#Microbiology

Prescott's MICROBIOLOGY

ELEVENTH EDITION

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Chapter 9

Antimicrobial Chemotherapy

Because learning changes everything.™

Chemotherapeutic Agents

Chemical agents used to treat disease.

Destroy pathogenic microbes or inhibit their growth within host.

Most are antibiotics.

- Microbial products or their derivatives that kill susceptible microbes or inhibit their growth.

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The Development of Chemotherapy

Paul Ehrlich (1904). → He showed that certain chemicals have selective Toxicity ⇒ meaning that these chemicals can kill microbes but unable to kill eukaryotic cells.

- √Developed concept of selective toxicity.
- √Identified dyes that effectively treated African sleeping sickness. → He also find out that some dyes → Kill tsytsi fly (A fly that if infect Human cause sleeping sickness)

Sahachiro Hato (1910). → Some compounds can treat Syphilis (Cherch. in Presence of Sores on gen)

- √Working with Ehrlich, identified arsenic compounds that effectively treated syphilis.

Gerhard Domagk, and Jacques and Therese Trefouel (1935).

- Discovered sulfonamides, or sulfa drugs.

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Penicillin

First discovered by Ernest Duchesne (1896), but discovery lost.

Accidentally discovered by Alexander Fleming (1928).

- Observed penicillin activity on contaminated plate.
- Did not think could be developed further.

Effectiveness demonstrated by Florey, Chain, and Heatley (1939).

Fleming, Florey, and Chain received Nobel Prize in 1945 for discovery and production of penicillin.

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Later Discoveries

Streptomycin, an antibiotic active against tuberculosis, was discovered by Selman Waksman (1944).

- Nobel Prize was awarded to Waksman in 1952 for this discovery.

By 1953 chloramphenicol, neomycin, oxytetracycline, and tetracycline isolated.

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General Characteristics of Antimicrobial Drugs 1

Selective toxicity.

- Ability of drug to kill or inhibit pathogen while damaging host as little as possible.

Therapeutic dose.

- Drug level required for clinical treatment.

Toxic dose.

- Drug level at which drug becomes too toxic for patient (i.e., produces side effects).

Therapeutic index.

- Ratio of toxic dose to therapeutic dose.

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General Characteristics of Antimicrobial Drugs 2

* when we think about Antimicrobial Growth we think about Common Criteria → Must Be Present in any antibiotic

Side effects—undesirable effects of drugs on host cells.

↳ Symptoms, negative effect,

Narrow-spectrum drugs—attack only a few different pathogens.

Broad-spectrum drugs—attack many different kinds of bacteria.

Cidal agent—kills the target pathogen.

Static agent—reversibly inhibits growth of microbes.

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Measuring Effectiveness of Antimicrobial Drugs

Effect of an agent may vary with concentration, microbe, host.

Effectiveness expressed in two ways:

- Minimal inhibitory concentration (MIC)—lowest concentration of drug that prevents growth of the pathogen.
- Minimal lethal concentration (MLC)—lowest concentration of drug that kills the pathogen.

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Antimicrobial Drugs—Main Modes of Action

1) Inhibitors of cell wall synthesis.
2) Protein synthesis inhibitors.
3) Metabolic antagonists.
4) Nucleic acid synthesis inhibition.
   DNA / RNA

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1 Inhibitors of Cell Wall Synthesis:

Penicillins

Most are 6-aminopenicillanic acid derivatives and differ in side chain attached to amino group.

Most crucial feature of molecule is the β-lactam ring.

- Essential for bioactivity.
- Many penicillin resistant organisms produce β-lactamase (penicillinase) which hydrolyzes a bond in this ring.

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Penicillins—Structures

Mode of action.

- Blocks the enzyme that catalyzes transpeptidation (formation of cross-links in peptidoglycan).
- Prevents the synthesis of complete cell walls leading to lysis of cell.
- Acts only on growing bacteria that are synthesizing new peptidoglycan.

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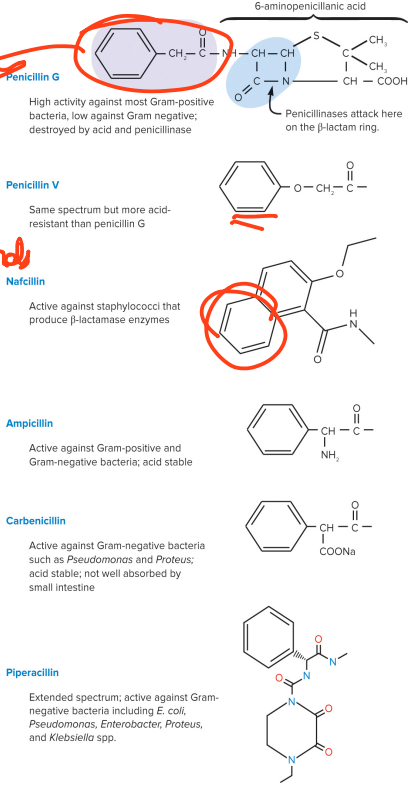

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Other Actions and Types of Penicillins

Binds to periplasmic proteins (penicillin-binding proteins, PBPs)

Naturally occurring penicillins:

- Penicillin V and G are narrow spectrum

Semisynthetic penicillins have a broader spectrum than naturally occurring ones.

- Bulkier side chains make them more difficult for β-lactamase enzymes to degrade.

Resistance to penicillins, including the semisynthetic analogs, continues to be a problem.

Aminopenicillins have broader coverage that includes many Gram-negative bacteria.

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B-lactam Antibiotics Block Transpeptidation

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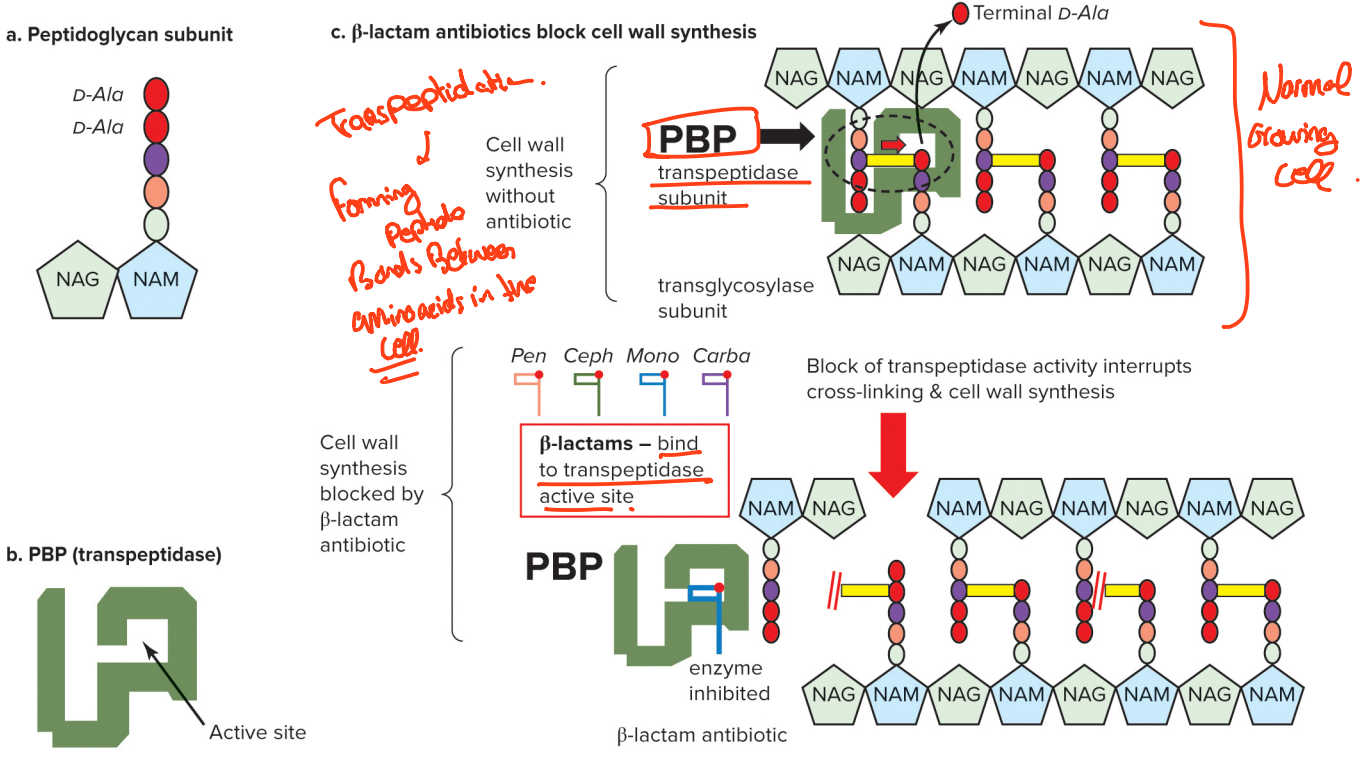

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* Some Microorganisms Are Resistant to Penicilin → So we need another Drug of choice

Cephalosporins

↳ For Penicilin Resistance Microbes.

Structurally and functionally similar to penicillins.

Broad-spectrum antibiotics that can be used by most patients that are allergic to penicillin.

Four categories based on their spectrum of activity.

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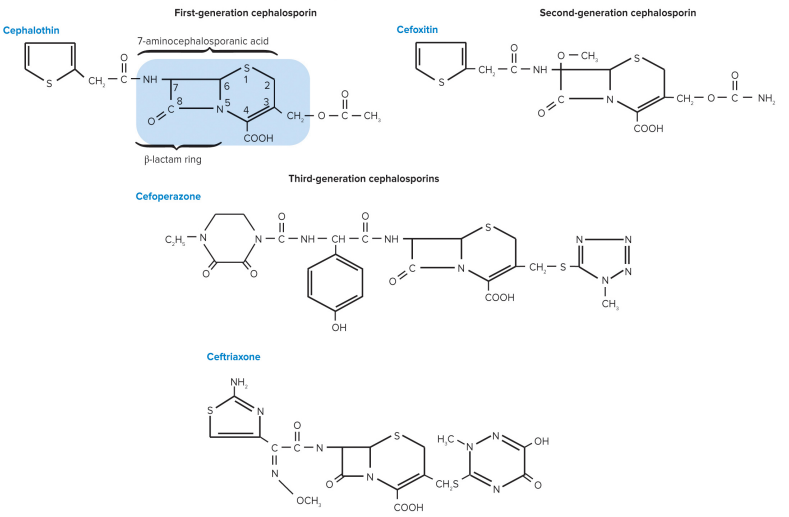

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MRSA – Methicillin Resistance S. Aureus. → Lead to Burns.

Used on Sides.

Vancomycin

→ Acts on the cell wall biosynthesis

→ Last Drug of Choice // Alternative to Penicillin.

Resistance to most of Antibiotics

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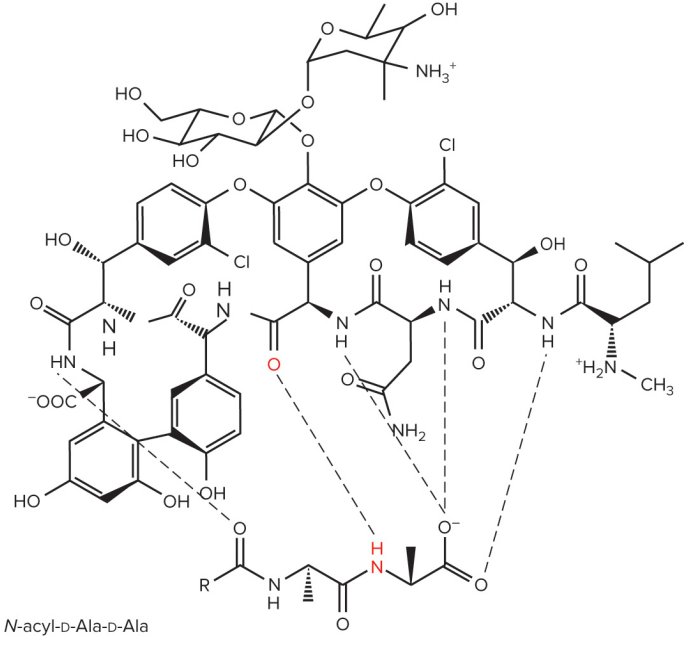

N-acyl-D-Ala-D-Ala

Glycopeptide antibiotic.

Inhibit cell wall synthesis.

Vancomycin—important for treatment of antibiotic-resistant staphylococcal and enterococcal infections.

Previously considered "drug of last resort" so rise in resistance to vancomycin is of great concern.

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Protein Synthesis Inhibitors

Many antibiotics bind specifically to the bacterial ribosome.

Target different steps in protein synthesis.

- Aminoacyl-tRNA binding.
- Peptide bond formation.
- mRNA reading.
- Translocation.

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Aminoglycosides

Large group, all with a cyclohexane ring, amino sugars.

Bind to 30S ribosomal subunit, interfere with protein synthesis by directly inhibiting the process and by causing misreading of the messenger RNA.

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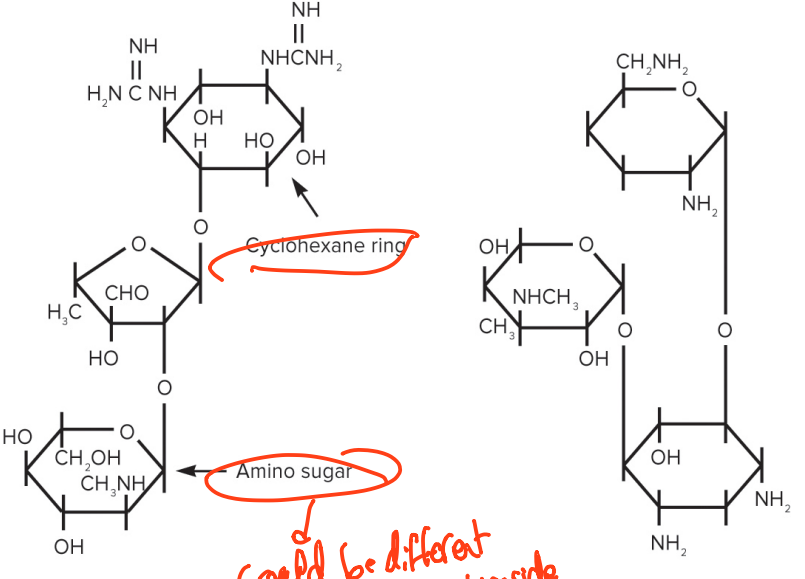

Could be different from one aminoglycoside to another.

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b Tetracyclines → 4 Rings.

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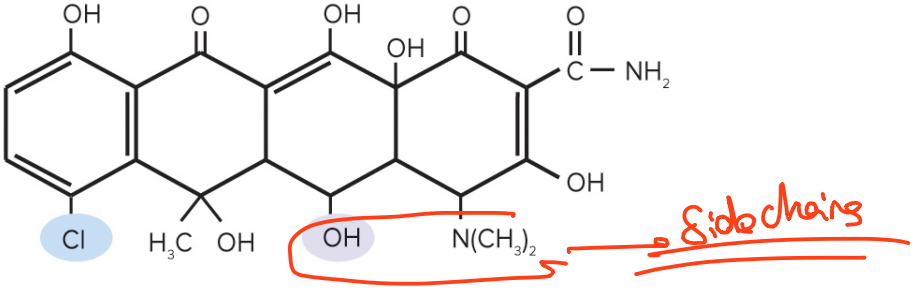
Tetracycline (chlortetracycline, doxycycline)



All have a four-ring structure to which a variety of side chains are attached.

Are broad spectrum, bacteriostatic. → don't kill but inhibit.

Target the 30S subunit of the ribosome inhibiting protein synthesis.

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Macrolides

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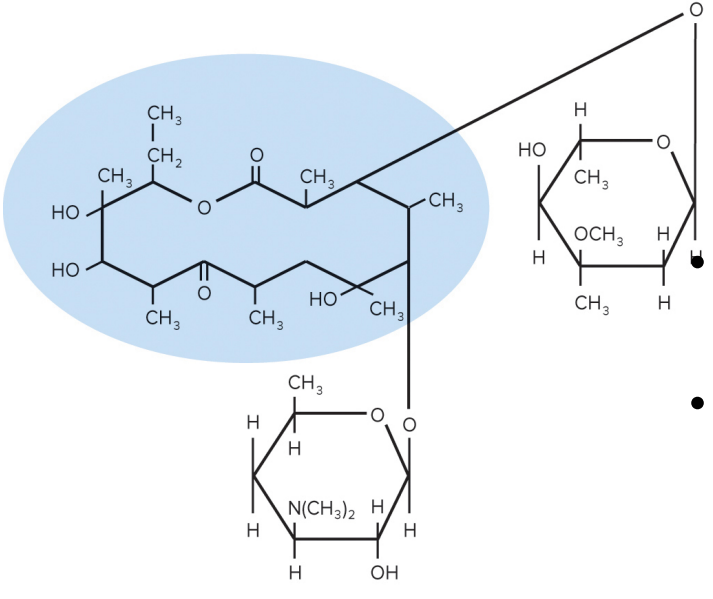

- Contain 12- to 22-carbon lactone rings linked to one or more sugars.
- For example, erythromycin.
  - Broad spectrum, usually bacteriostatic.
  - Binds to 50S ribosomal subunit to inhibit bacterial protein elongation .
- Used for patients allergic to penicillin.

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Chloramphenicol

Now is chemically synthesized.

Binds the 50S ribosomal subunit to inhibit bacterial protein synthesis.

Toxic with numerous side effects so only used in life-threatening situations.

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③ Metabolic Antagonists

Produce Metabolites → are structurally similar to metabolites in eukaryotic cells.

Act as antimetabolites.

- Antagonize or block functioning of metabolic pathways by competitively inhibiting the use of metabolites by key enzymes.

Are structural analogs.

- Molecules that are structurally similar to, and compete with, naturally occurring metabolic intermediates to block normal cellular metabolism.

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Sulfonamides or Sulfa Drugs

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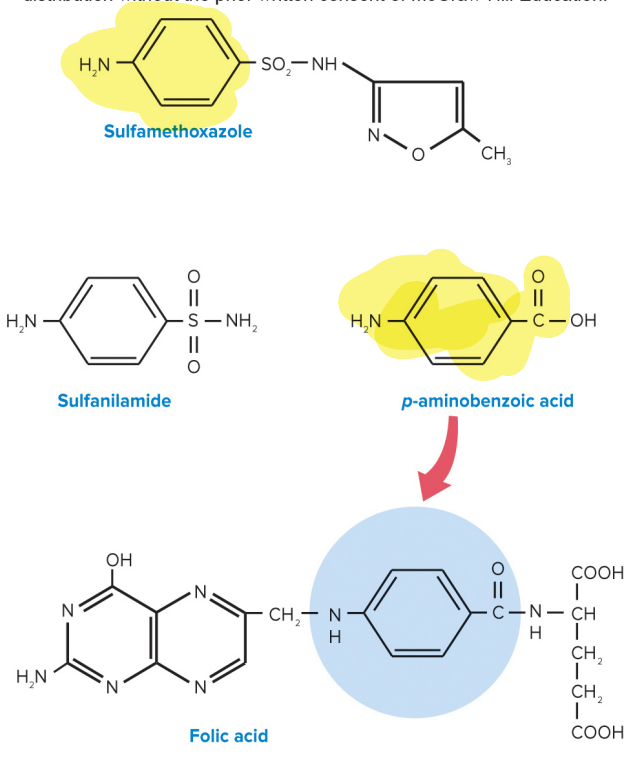

Structurally related to sulfanilamide, a para aminobenzoic acid (PABA) analog.

PABA used for the synthesis of folic acid and is made by many pathogens.

- Sulfa drugs are selectively toxic due to competitive inhibition of folic acid synthesis enzymes.

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Trimethoprim

Synthetic antibiotic that also interferes with folic acid production.

Broad spectrum.

Can be combined with sulfa drugs to increase efficacy of treatment.

- Combination blocks two steps in folic acid pathway.

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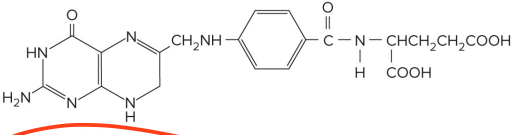
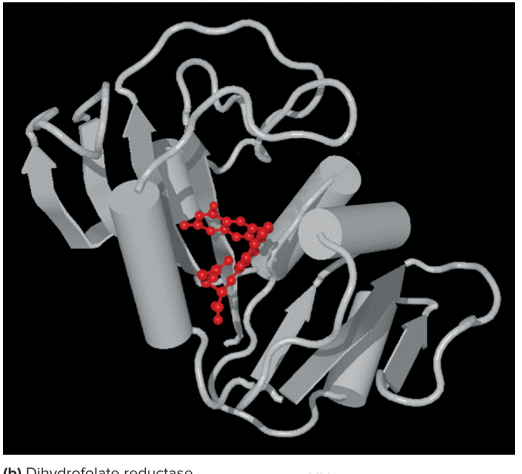
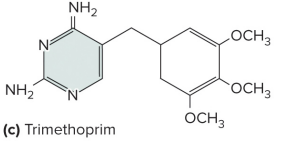


(a) Dihydrofolic acid (DFA)



(b) Dihydrofolate reductase



(c) Trimethoprim

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Nucleic Acid Synthesis Inhibition

The most commonly used antibacterial drugs that inhibit nucleic acid synthesis function by inhibiting:

- DNA polymerase and topoisomerases (fluoroquinolones).
- RNA polymerase (rifamycins).

Drugs not as selectively toxic as other antibiotics because bacteria and eukaryotes do not differ greatly in the way they synthesize nucleic acids.

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Fluoroquinolones

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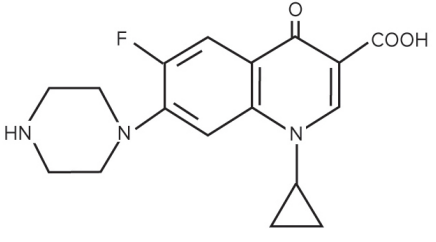

Ciprofloxacin

Synthetic drugs containing the 4-quinolone ring.

Act by inhibiting bacterial DNA gyrase and topoisomerase II.

Broad spectrum, bactericidal, treat a wide variety of infections.

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*Once viruses enter the Host cell they start Replicating and assmlang and forming their own structure

Antiviral Drugs →

they are challenging Because viruses are Multiling Organisms.

Drug development has been slow because it is difficult to specifically target viral replication.

Antiviral drugs have had mixed success and the vast majority of viral infections cannot be cured.

Some antiviral drugs simply limit the duration of the illness (For example, flu) or its severity (For example, herpes, HIV).

*they are not Good Because they affect cukaryots and we need selective toxicity.

Drugs currently used inhibit virus-specific enzymes and life cycle processes .

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Antiviral Drugs for Influenza

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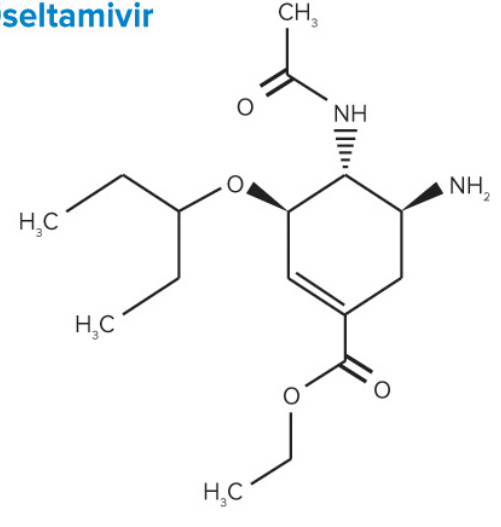
e. Neuraminidase inhibitor

Oseltamivir



Tamiflu.

- Anti-influenza agent.
- A neuraminidase inhibitor.
- Though not a cure for influenza, has been shown to shorten course of illness.

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Antiviral Drugs for Viruses With DNA Genomes

Acyclovir and vidarabine

- Used to treat herpes infections and shingles.

Ganciclovir.

- Used to treat systemic cytomegalovirus illness.

Foscarnet.

- Used in cases of acyclovir or ganciclovir resistance.
- Treats illnesses caused by both herpes simplex viruses and cytomegalovirus.

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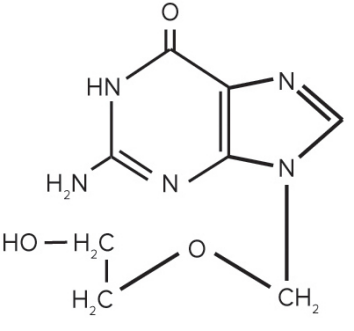
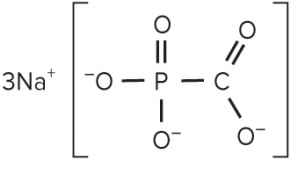
d. Inhibitors of viral DNA polymerase

Acyclovir



c. Viral fusion inhibitor

Foscarnet



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Broad Spectrum Antiviral Drugs

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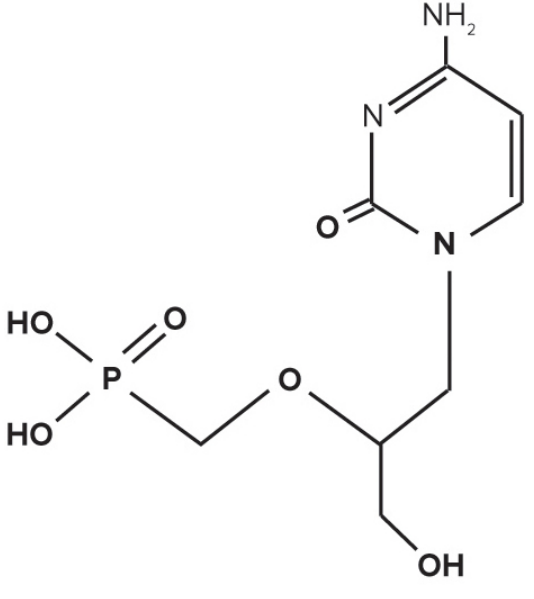
d. Inhibitors of viral DNA polymerase

Cidofovir



Cidofovir.

- Inhibits viral DNA polymerase.

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Anti-HIV Drugs 1

- Nucleoside reverse transcriptase inhibitors (NRTIs).
  - Target and interfere with critical steps in viral replicative processes.
- Protease inhibitors (PIs).
  - block the activity of the HIV protease needed for the production of all viral proteins.

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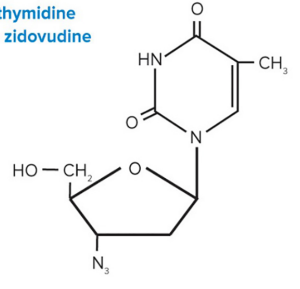
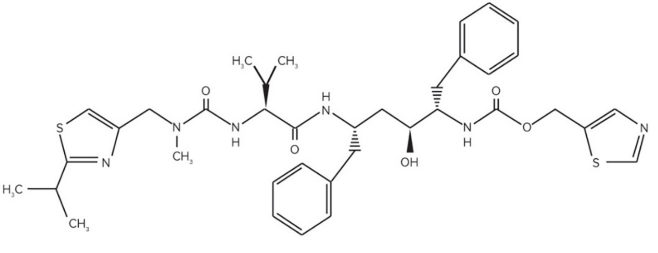
a. Nucleoside reverse transcriptase inhibitor

Azidothymidine (AZT) or zidovudine



b. Viral protease inhibitor

Ritonavir



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Anti-HIV Drugs 2

this virus is made of RNA → can convert to DNA.

✓ Nonnucleoside reverse transcriptase inhibitors (NNRTIs).

- Prevent HIV DNA synthesis by selectively binding to and inhibiting the viral reverse transcriptase enzyme.

✓ Integrase inhibitors.

- Prevent the incorporation of the HIV genome into the host's chromosomes.

✓ Fusion inhibitors.

- Prevent HIV entry into cells.

Most successful are drug cocktails to curtail resistance.

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Identifying Targets for Anti-HIV Drugs

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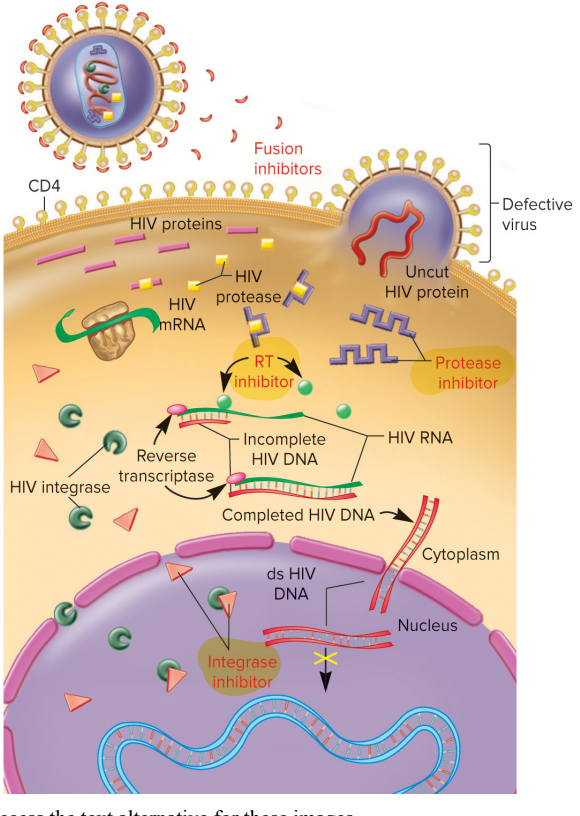
Infection begins with HIV fusion.
Fusion inhibitors block this step.

Once inside a host cell, HIV uncoats and its reverse transcriptase (RT) makes DNA from the viral RNA genome.
RT inhibitors block this step.

Viral DNA is transcribed and translated into polyproteins that are cut to release viral proteins.
Protease inhibitors block this step.

Viral DNA is added to the host DNA by the action of a viral integrase.
Integrase inhibitors block this step.



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Antifungal Drugs

↳ least effective drugs

Fewer effective agents because of similarity of eukaryotic fungal cells and human cells.

- Many have low therapeutic index and are toxic.

Easier to treat superficial mycoses than systemic infections.

↳ outside (surfaces) ✓.

- Combinations of drugs may be used.

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Treating Mycoses

Superficial mycoses.

- For example, *Candida*.
- Topical and oral.
- Disrupt membrane permeability and inhibit sterol synthesis.
- Disrupts mitotic spindle; may inhibit protein and DNA synthesis.

Systemic mycoses.

- Difficult to control and can be fatal.
- Three common drugs.
  - Amphotericin B—binds sterols in membranes.
  - 5-flucytosine—disrupts RNA function.
  - Fluconazole—low side effects, used prophylactically.

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Common Antifungal Drugs

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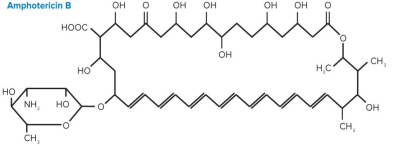
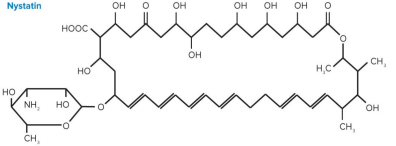
a. Polyenes bind to sterols, resulting in membrane damage

Amphotericin B

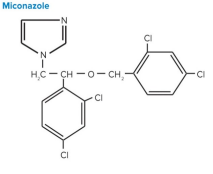


Nystatin

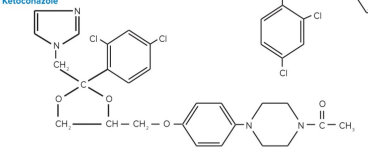


b. Azoles inhibit sterol synthesis, resulting in altered membrane permeability

Miconazole

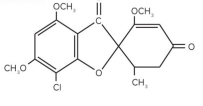


Ketoconazole



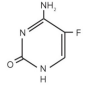
c. Drug that inhibits nucleic acid synthesis, protein synthesis, or cell division

Griseofulvin



d. Drug that disrupts RNA function

5-flucytosine



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Types of Drug Resistance

Intrinsic

- Mycoplasma resistance to β-lactam antibiotics and other cell wall inhibitors simply because these bacteria lack a cell wall.

Acquired—occurs when there is a change in the genome of a bacterium that converts it from one that is sensitive to an antibiotic to one that is resistant.

Drug-tolerant bacteria (persisters) lack the mechanisms for antibiotic resistance and "ignore" the presence of antibiotics, usually because they are embedded in biofilms that antibiotics cannot effectively penetrate or are growing too slowly to be inhibited.

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How do Bacteria Resist Antibiotics? → Several means. → Efflux drugs.

Mechanisms of Drug Resistance

- Modify the target of the antibiotic.
- Drug inactivation.
- Minimize the concentration of antibiotic in the cell.
- Bypass the biochemical reaction inhibited by the agent or increase the production of the target metabolite.

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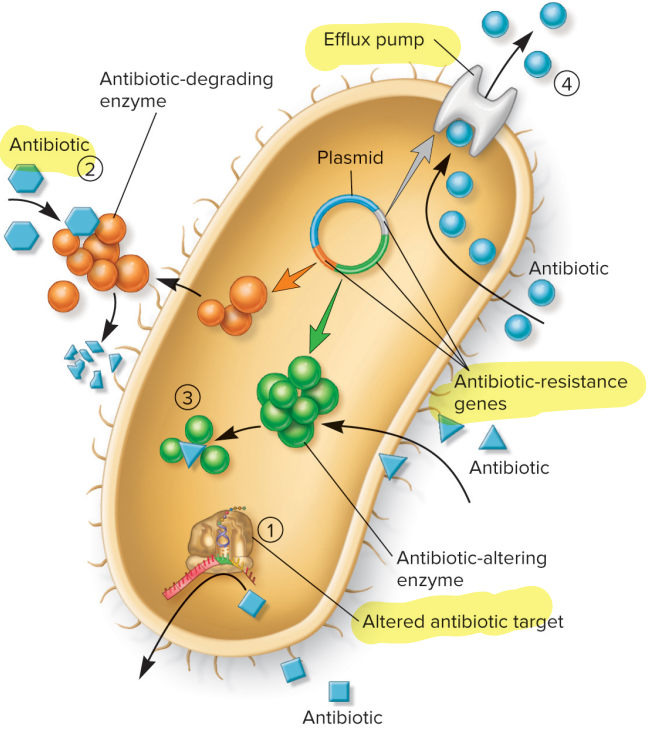

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PCR → Amplification and taking Bacterial Genome

Detecting Drug Resistance

Commercial gene expression systems are designed to identify the production of specific resistance factors, such as a target-modifying enzyme.

Several test systems measure the color change induced when a chromophore is acted upon by either a β-lactamase or an antibiotic-modifying enzyme.

- Color changes are measured spectrophotometrically and protein concentration is extrapolated from a standardized curve.

Detection systems are also commercially available to identify genes encoding drug resistance factors using polymerase chain reactions (PCRs).

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Overcoming Drug Resistance

Give drug in appropriate concentrations to destroy susceptible microbes and most spontaneous mutants.

Give two or more drugs at same time.

Use drugs only when necessary.

Possible future solutions.

- Continued development of new drugs.
- Use of bacteriophages to treat bacterial disease.

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