINDAMYCIN

Mechanism of action: inhibition of protein synthesis.

Antimicrobial spectrum: anaerobic bacteria (gram negative and gram-positive)

CHLORAMPHENICOL

A broad spectrum antibiotic with the potential of causing FATAL aplastic anemia. Use of the drug is limited to treatment of severe infections for which less toxic drugs are ineffective.

AMINOGLYCOSIDES

Mechanism of action: disruption of bacterial protein synthesis.

Antimicrobial spectrum: aerobic gram-negative bacilli (E.Coli,Klebsiella pneumoniae,Proteus Mirabilis,Pseudomonas Aeruginosa).The drugs are inactive against most gram-positive bacteria.the drugs are ineffective against anaerobes.

SULFONAMIDES AND TRIMETHOPRIM

Sulfonamides

Mechanism of action: suppression of bacterial growth by inhibiting synthesis of of folic acid (required for the synthesis of DNA, RNA, proteins).

Antimicrobial spectrum: broad antibiotics

Therapeutic uses: urinary tract infections

Trimethoprim

Mechanism of action: inhibitor of dihydrofolate reductase (-->suppresses bacterial synthesis of DNA, RNA and proteins).

Therapeutic uses: it is approved only for initial treatment of acute uncomplicated urinary tract infections due to susceptible organisms (E. coli, Proteus Mirabilis etc).

Trimethoprim-sulfamethoxazole

Therapeutic uses: urinary tract infections, otitis media, bronchitis, shingellosis, pneumonia, Pneumocystis Carinii pneumonia.

Antituberculus drugs

Isoniazid

Therapeutic uses: prophylaxis and treatment of tuberculosis.

Adverse effects

- ❒ Peripheral Neuropathy (dose-related): peripheral paresthesias of hands and feet, cluminess, unsteadiness, muscle aches (->administer pyridoxine).
- ❒ Hepatotoxicity (incidence increases with age)

Rifampin

Therapeutic use: treatment of tuberculosis and leprosy.

Fluoroquinolones

Ciprofloxacin

Mechanism of action: inhibits DNA replication

Therapeutic uses: infections of respiratory tract,GI tract,bones,joints,skin and soft tissues.

Metronidazole

Mechanism of action: inhibition of nucleic acids synthesis.

Therapeutic uses: The drug is active against obligate anaerobes only.It is used in CNS infections, abdominal organs, bones, joints, skin, and soft. tissues and genitourinary tract.It is used in combination against Helicobacter Pylori.

Mechanism of action

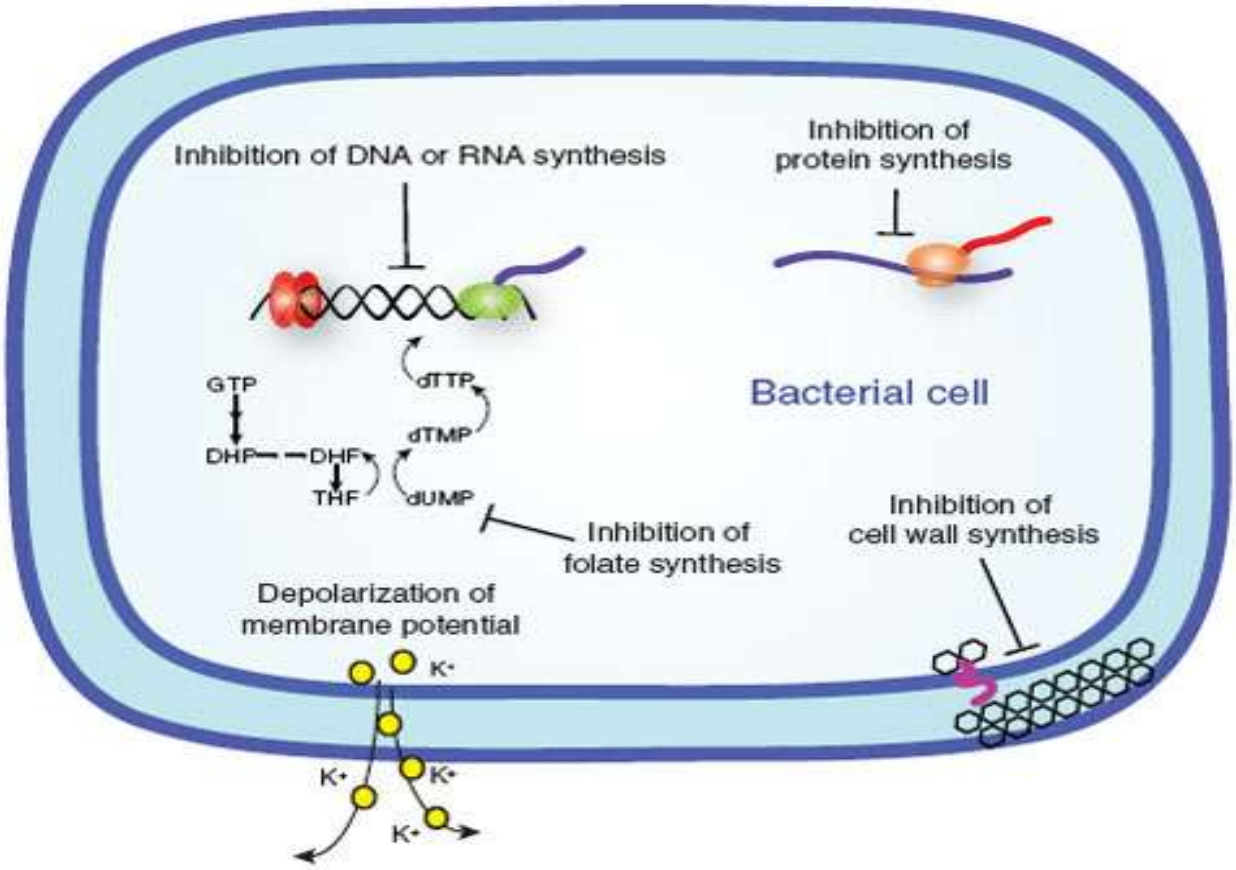


TABLE 24-5 A Summary of Common Antibiotics

Antibiotic or synthetic drug	Mechanism of action	Target bacteria
Penicillin	inhibits cell-wall synthesis	Gram-positive bacteria
Ampicillin	inhibits cell-wall synthesis	broad spectrum
Bacitracin	inhibits cell-wall synthesis	Gram-positive bacteria; used as a skin-ointment
Cephalosporin	inhibits cell-wall synthesis	Gram-positive bacteria
Tetracycline	inhibits protein synthesis	broad spectrum
Streptomycin	inhibits protein synthesis	Gram-negative bacteria, tuberculosis
Sulfa drug	inhibit cell metabolism	bacterial meningitis, urinary-tract infections
Rifampin	inhibits RNA synthesis	Gram-positive bacteria and some Gram-negative bacteria
Quinolines	inhibit DNA synthesis	urinary-tract infections

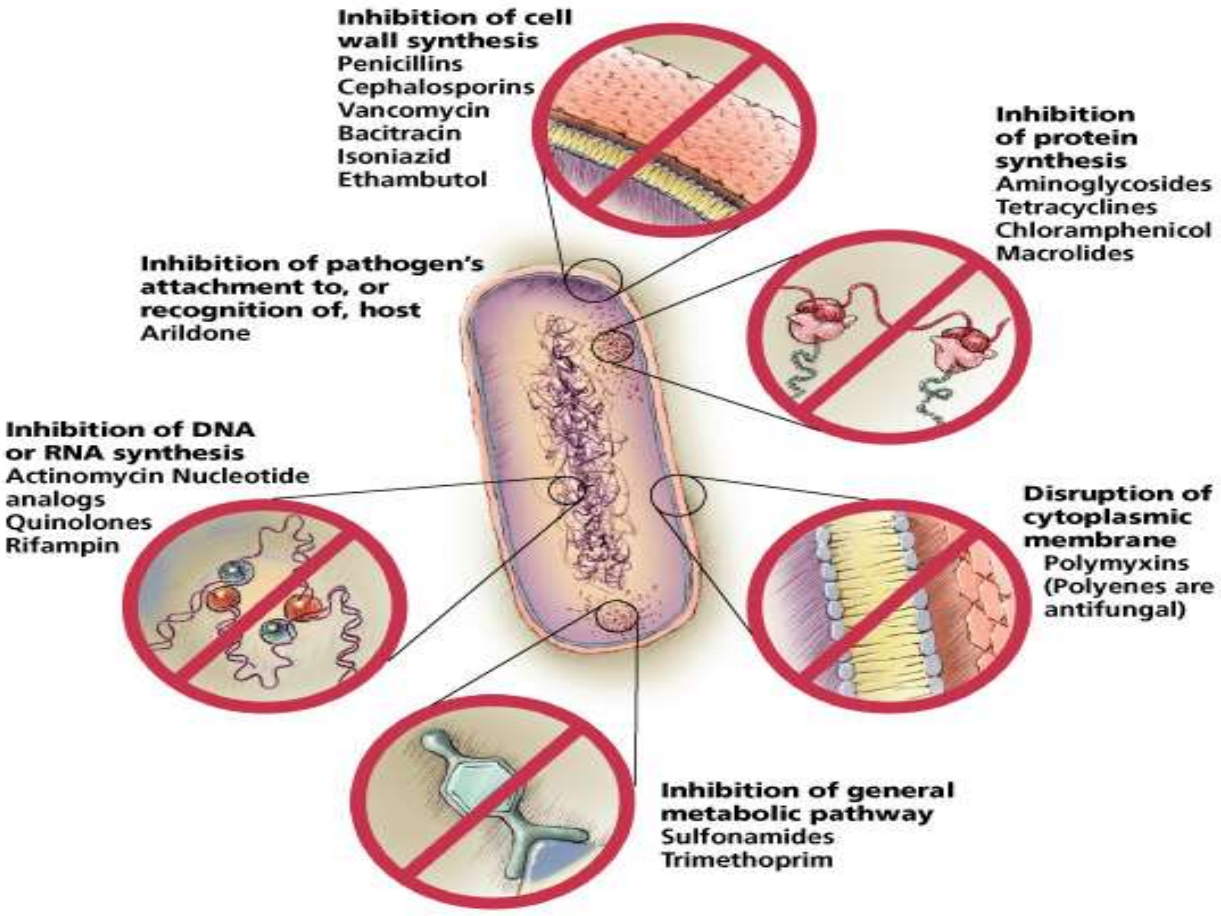


Table 10.4 Antifungal Drugs

Drug	Description and Mode of Action	Clinical Considerations
Antifungal Drugs That Inhibit Cell Membrane		
Polyenes Representatives: Amphotericin B Nystatin	Associate with molecules of ergosterol, forming a pore through the fungal membrane, which leads to leakage of essential ions from the cell; amphotericin B is produced by *Streptomyces nodosus*	**Spectrum of Action:** Fungi **Route of Administration:** Amphotericin B: IV; nystatin: topical **Adverse Effects:** Chills, vomiting, fever
Azoles Representatives: Miconazole Ketoconazole	Antifungal action due to inhibition of ergosterol synthesis	**Spectrum of Action:** Fungi, G+ bacteria, and parasitic protozoa **Route of Administration:** Topical, IV **Adverse Effects:** Possibly causes cancer in humans
Other Antifungal Drugs		
5-Fluorocytosine	Fungi, but not mammals, have an enzyme that converts this drug into 5-fluorouracil, an analog of uracil that inhibits RNA function	**Spectrum of Action:** *Candida, Cryptococcus, Aspergillus* **Route of Administration:** Oral **Adverse Effects:** None
Griseofulvin	Isolated from *Penicillium griseofulvum*; deactivates tubulin, preventing cytokinesis and segregation of chromosomes during mitosis	**Spectrum of Action:** Molds of ringworm (tinea) **Route of Administration:** Topical, oral **Adverse Effects:** None