Antimicrobial drugs

Chapter 20

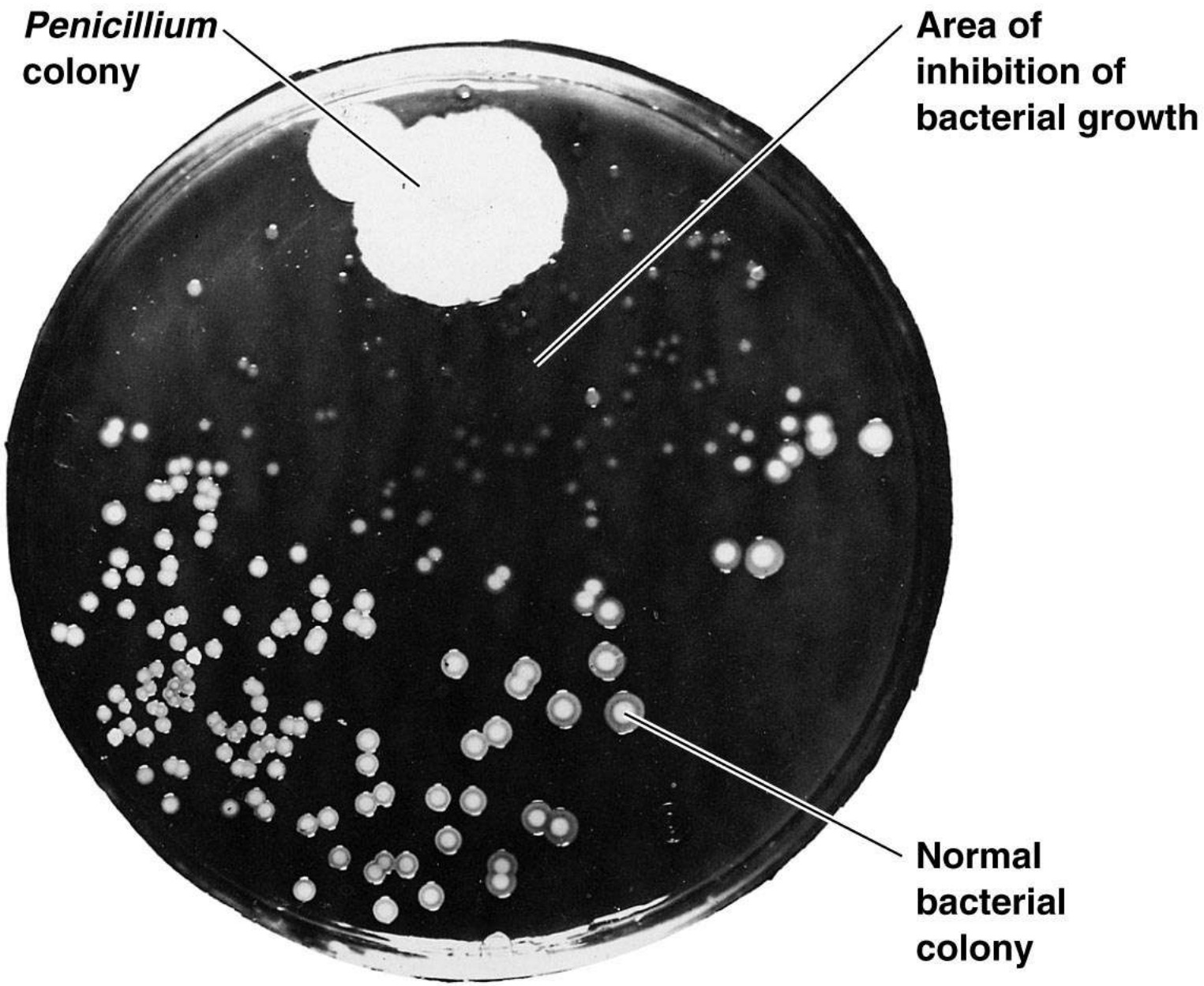


Figure 20.1

I. The Spectrum of Antimicrobial Activity

- A. Antibacterial drugs can affect many prokaryotic targets while fungal, protozoan, virally infected host cells, and helminthic infections are more difficult to treat because these organisms have eukaryotic cells.
  - Goal is to have selective toxicity for microbe without harm to the host.
- B. Narrow-spectrum drugs affect only a select group of microbes: gram positive cells for example; broad spectrum drugs affect a large number of microbes
  - Problem with using broad spectrum antibiotics is that it also kills normal flora and then opportunistic pathogens can survive.
    - *Candida albicans* is resistant to bacterial antibiotics

I. The Spectrum of Antimicrobial Activity

TABLE 20.2 **The Spectrum of Activity of Antibiotics and Other Antimicrobial Drugs**

Prokaryotes				Eukaryotes			
Mycobacteria*	Gram-Negative Bacteria	Gram-Positive Bacteria	Chlamydias, Rickettsias†	Fungi	Protozoa	Helminths	Viruses
		Penicillin G ⟷		Ketoconazole ⟷		Niclosamide (tapeworms) ⟷	
Streptomycin ⟷					Mefloquine (malaria) ⟷		
							Acyclovir ⟷
						Praziquantel (flukes) ⟷	
	Tetracycline ⟷						
Isoniazid ⟷							

*Growth of these bacteria frequently occurs within macrophages or tissue structures.

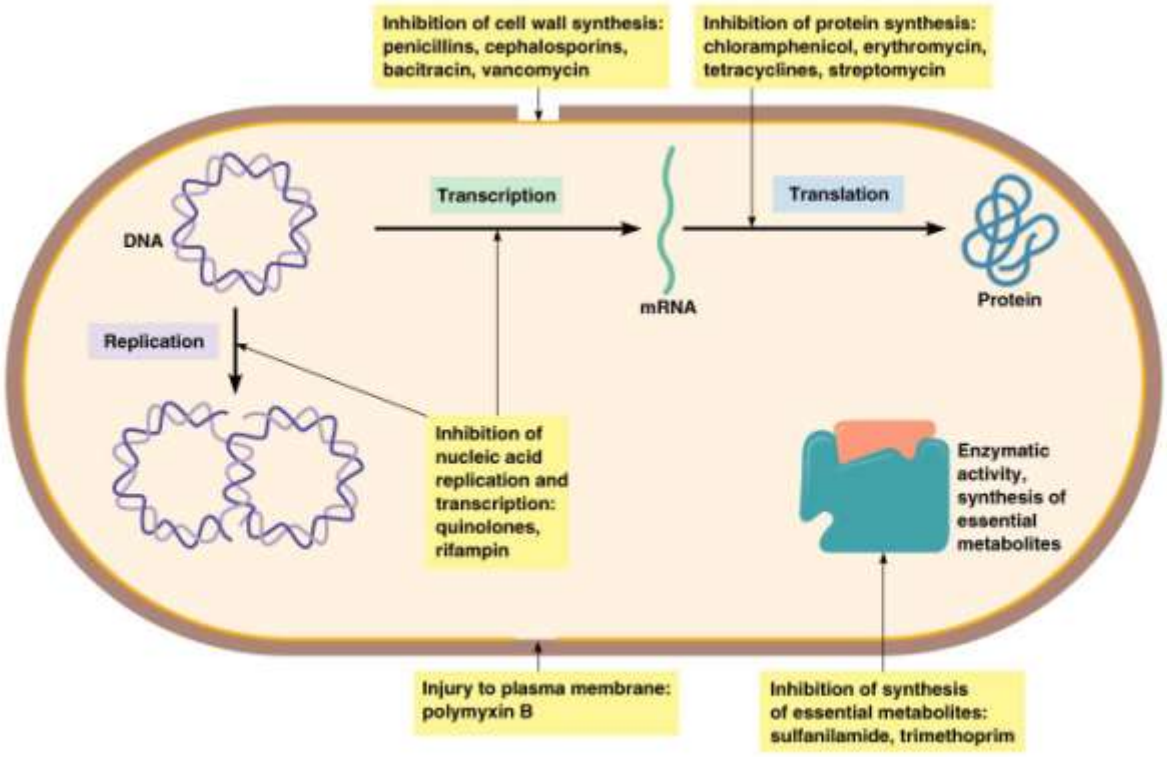
†Obligately intracellular bacteria.

TABLE 20.1 Representative Sources of Antibiotics

Microorganism	Antibiotic
Gram-Positive Rods	
Bacillus subtilis	Bacitracin
Paenibacillus polymyxa	Polymyxin
Actinomycetes	
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 griseofulvum	Griseofulvin
Penicillium chrysogenum	Penicillin

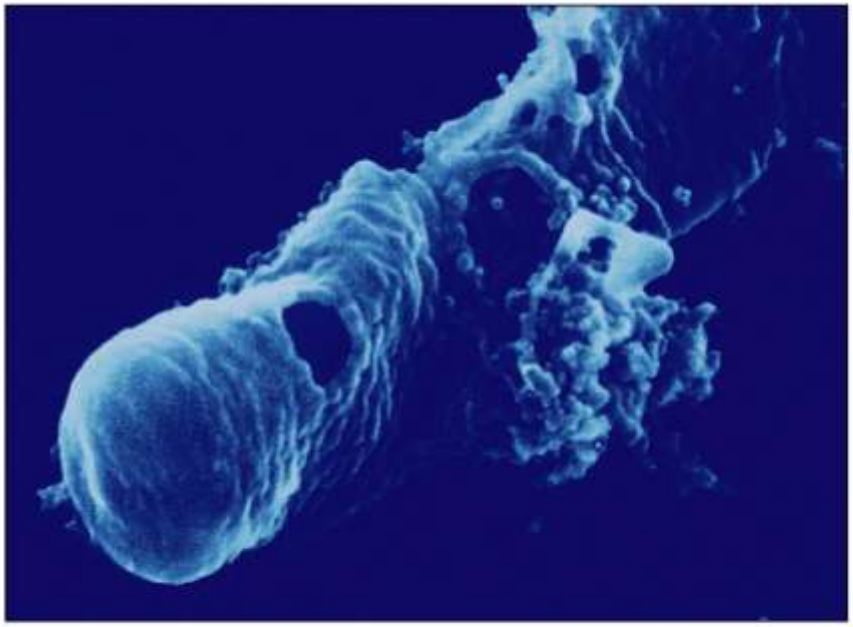
II. The Action of Microbial Drugs

- A. Mechanisms
  - 1. Bactericidal – Kill microbes directly
  - 2. Bacteriostatic – Prevents microbes from growing. Host defenses then usually destroy pathogen.
  - 3. Modes of Action: Inhibition of cell wall, protein, nucleic acid, and essential metabolite synthesis, or injury to plasma membrane.

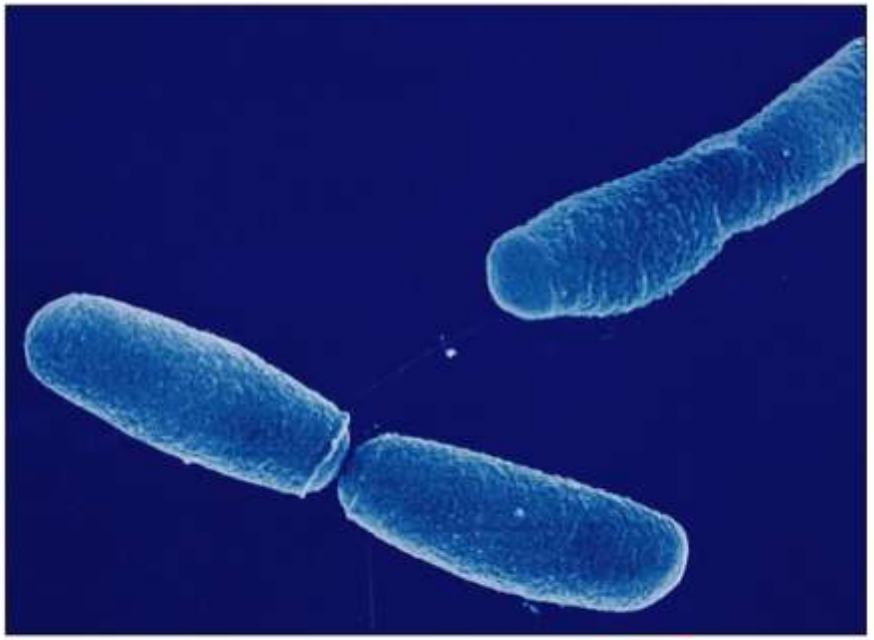


III. Antibacterial Antibiotics

- A. The Inhibition of Cell Wall Synthesis
  - 1. Act on peptidoglycan in different ways, either by inhibiting synthesis of linear strands (bacitracin and vancomycin) or preventing final cross-linking (penicillin and cephalosporin). Cell undergoes osmotic lysis. Drugs in this group include (a-f):



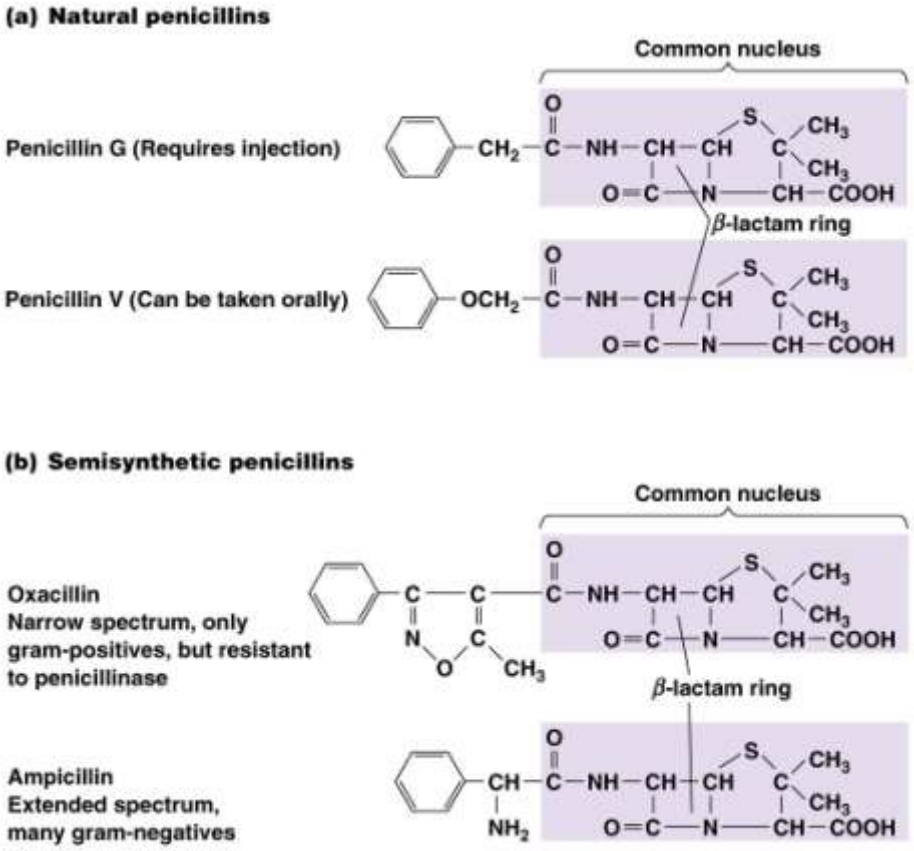
(b) The bacterial cell is lysing as penicillin weakens the cell wall.



(a) Rod-shaped bacterium before penicillin.

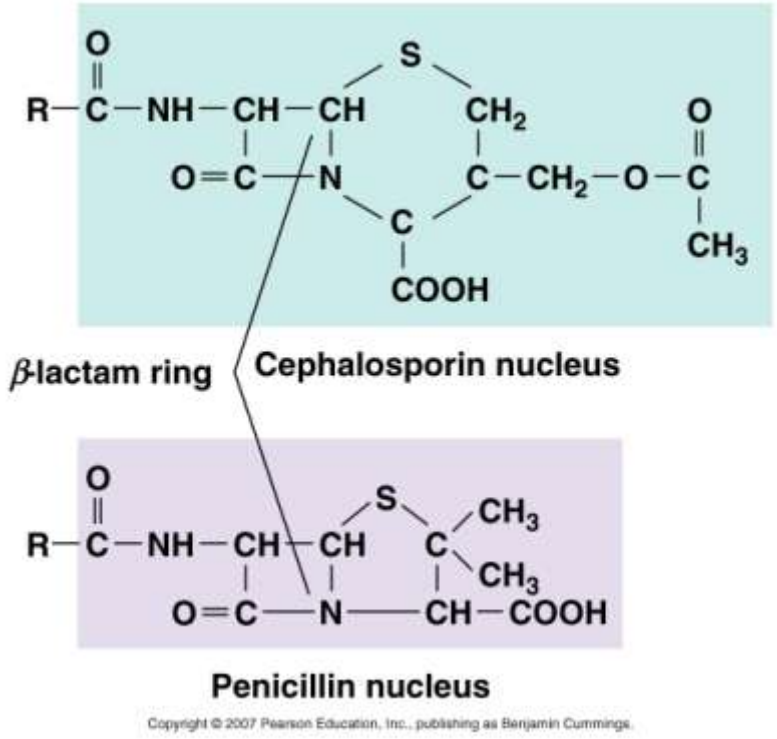
III. Antibacterial Antibiotics

- A. The Inhibition of Cell Wall Synthesis
  - a. Penicillin – A group of over 50 chemically related antibiotics, both natural and semisynthetic. Narrow to broad spectrum. Bacteria produced penicillinase (beta-lactamase) breaks beta-lactam ring.



III. Antibacterial Antibiotics:
The Inhibition of Cell Wall Synthesis

- b. Carbapenems – Semisynthetic penecillin with modified beta-lactam structure. Very broad spectrum.
  - Primaxin (effective on 98% of all hospital isolates).
- c. Monobactams – Synthetic penicillin that has only one beta-lactam ring (as opposed to double ring) and thus avoids beta-lactamase.
  - Aztreonam used for some gram-negative bacteria including Pseudomonas and E. coli.
- d. Cephalosporins – Modified penicillin ring. Large group >70. Resistant to some beta-lactamases and more effective against gram-negative organisms than penicillin.



III. Antibacterial Antibiotics:

The Inhibition of Cell Wall Synthesis

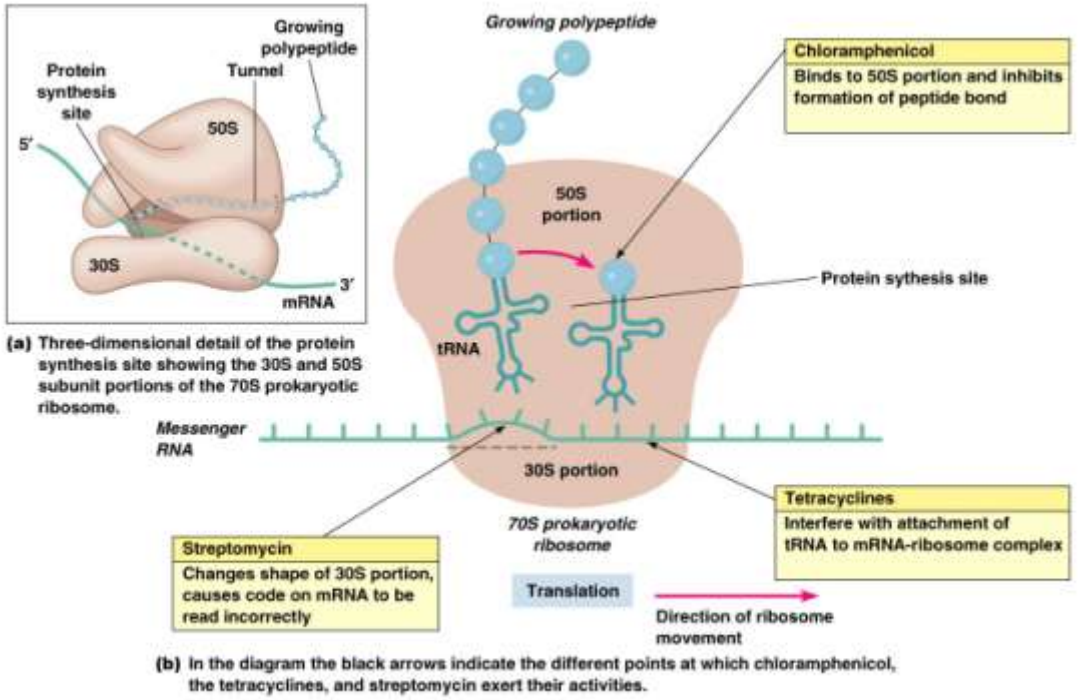
- e. Bacitracin – A polypeptide. Most useful against gram-positives and sold over the counter as a topical use only antibiotic.
- f. Vancomycin – A glycopeptide. Toxic drug that has a narrow spectrum of activity. Very important clinically because it is reserved for Staph (especially MRSA) and Enterococcus (except VRE) infections that are resistant to penicillin.

– 2. Act on Mycolic Acids in mycobacteria

- Isoniazid (INH) – Effective against Mycobacterium tuberculosis. Inhibits mycolic acid in cell wall. Given in drug combo.
  - E.g. Rifampin and ethambutol

III. Antibacterial Antibiotics

- B. The Inhibition of Protein Synthesis
  - 1. Most typical of broad spectrum antibiotics.
    - Affect 50S and 30S subunits of 70S prokaryotic ribosomes vs 80S eukaryotic ribosomes (may have adverse effect on 70S ribosomes in mitochondria of host).

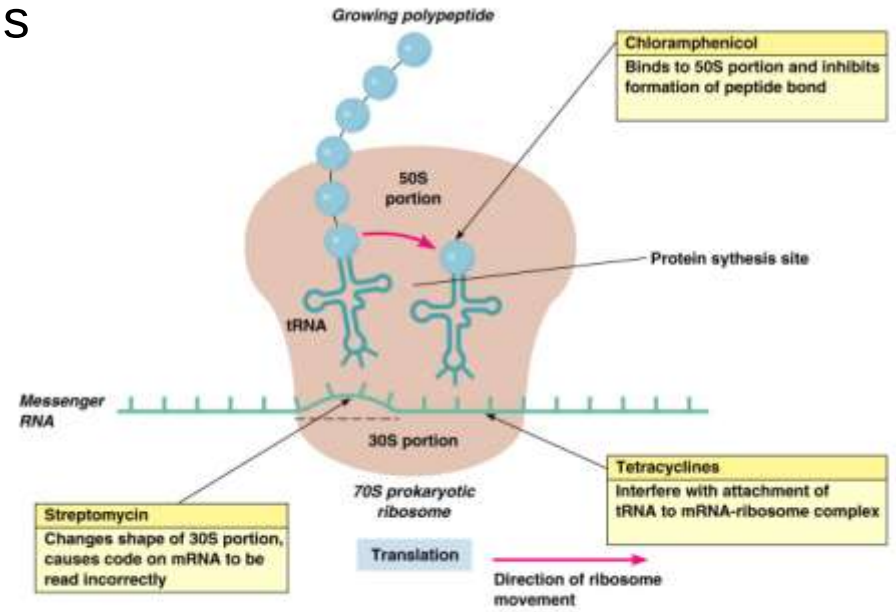


III. Antibacterial Antibiotics

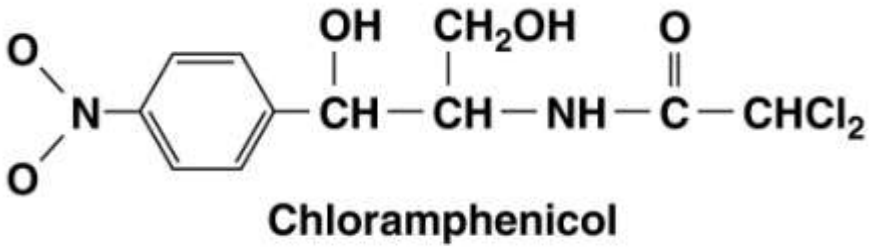
B. The Inhibition of Protein Synthesis

– a. Chloramphenicol – Bacteriostatic – Cheap and because of small size can penetrate into areas that other antibiotics can't reach.

-But has serious side effects, most notable bone marrow depression, so save for serious infections only.



(b) In the diagram the black arrows indicate the different points at which chloramphenicol, the tetracyclines, and streptomycin exert their activities.



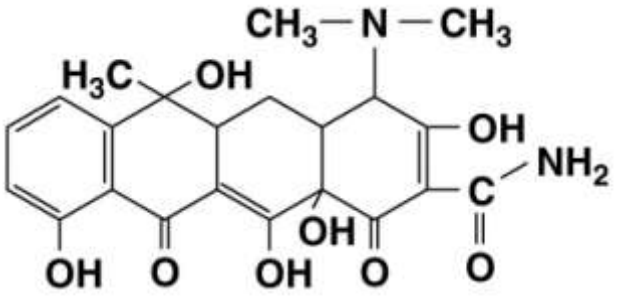
Chloramphenicol

III. Antibacterial Antibiotics

- B. The Inhibition of Protein Synthesis
  - b. Aminoglycosides – Amino sugars are linked by glycoside bonds. Toxic to auditory nerve and maybe kidneys.
    - Streptomycin – Alternative drug in TB
    - Neomycin – Present in topical preparations
    - Gentamicin (and tobramicin) – Used in gram-negative enteric infections and Pseudomonas aeruginosa

III. Antibacterial Antibiotics

- B. The Inhibition of Protein Synthesis
  - c. Tetracycline – Used for both gram negative and gram positive organisms. Penetrate body tissues well and so are effective against intracellular rickettsias and chlamydias.
    - Used to treat many UTI's as well as mycoplasmal pneumonia.
    - Frequently used as alternative drug for syphilis and gonorrhea.
    - Can suppress normal flora causing gastric upset or lead to opportunistic superinfections, especially *C. albicans*.
    - May discolor teeth in children and liver damage in pregnant women.



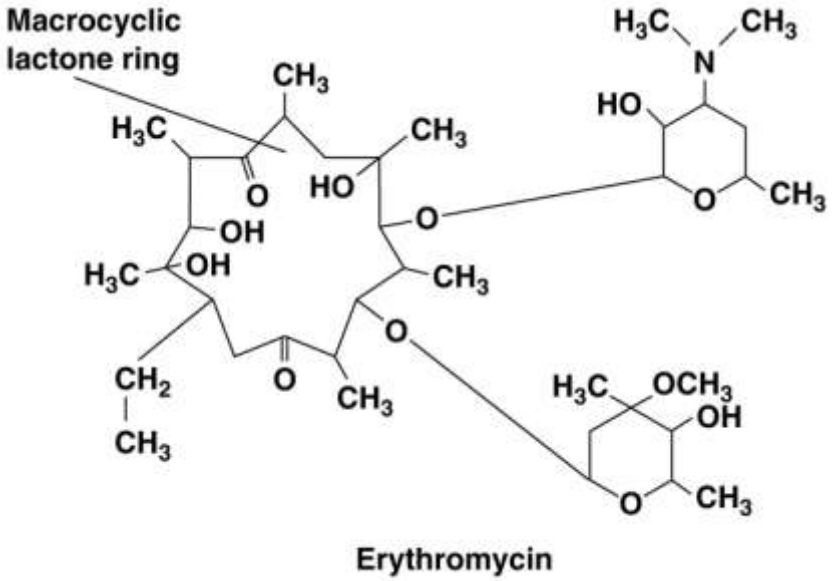
Tetracycline

III. Antibacterial Antibiotics

B. The Inhibition of Protein Synthesis

d. Macrolides – Have a macrocyclic lactone ring

- Erythromycin – Unable to penetrate cell wall of gram negative bacilli, so is used for gram positives. Can be used orally so popular use with children. Drug of choice for treatment of legionellosis and mycoplasma pneumonia.



Erythromycin

III. Antibacterial Antibiotics

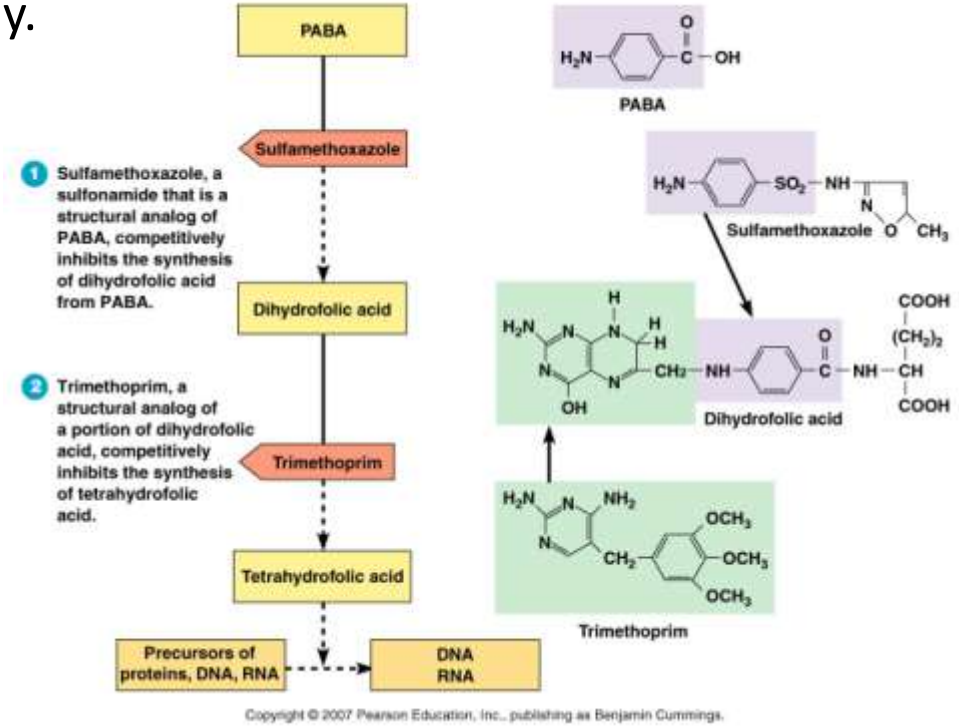
- C. Injury to the Plasma Membrane
  - 1. Change permeability of plasma membrane and result in loss of metabolites.
    - Polymyxin B – Effective against gram negative. Not used much except in topical preparations.
    - Bacitracin (gram positive) and polymyxin B (gram negative) are available as an ointment mixed with neomycin (broad spectrum) as OTC preparation.

III. Antibacterial Antibiotics

- D. Inhibitors of Nucleic Acid (DNA/RNA) Synthesis
  - 1. Interfere with DNA or RNA synthesis. Use limited because also interfere with mammalian DNA. Have to have selective toxicity.
    - a. Rifamycins – Structurally related to macrolides
      - Drug is rifampin (inhibits mRNA) – Effective against mycobacteria and used in the treatment of TB. Valuable characteristic is ability to penetrate tissue where TB organism resides, especially CNS and abscesses. Makes urine and other body fluids orange-red.
    - b. Quinolones
      - Nalidixic Acid – Selectively inhibits an enzyme (DNA gyrase) needed for replication of DNA. Only used in UTI's now.
    - c. Fluoroquinolones – Newer class based on quinolones
      - Norfloxacin and Ciprofloxacin (trials done at KMC) – Broad spectrum, penetrate tissue well. Safe for adults and used for UTI's. May adversely affect development of cartilage and so use is limited in children, adolescents, and pregnant women.

III. Antibacterial Antibiotics

- E. Competitive Inhibitors of the Synthesis of Essential Metabolites
  - 1. A substance structurally related to another inhibits an essential reaction in a metabolic pathway.



• Example: In the presence of sulfonamides (sulfa drugs) the enzyme that normally converts PABA to folic acid combines with the sulfa drugs and this prevents formation of dihydrofolic acid. Folic acid is a vitamin that functions as a coenzyme to the synthesis of purine and pyrimidine bases of nucleic acids and many amino acids.

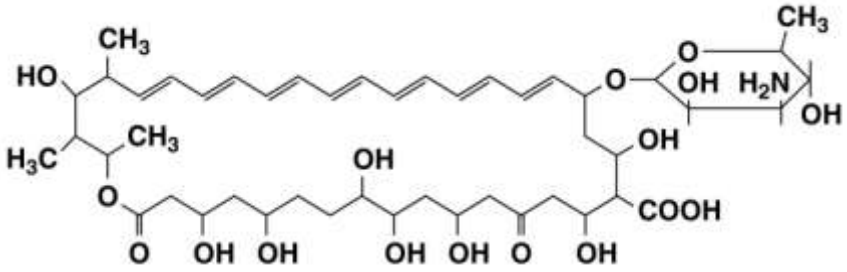
•Sulfonamides (Used in UTI) are bacteriostatic.

•Silver sulfadiazine – Used in burn patients

•Trimethoprims and Sulfamethoxazole (TMP-SMZ) – Most widely used today. Example of synergism. Used especially against many gram-negative pathogens of the UTI and intestinal tract.

IV. Antifungal Drugs

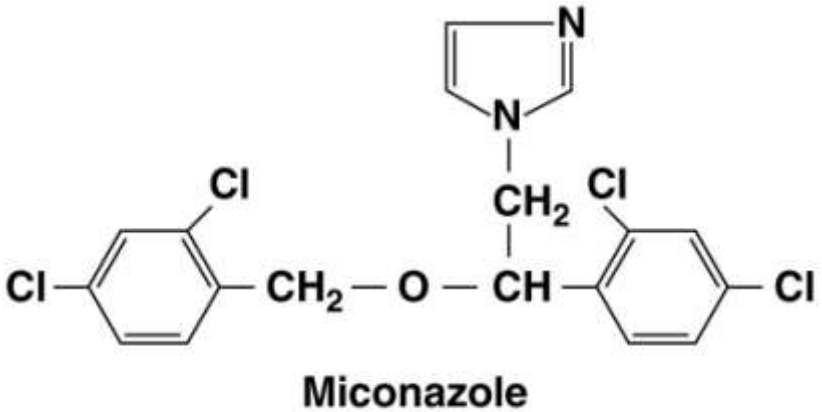
- A. Fungal infections are becoming more prevalent because of immunocompromised patients. Fungal antibiotic testing is becoming more and more important. Many of these drugs interfere with sterols in plasma membrane causing them to leak and kill the cell. Sterol in fungi membrane is ergosterol, while in animals is cholesterol.
  - 1. Polyenes – Combine with sterols in the cell membrane making them permeable and killing the cell.
    - Amphotericin B – For many years was the mainstay for coccidiomycosis, histoplasmosis, and blastomycosis. Toxicity to kidneys limits its use.



Amphotericin B

IV. Antifungal Drugs

- 2. Azoles- Interfere with sterol synthesis.
  - Imidazoles
    - a. Clotrimazole and Miconazole – Generally used topically and sold without a prescription. Used for athlete's foot and vaginal yeast infections.
    - b. Ketoconazole – Orally, a less toxic alternative to Amphotericin B, occasional liver damage reported. Ointments are used to treat dermatomycoses. Broad spectrum of activity.
  - Triazoles – Also interfere with sterol synthesis.
    - a. Fluconazole and Itraconazole – Very water soluble and effective against systemic fungi, but are less toxic.



Miconazole

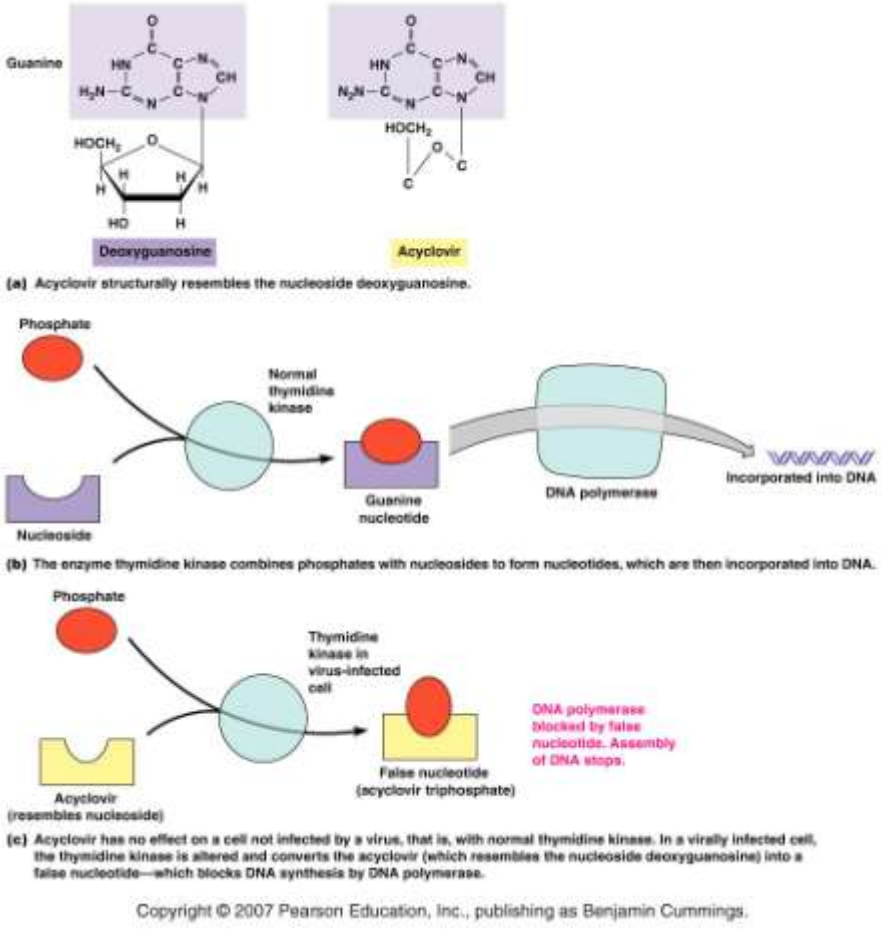
IV. Antifungal Drugs

- 3. Griseofulvin – Active against superficial dermatophytic fungal infections of the hair and nails even though given orally.
  - Binds selectively to keratin. Interferes with mitosis and limits fungal reproduction.
- 4. Other antifungal drugs – tolnafate and undecylenic acid.

V. Antiviral Drugs

A. Limited number of drugs against a few diseases. Most for HIV.

- 1. Nucleoside Analogs – Interferes with nucleic acid synthesis
  - Acyclovir – A guanine analog. Limited to herpesviruses. Widely used for genital herpes. Available topically, orally, or by injection.
  - Ribavirin – Used to treat infants suffering from rotavirus-caused pneumonia via aerosol delivery.
  - Ganciclovir – Used against cytomegalovirus (CMV)
  - Zidovudine (AZT) – A thymidine analog that blocks reverse transcriptase in HIV. Early drug used to treat AIDS.



V. Antiviral Drugs

- B. Other Enzyme Inhibitors
  - 1. Nevirapine – Inactivates the enzyme reverse transcriptase by binding to it. Anti-HIV drug.
  - 2. Protease inhibitors – Inhibits proteases required for intracellular viral maturation.
    - Indinavir for HIV (use drugs in combination)
  - 3. Neuraminidase inhibitors for treatment of influenza.
    - Zanamivir (Relenza)
- C. Interferons – Cells infected with virus produce interferon (a cytokine) that inhibits further spread of virus. Manufactured for use as a drug.
  - Alpha interferon used as drug for viral hepatitis.

VI. Antiprotozoan and Antihelminthic Drugs

- A. Antiprotozoan Drugs
  - 1. Quinine – Old malaria treatment of botanical origin from 1600's
  - 2. Chloroquine –Synthetic derivative that replaced quinine, but drug resistant strains have developed.
  - 3. Mefloquine – Newer drug for resistant malaria.
  - 4. Quinacrine – Drug of choice for giardiasis.
  - 5. Diidohydroquin (Iodoquinol) – Used to treat several intestinal amoebic diseases. Optic nerve toxicity.
  - 6. Metronidazole (Flagyl) – Widely used. Effective against protozoa as well as anaerobic bacteria. *Trichomonas vaginalis*, giardiasis, and amoebic dysentery. Converted in anaerobic metabolism to DNA damaging agent.

VI. Antiprotozoan and Antihelminthic Drugs

- B. Antihelminthic Drugs
  - 1. Niclosamide – Tapeworm – Inhibits ATP production under aerobic conditions.
  - 2. Praziquantel – Kills worms by altering the permeability of heir plasma membranes.
    - Broad specturm and recommended for treating several fluke caused diseases especially schistosomiasis.
    - Causes the helminths to undergo muscular spasms and apparently makes them susceptible to the immune system.
  - 3. Mebendazole – Treats nematodes (round worms: ascaris, pinworm, whipworms) with few side affects.
  - 4. Ivermectin – Used as broad spectrum antihelminthic, primarily for nematodes.
    - Causes paralysis and death of the worm and some arthropods (scabies, ticks, lice).

TABLE 20.3 Antibacterial Drugs

Drugs by Mode of Action	Comments
Inhibitors of Cell Wall Synthesis	
Natural Penicillins	
Penicillin G	Against gram-positive bacteria, requires injection
Penicillin V	Against gram-positive bacteria, oral administration
Semisynthetic Penicillins	
Oxacillin	Resistant to penicillinase
Ampicillin	Broad spectrum
Amoxicillin	Broad spectrum; combined with inhibitor of penicillinase
Aztreonam	A monobactam; effective for gram-negative bacteria, including *Pseudomonas* spp.
Imipenem	A carbapenem; very broad spectrum
Cephalosporins	
Cephalothin	First-generation cephalosporin; activity similar to penicillin; requires injection
Cefixime	Third-generation cephalosporin; oral administration

TABLE 20.3 Antibacterial Drugs *(continued)*

Drugs by Mode of Action	Comments
Polypeptide Antibiotics	
Bacitracin	Against gram-positive bacteria; topical application
Vancomycin	A glycopeptide type; penicillinase-resistant; against gram-positive bacteria
Antimycobacterial Antibiotics	
Isoniazid	Inhibits synthesis of mycolic acid component of cell wall of *Mycobacterium* spp.
Ethambutol	Inhibits incorporation of mycolic acid into cell wall of *Mycobacterium* spp.
Inhibitors of Protein Synthesis	
Chloramphenicol	Broad spectrum, potentially toxic
Aminoglycosides	
Streptomycin	Broad spectrum, including mycobacteria
Neomycin	Topical use, broad spectrum
Gentamicin	Broad spectrum, including *Pseudomonas* spp.
Tetracyclines	
Tetracycline, oxytetracycline, chlortetracycline	Broad spectrum, including chlamydias and rickettsias; animal feed additives
Macrolides	
Erythromycin	Alternative to penicillin
Azithromycin, clarithromycin	Semisynthetic; broader spectrum and better tissue penetration than erythromycin
Telithromycin (Ketek)	New generation of semisynthetic macrolides; used to cope with resistance to other macrolides

TABLE 20.3 Antibacterial Drugs *(continued)*

Drugs by Mode of Action	Comments
Streptogramins	
Quinupristin and dalfopristin (Synercid)	Alternative for treating vancomycin-resistant gram-positive bacteria
Oxazolidinones	
Linezolid (Zyvox)	Useful primarily against penicillin-resistant gram-positive bacteria
Injury to the Plasma Membrane	
Polymyxin B	Topical use, gram-negative bacteria, including *Pseudomonas* spp.
Inhibitors of Nucleic Acid Synthesis	
Rifamycins	
Rifampin (or rifampicin)	Inhibits synthesis of mRNA; treatment of tuberculosis
Quinolones and Fluoroquinolones	
Nalidixic acid, nofloxacin, ciprofloxacin	Inhibit DNA synthesis; broad spectrum; urinary tract infections
Gatifloxacin	Newest generation quinolone; increased potency against gram-positive bacteria
Competitive Inhibitors of the Synthesis of Essential Metabolites	
Sulfonamides	
Trimethoprim-sulfamethoxazole	Broad spectrum; combination is widely used

TABLE 20.4 Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs

	Mode of Action	Comments
Antifungal Drugs		
Agents Affecting Fungal Sterols (Plasma Membrane)		
Polyenes		
Amphotericin B	Injury to plasma membrane	Systemic fungal infections; fungicidal
Azoles		
Clotrimazole, miconazole	Inhibit synthesis of plasma membrane	Topical use
Ketoconazole	Inhibits synthesis of plasma membrane	Can be taken orally for systemic fungal infections
Voriconazole	Inhibits synthesis of plasma membrane	Can penetrate blood–brain barrier to treat aspergillosis of the central nervous system
Allylamines		
Terbinafine, naftifine	Inhibits synthesis of plasma membrane	New class of antifungals frequently used to treat diseases resistant to azoles
Agents Affecting Fungal Cell Walls		
Echinocandins		
Caspofungin (Cancidas)	New class of antifungals that inhibit synthesis of cell wall	

TABLE 20.4 Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs *(continued)*

	Mode of Action	Comments
Agents Inhibiting Nucleic Acids		
Flucytosine	Inhibits synthesis of RNA and therefore protein synthesis	
Other Antifungal Drugs		
Griseofulvin	Inhibition of mitotic microtubules	Fungal infections of the skin
Tolnaftate	Unknown	Athlete's foot
Antiviral Drugs (See also Table 20.5, Drugs for Chemotherapy of HIV)		
Nucleoside and Nucleotide Analogs		
Acyclovir, ganciclovir, ribavirin, lamivudine	Inhibit DNA or RNA synthesis	Used primarily against herpesviruses
Cidofovir	Inhibits DNA or RNA synthesis	Cytomegalovirus infections; possibly effective against smallpox
Adefovir dipivoxil (Hepsera)		For resistance against lamivudine
Attachment and Uncoating		
Zanamivir, oseltamivir	Inhibit neuraminidase on influenza virus	Treatment of influenza
Amantadine, zimantadine	Inhibit uncoating	Treatment of influenza
Interferons		
alpha-interferon	Inhibits spread of virus to new cells	Viral hepatitis

TABLE 20.4 **Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs** *(continued)*

	Mode of Action	Comments
Antiprotozoan Drugs		
Chloroquine	Inhibits DNA synthesis	Malaria; effective against red blood cell stage only
Diiodohydroxyquin	Unknown	Amoebic infections; amoebicidal
Metronidazole, Tinidazole	Interferes with anaerobic metabolisms	Giardiasis, amebiasis, trichomoniasis
Nitazoxanide	Interferes with anaerobic metabolism	Giardiasis; only drug approved for cryptosporidiosis
Antihelminthic Drugs		
Niclosamide	Prevents ATP generation in mitochondria	Tapeworm infections; kills tapeworms
Praziquantel	Alters permeability of plasma membranes	Tapeworm and fluke infections; kills flatworms
Pyantel pamoate	Neuromuscular block	Intestinal roundworms; kills roundworms
Mebendazole, albendazole	Inhibit absorption of nutrients	Intestinal roundworms
Ivermectin	Paralyzes worm	Intestinal roundworms primarily; occasional use for scabies mite and lice