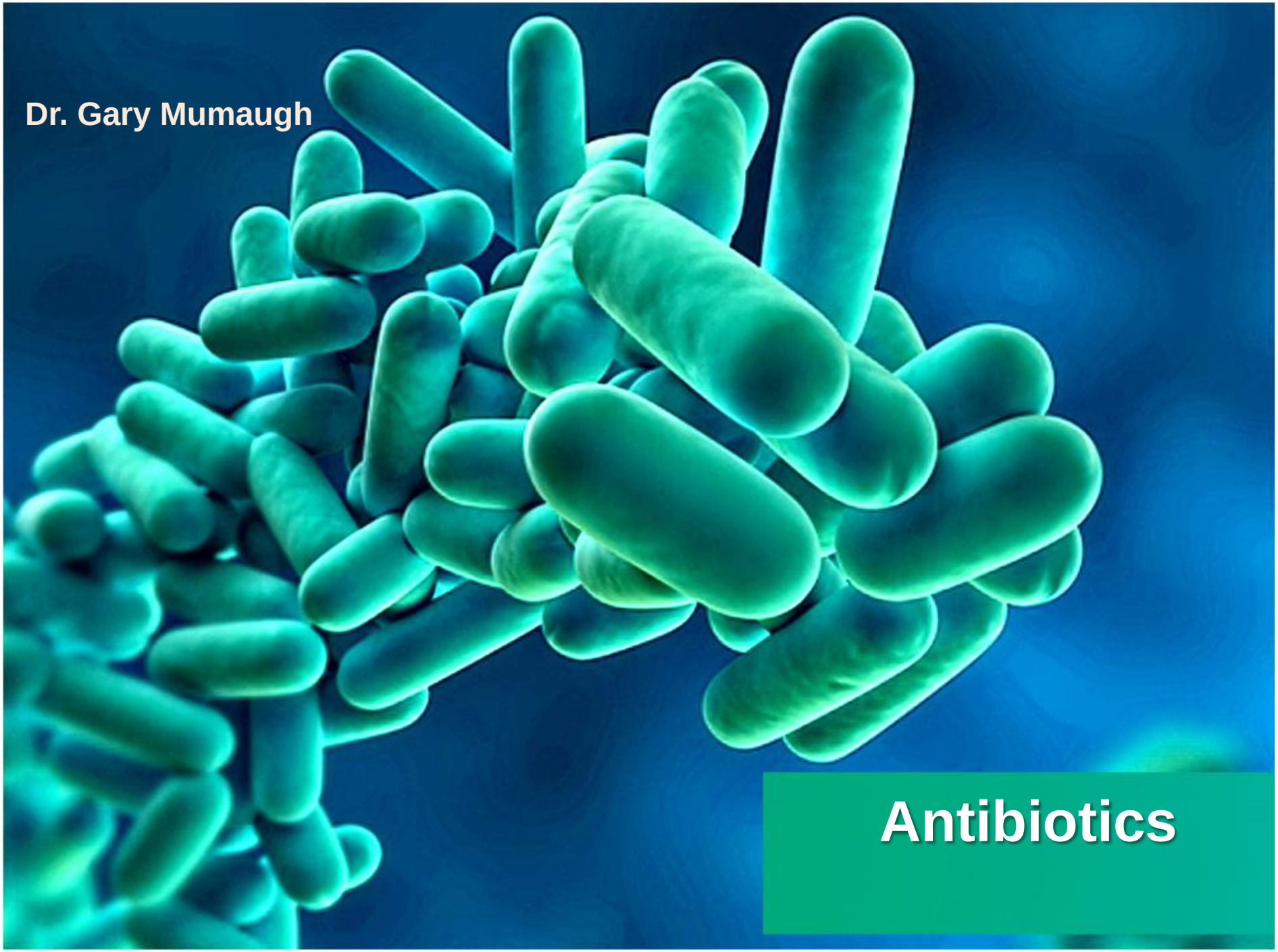

Dr. Gary Mumaugh
Antibiotics

- Antibiotics are products of microorganisms that react with and inhibit the growth of other microorganisms.
- An antibiotic should be

1. selectively toxic to pathogenic microorganisms,
2. should not incite an allergic response in the body,
3. should not upset the normal microbial population of various body sites, and
4. should not foster the development of drug resistance.

- A chemotherapeutic agent must have selective toxicity: it must kill or inhibit the microbial pathogen while damaging the host as little as possible.
- The degree of selective toxicity may be expressed in terms of

  (1) the therapeutic dose, the drug level required for clinical treatment of a particular infection, and

  (2) the toxic dose, the drug level at which the agent becomes too toxic for the host.
- The therapeutic index is the ratio of the toxic dose to the therapeutic dose.
- The larger the therapeutic index, the better the chemotherapeutic agent.

- A drug that disrupts a microbial function not found in eucaryotic animal cells often has a greater selective toxicity and a higher therapeutic index.
- For example, penicillin inhibits bacterial cell wall peptidoglycan synthesis but has little effect on host cells because they lack cell walls; therefore penicillin's therapeutic index is high.
- Drugs vary considerably in their range of effectiveness.
- Many are narrow-spectrum drugs—that is, they are effective only against a limited variety of pathogens.
- Others are broad spectrum drugs and attack many different kinds of pathogens.

- Chemotherapeutic agents can be either cidal or static
- Static agents reversibly inhibit growth; if the agent is removed, the microorganisms will recover and grow again.
- Some idea of the effectiveness of a chemotherapeutic agent against a pathogen can be obtained from the minimal inhibitory concentration (MIC). The MIC is the lowest concentration of a drug that prevents growth of a particular pathogen.
- The minimal lethal concentration (MLC) is the lowest drug concentration that kills the pathogen.

Drug	Primary Effect	Spectrum	Side Effects[a]
Ampicillin	Cidal	Broad (gram +, some –)	Allergic responses (diarrhea, anemia)
Bacitracin	Cidal	Narrow (gram +)	Renal injury if injected
Carbenicillin	Cidal	Broad (gram +, many –)	Allergic responses (nausea, anemia)
Cephalosporins	Cidal	Broad (gram +, some –)	(Allergic responses, thrombophlebitis, renal injury)
Chloramphenicol	Static	Broad (gram +, –; rickettsia and chlamydia)	Depressed bone marrow function, allergic reactions
Ciprofloxacin	Cidal	Broad (gram +, –)	Gastrointestinal upset, allergic responses
Clindamycin	Static	Narrow (gram +, anaerobes)	Diarrhea
Dapsone	Static	Narrow (mycobacteria)	(Anemia, allergic responses)
Erythromycin	Static	Narrow (gram +, mycoplasma)	(Gastrointestinal upset, hepatic injury)
Gentamicin	Cidal	Narrow (gram –)	(Allergic responses, nausea, loss of hearing, renal damage)
Isoniazid	Static or cidal	Narrow (mycobacteria)	(Allergic reactions, gastrointestinal upset, hepatic injury)
Methicillin	Cidal	Narrow (gram +)	Allergic responses (renal toxicity, anemia)
Penicillin	Cidal	Narrow (gram +)	Allergic responses (nausea, anemia)
Polymyxin B	Cidal	Narrow (gram –)	(Renal damage, neurotoxic reactions)
Rifampin	Static	Broad (gram +, mycobacteria)	(Hepatic injury, nausea, allergic responses)
Streptomycin	Cidal	Broad (gram +, –; mycobacteria)	(Allergic responses, nausea, loss of hearing, renal damage)
Sulfonamides	Static	Broad (gram +, –)	Allergic responses (renal and hepatic injury, anemia)
Tetracyclines	Static	Broad (gram +, –; rickettsia and chlamydia)	Gastrointestinal upset, teeth discoloration (renal and hepatic injury)
Trimethoprim	Cidal	Broad (gram +, –)	(Allergic responses, rash, nausea, leukopenia)
Vancomycin	Cidal	Narrow (gram +)	Hypotension, neutropenia, kidney damage, allergic reactions

Features of Antimicrobial Drugs

- Most modern antibiotics come from organisms living in the soil
  - Includes bacterial species *Streptomyces* and *Bacillus* as well as fungi *Penicillium* and *Cephalosporium*
- To commercially produce antibiotics
  - Strain is inoculated into broth medium
  - Incubated until maximum antibiotic concentration is reached
  - Drug is extracted from broth medium
  - Antibiotic extensively purified
  - In some cases drugs are chemically altered to impart new characteristics

Features of Antimicrobial Drugs

- Selective toxicity
  - Antibiotics cause greater harm to microorganisms than to human host
    - Generally by interfering with biological structures or biochemical processes common to bacteria but not to humans
  - Toxicity of drug is expressed as therapeutic index
    - Lowest dose toxic to patient divided by dose typically used for treatment
      - High therapeutic index = less toxic to patient

Features of Antimicrobial Drugs

- Antimicrobial action
  - Drugs may kill or inhibit bacterial growth
    - Inhibit = bacteriostatic
    - Kill = bacteriocidal
  - Bacteriostatic drugs rely on host immunity to eliminate pathogen
  - Bacteriocidal drugs are useful in situations when host defenses cannot be relied upon to control pathogen

Features of Antimicrobial Drugs

- Spectrum of activity
  - Antimicrobials vary with respect to range of organisms controlled
    - Narrow spectrum
      - Work on narrow range of organisms
        - » Gram-positive only OR Gram-negative only
    - Broad spectrum
      - Work on broad range of organisms
        - » Gram-positive AND Gram-negative
      - Disadvantage of broad spectrum is disruption of normal flora

Features of Antimicrobial Drugs

- Tissue distribution, metabolism and excretion
  - Drugs differ in how they are distributed, metabolized and excreted
    - Important factor for consideration when prescribing
  - Rate of elimination of drug from body expressed in half-life
    - Time it takes for the body to eliminate one half the original dose in serum
    - Half-life dictates frequency of dosage
  - Patients with liver or kidney damage tend to excrete drugs more slowly

Features of Antimicrobial Drugs

- Effects of combinations of antimicrobial drugs
  - Combination sometimes used to treat infections
  - When action of one drug enhances another, effect is synergistic
  - When action of one drug interferes with another, effect is antagonistic
  - When effect of combination is neither synergistic or antagonistic, effect said to be additive

Features of Antimicrobial Drugs

- Adverse effects
  - Allergic reactions
    - Allergies to penicillin
      - Allergies often life threatening
  - Toxic effects
    - Aplastic anemia
      - Body cannot make RBC or WBC
  - Suppression of normal flora
    - Antibiotic associated colitis
      - Toxic organisms given opportunity to establish themselves
  - Antimicrobial resistance
    - Microorganisms have innate or adaptive resistance to antibiotics

Mechanisms of Action of Antimicrobial Agents

- Antimicrobial drugs can damage pathogens in several ways.
- The most selective antibiotics are those that interfere with the synthesis of bacterial cell walls (e.g., penicillins, cephalosporins, vancomycin, and bacitracin).
- These drugs have a high therapeutic index because bacterial cell walls have a unique structure not found in eucaryotic cells.
- Streptomycin, gentamicin, spectinomycin, clindamycin, chloramphenicol, tetracyclines, erythromycin, and many other antibiotics inhibit protein synthesis by binding with the procaryotic ribosome.

- Because these drugs discriminate between procaryotic and eucaryotic ribosomes, their therapeutic index is fairly high, but not as favorable as that of cell wall synthesis inhibitors.
- The antibacterial drugs that inhibit nucleic acid synthesis or damage cell membranes often are not as selectively toxic as other antibiotics. This is because procaryotes and eucaryotes do not differ as greatly with respect to nucleic acid synthetic mechanisms or cell membrane structure.

- Several valuable drugs act as antimetabolites: they block the functioning of metabolic pathways by competitively inhibiting the use of metabolites by key enzymes.
- Sulfonamides and several other drugs inhibit folic acid metabolism.
  - Sulfonamides(e.g.,sulfanilamide,sulfamethoxazole, and sulfacetamide) have a high therapeutic index because humans cannot synthesize folic acid and must obtain it in their diet.
- Most bacterial pathogens synthesize their own folic acid and are therefore susceptible to inhibitors of folate metabolism.

Drug	Mechanism of Action
Cell Wall Synthesis Inhibition	
Penicillin Ampicillin Carbenicillin Methicillin Cephalosporins	Inhibit transpeptidation enzymes involved in the cross-linking of the polysaccharide chains of the bacterial cell wall peptidoglycan. Activate cell wall lytic enzymes.
Vancomycin	Binds directly to the D-Ala-D-Ala terminus and inhibits transpeptidation.
Bacitracin	Inhibits cell wall synthesis by interfering with action of the lipid carrier that transports wall precursors across the plasma membrane.
Protein Synthesis Inhibition	
Streptomycin Gentamicin	Binds with the 30S subunit of the bacterial ribosome to inhibit protein synthesis and causes misreading of mRNA.
Chloramphenicol	Binds to the 50S ribosomal subunit and blocks peptide bond formation through inhibition of peptidyl transferase.
Tetracyclines	Bind to the 30S ribosomal subunit and interfere with aminoacyl-tRNA binding.
Erythromycin and clindamycin	Bind to the 50S ribosomal subunit and inhibit peptide chain elongation.
Fusidic acid	Binds to EF-G and blocks translocation.
Nucleic Acid Synthesis Inhibition	
Ciprofloxacin and other quinolones	Inhibit bacterial DNA gyrase and thus interfere with DNA replication, transcription, and other activities involving DNA.
Rifampin	Blocks RNA synthesis by binding to and inhibiting the DNA-dependent RNA polymerase.
Cell Membrane Disruption	
Polymyxin B	Binds to the plasma membrane and disrupts its structure and permeability properties.
Metabolic Antagonism	
Sulfonamides	Inhibit folic acid synthesis by competition with *p*-aminobenzoic acid.
Trimethoprim	Blocks tetrahydrofolate synthesis through inhibition of the enzyme dihydrofolate reductase.
Dapsone	Interferes with folic acid synthesis.
Isoniazid	May disrupt pyridoxal or NAD metabolism and functioning. Inhibits the synthesis of the mycolic acid "cord factor."

Antibacterial Drugs

- Sulfonamides or Sulfa Drugs
- Quinolones
- Penicillins
- Cephalosporins
- The Tetracyclines
- Aminoglycoside Antibiotics
- Erythromycin and Other Macrolides
- Vancomycin and Teicoplanin
- Chloramphenicol

Sulfonamides or Sulfa Drugs

- A good way to inhibit or kill pathogens is by use of compounds that are structural analogues, molecules structurally similar to metabolic intermediates.
- These analogues compete with metabolites in metabolic processes because of their similarity, but are just different enough so that they cannot function normally in cellular metabolism.
- Sulfonamides or sulfa drugs are structurally related to sulfanilamide, an analogue of *p-aminobenzoic acid.*

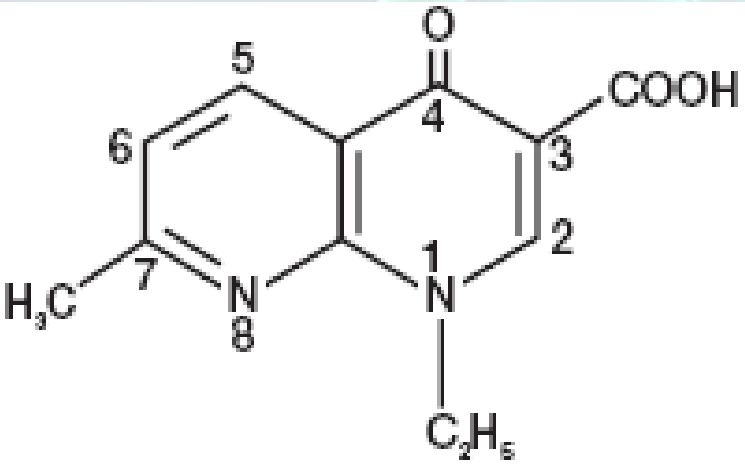
- When sulfanilamide or another sulfonamide enters a bacterial cell, it competes with p-aminobenzoic acid for the active site of an enzyme involved in folic acid synthesis, and the folate concentration decreases.
- The decline in folic acid is detrimental to the bacterium because folic acid is essential to the synthesis of purines and pyrimidines, the bases used in the construction of DNA, RNA, and other important cell constituents.
- The resulting inhibition of purine and pyrimidine synthesis leads to cessation of bacterial growth or death of the pathogen.

Quinolones

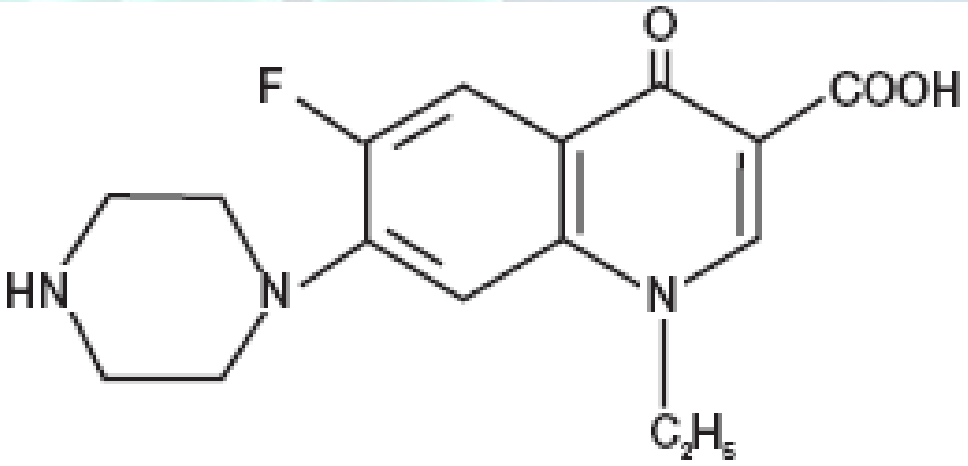
- A second group of synthetic antimicrobial agents are increasingly used to treat a wide variety of infections.
- The quinolones are synthetic drugs that contain the 4-quinolone ring.
- Quinolones are effective when administered orally. They sometimes cause adverse side effects, particularly gastrointestinal upset.
- Quinolones act by inhibiting the bacterial DNA gyrase or topoisomerase II, probably by binding to the DNA gyrase complex.
- This enzyme introduces negative twists in DNA and helps separate its strands.

- Disrupts DNA replication and repair, transcription, bacterial chromosome separation during division, and other cell processes involving DNA.
- Fluoroquinolones also inhibit topoisomerase IV, another enzyme that untangles DNA during replication.
- The quinolones are broad-spectrum drugs. They are highly effective against enteric bacteria such as *E. coli and Klebsiella pneumoniae.*
- They can be used with *Haemophilus, Neisseria, Pseudomonas aeruginosa*, and other gram-negative pathogens.

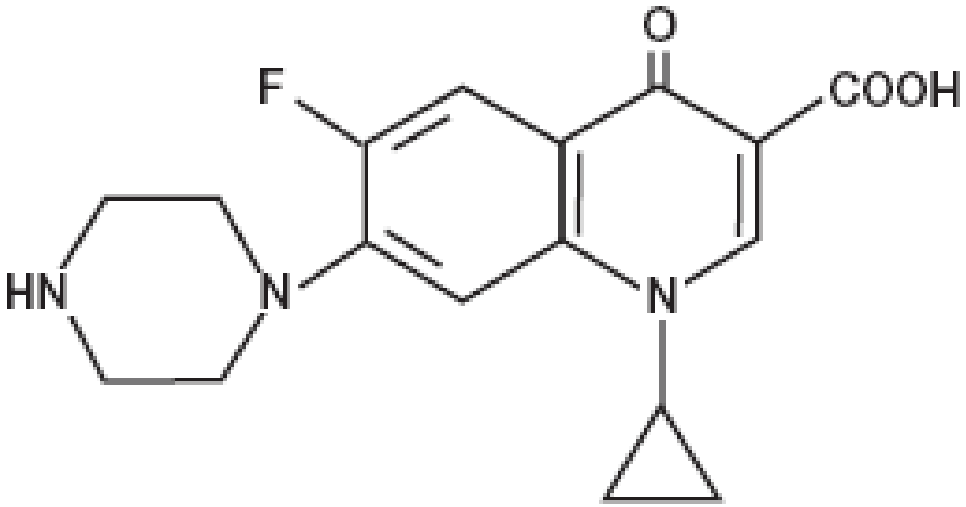
- The quinolones also are active against gram-positive bacteria such as *Staphylococcus aureus, Streptococcus pyogenes, and Mycobacterium tuberculosis.*
- *Currently they are used in treating* urinary tract infections, sexually transmitted diseases caused by *Neisseria and Chlamydia, gastrointestinal infections, respiratory* tract infections, skin infections, and osteomyelitis.
- More recently a family of fluoroquinolones has been produced. Three of these—ciprofloxacin, norfloxacin, and ofloxacin—are currently used.



Nalidixic acid



Norfloxacin



Ciprofloxacin

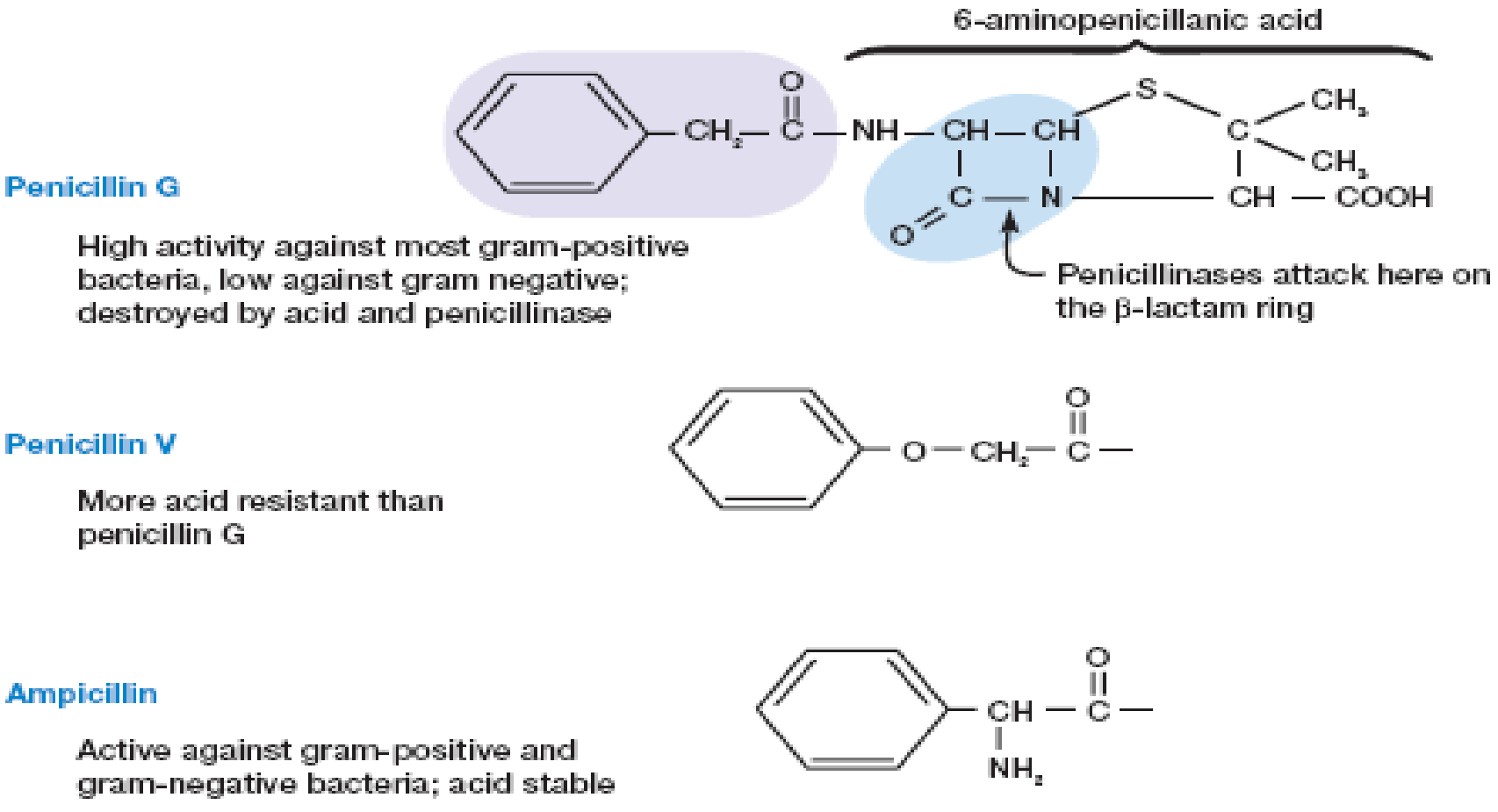
Penicillins

- Penicillin G or benzylpenicillin, the first antibiotic to be widely used in medicine, has the structural properties characteristic of the penicillin family.
- Most penicillins are derivatives of 6-aminopenicillanic acid and differ from one another only with respect to the side chain attached to its amino group.
- The most crucial feature of the molecule is the β-lactam ring, which appears to be essential for activity.
- Penicillinase, the enzyme synthesized by many penicillin-resistant bacteria, destroys penicillin activity by hydrolyzing a bond in this ring.

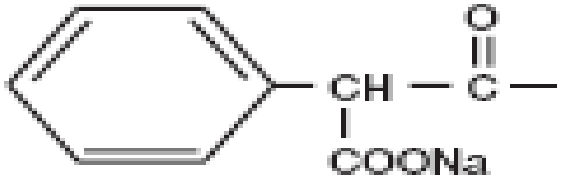
- The mechanism of action of penicillins is still not completely known.
- It has been proposed that penicillins inhibit the enzyme catalyzing the transpeptidation reaction because of their structural similarity, which would block the synthesis of a complete, fully cross-linked peptidoglycan and lead to osmotic lysis.

- Penicillins differ from each other in several ways.
- Penicillin G is effective against gonococci, meningococci, and several gram-positive pathogens such as streptococci and staphylococci but it must be administered parenterally because it is destroyed by stomach acid.
- Penicillin V is similar to penicillin G, but it is more acid resistant and can be given orally.
- Ampicillin can be administered orally and has a broader spectrum of activity as it is effective against gram-negative bacteria such as *Haemophilus, Salmonella,* and *Shigella. Carbenicillin and ticarcillin also are broad* spectrum and particularly potent against *Pseudomonas and Proteus.*

- An increasing number of bacteria are penicillin resistant. Penicillinase-resistant penicillins such as methicillin, nafcillin, and oxacillin are frequently employed against these bacterial pathogens.

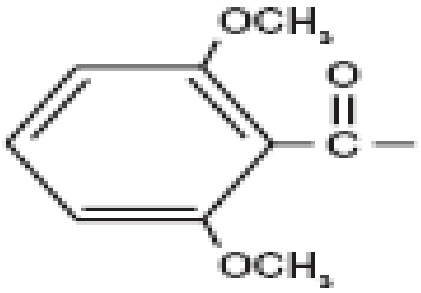


Carbenicillin



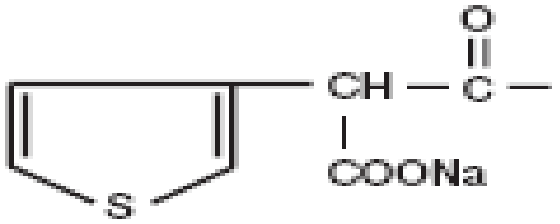
Active against gram-negative bacteria like *Pseudomonas* and *Proteus*; acid stable; not well absorbed by small intestine

Methicillin



Penicillinase-resistant, but less active than penicillin G; acid-labile

Ticarcillin



Similar to carbenicillin, but more active against *Pseudomonas*

Penicillins. The structures and characteristics of representative penicillins. All are derivatives of 6-aminopenicillanic acid; in each case the purple shaded portion of penicillin G is replaced by the side chain indicated. The β-lactam ring is also shaded (blue), and an arrow points to the bond that is hydrolyzed by penicillinase.

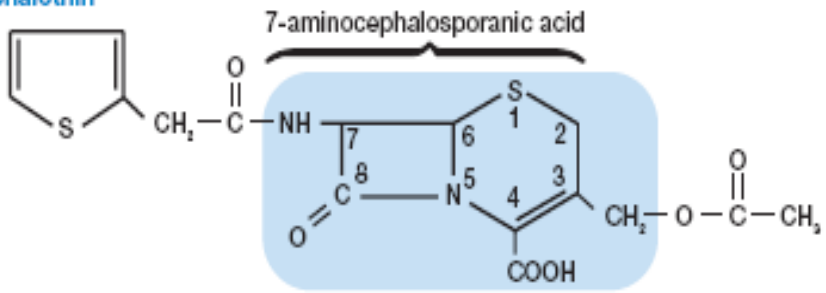
Cephalosporins

- Cephalosporins are a family of antibiotics originally isolated in 1948 from the fungus *Cephalosporium, and their β-lactam structure* is very similar to that of the penicillins.
- Cephalosporins resemble penicillins in inhibiting the transpeptidation reaction during peptidoglycan synthesis.
- They are broad-spectrum drugs frequently given to patients with penicillin allergies.
- Many cephalosporins are in use. There are three groups or generations of these drugs that differ in their spectrum of activity.
- First-generation cephalosporins are more effective against gram-positive than gram-negative pathogens.

- Second generation drugs act against many gram-negative as well as gram positive pathogens.
- Third-generation drugs are particularly effective against gram-negative pathogens, and often also reach the central nervous system.
- Most cephalosporins (including cephalothin, cefoxitin, ceftriaxone, and cefoperazone) are administered parenterally.
- Cefoperazone is resistant to destruction by -lactamases and effective against many gram-negative bacteria, including *Pseudomonas aeruginosa.*
- *Cephalexine and cefixime are given orally rather than* by injection.

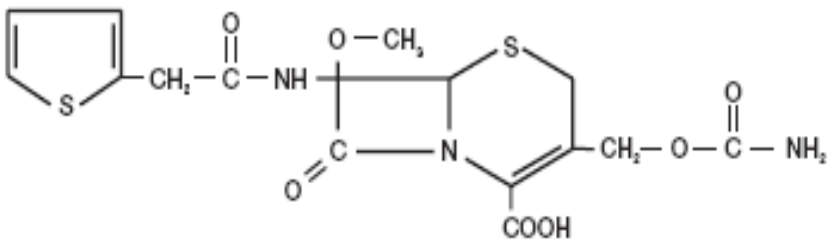
First-generation cephalosporin

Cephalothin



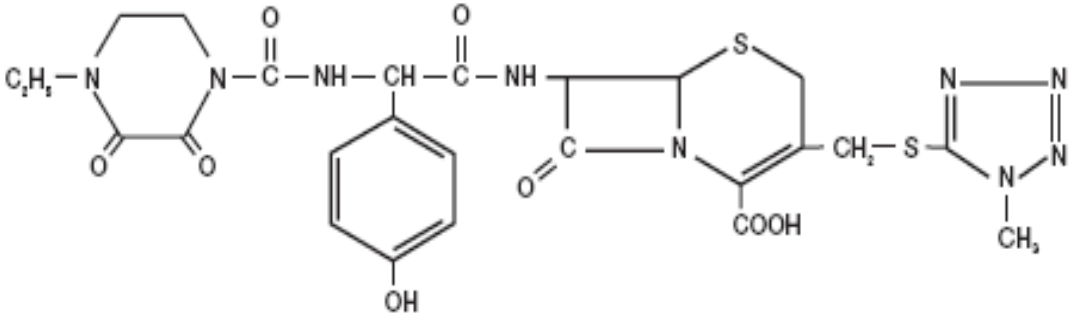
Second-generation cephalosporin

Cefoxitin

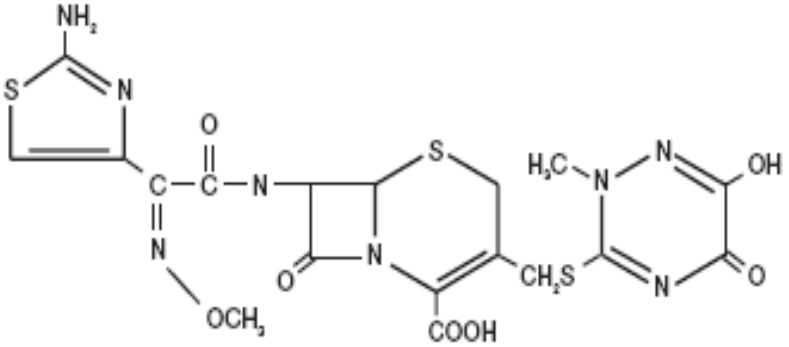


Third-generation cephalosporins

Cefoperazone



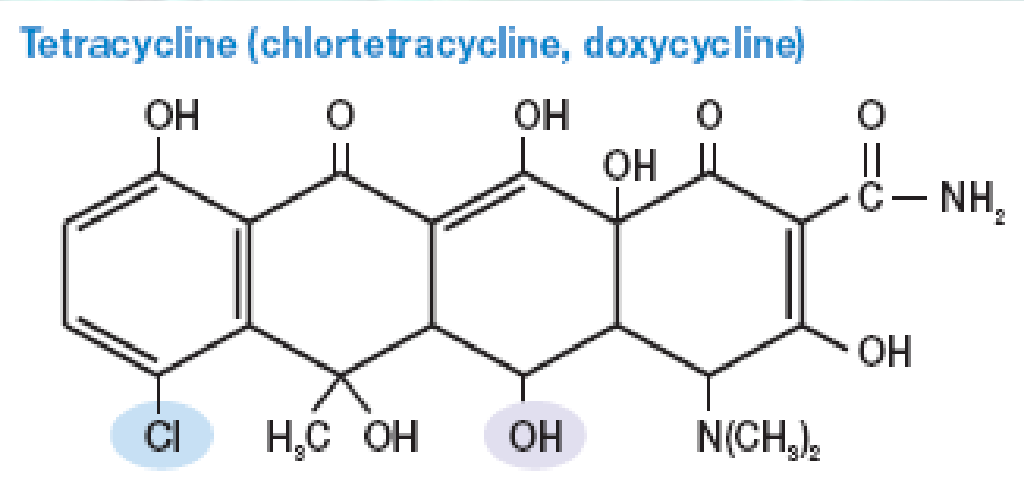
Ceftriaxone



The Tetracyclines

- These antibiotics inhibit protein synthesis of the ribosome and inhibiting the binding of aminoacyl-tRNA molecules to the ribosomal A site.
- Because their action is only bacteriostatic, the effectiveness of treatment depends on active host resistance to the pathogen.

- Tetracyclines are broad-spectrum antibiotics active against gram-negative bacteria, gram-positive bacteria, rickettsias, chlamydiae, and mycoplasmas.
- High doses may result in nausea, diarrhea, yellowing of teeth in children, and damage to the liver and kidneys.

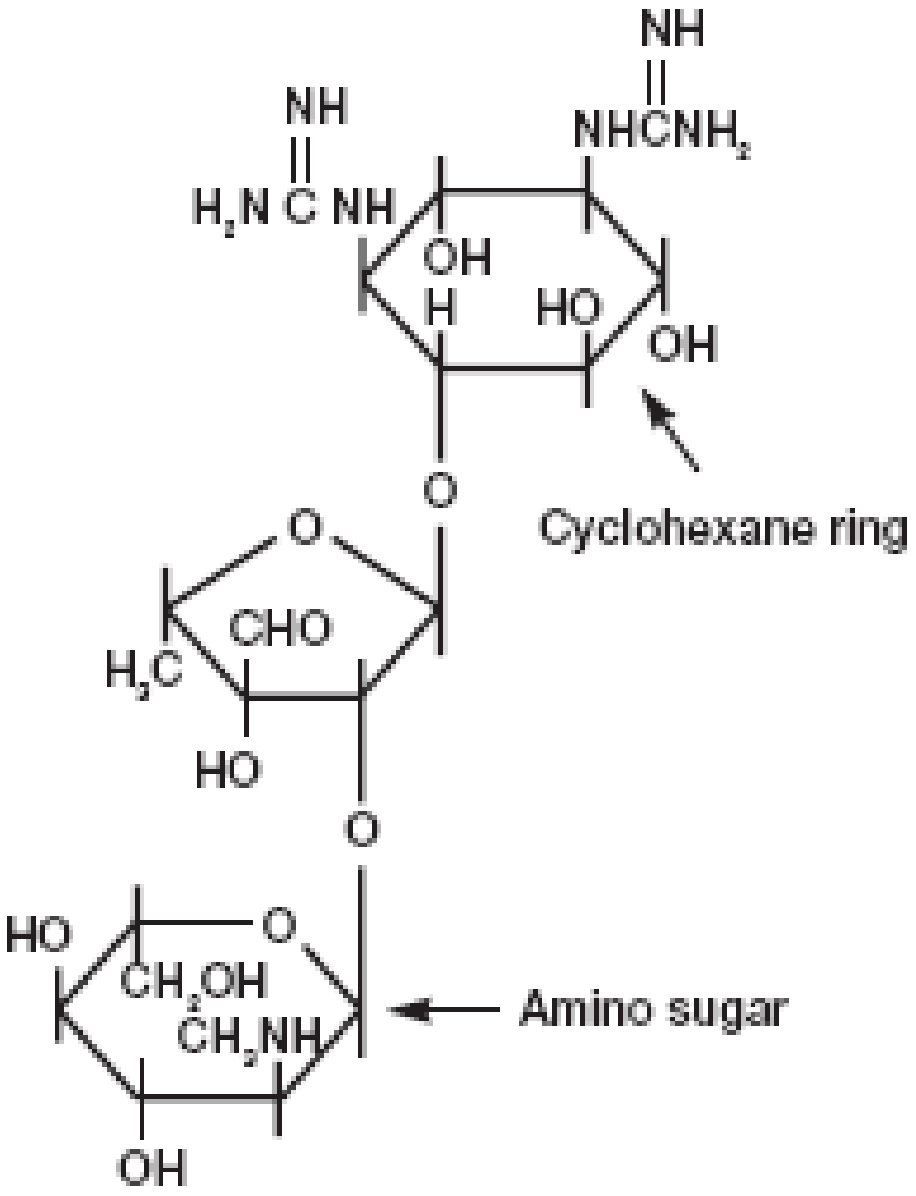


Tetracyclines. Three members of the tetracycline family. Tetracycline lacks both of the groups that are shaded. Chlortetracycline (aureomycin) differs from tetracycline in having a chlorine atom (blue); doxycycline consists of tetracycline with an extra hydroxyl (purple).

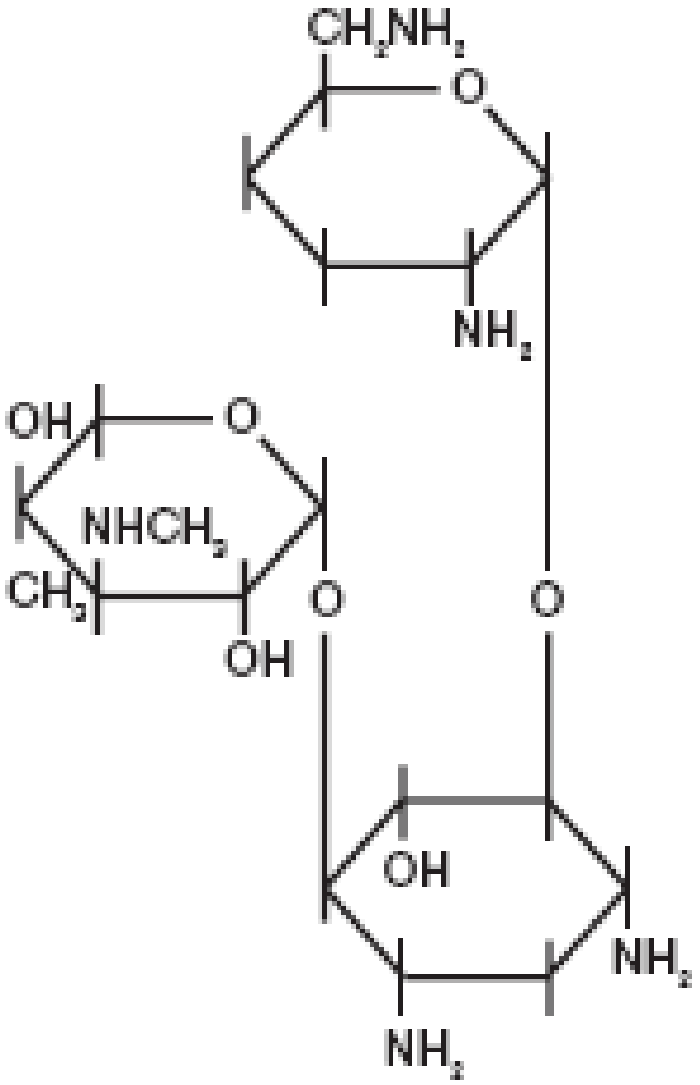
Aminoglycoside Antibiotics

- There are several important aminoglycoside antibiotics. Streptomycin, kanamycin, neomycin, and tobramycin are synthesized by *Streptomyces, whereas gentamicin comes from a related bacterium, Micromonospora purpurea.*
- Aminoglycosides bind to the small ribosomal subunit and interfere with protein synthesis in at least two ways. They directly inhibit protein synthesis and also cause misreading of the genetic message carried by mRNA.

- The aminoglycosides are bactericidal and tend to be most active against gram-negative pathogens.
- Streptomycin’s usefulness has decreased greatly due to widespread drug resistance, but it is still effective against tuberculosis and plague.
- Gentamicin is used to treat *Proteus, Escherichia, Klebsiella, and Serratia infections.*
- Aminoglycosides are quite toxic and can cause deafness, renal damage, loss of balance, nausea, and allergic responses.



Streptomycin

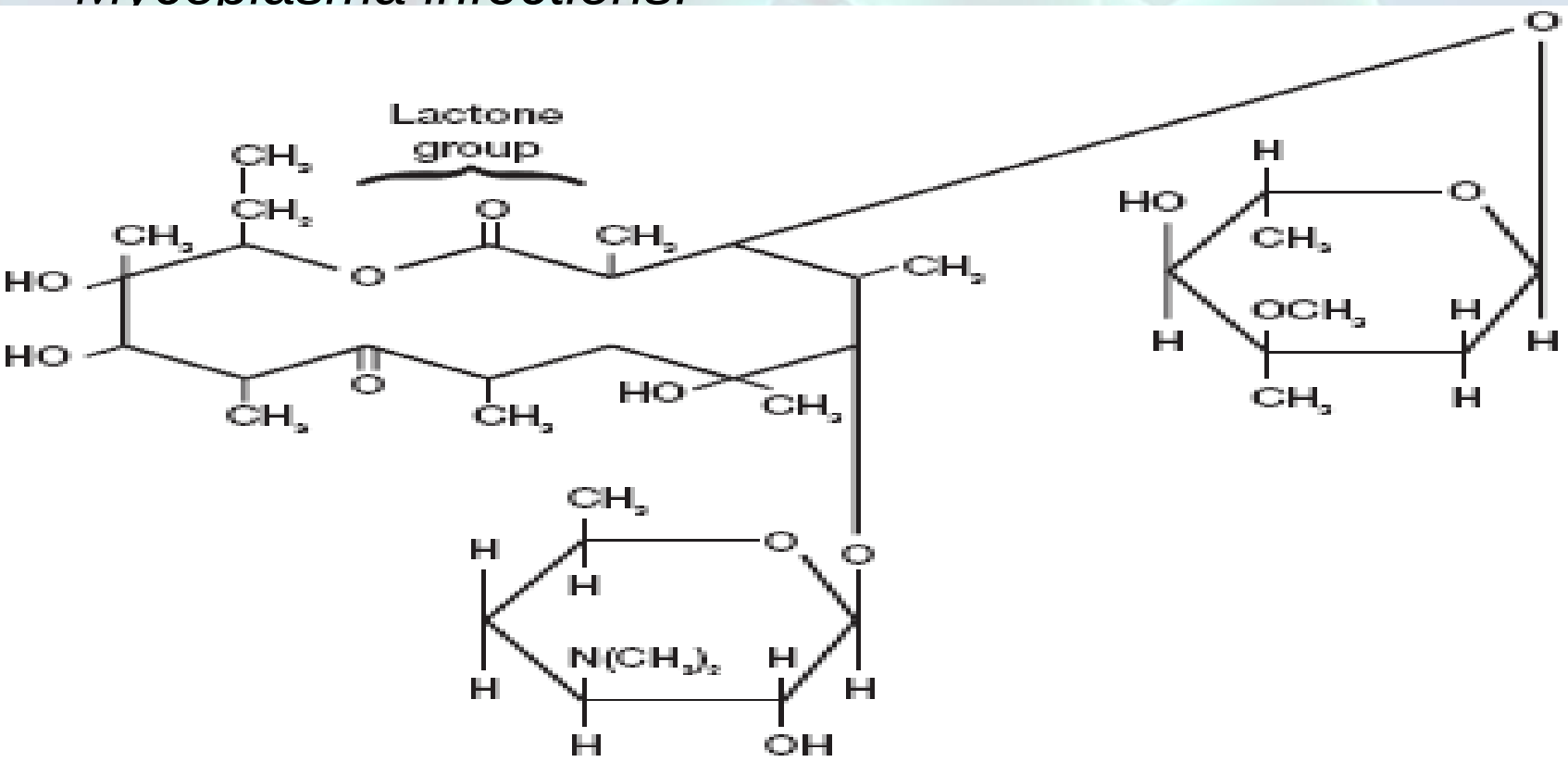


Gentamicin C_{1a}

Erythromycin and Other Macrolides

- Erythromycin, the most frequently used macrolide antibiotic, is synthesized by *Streptomyces erythraeus.*
- *The macrolides contain* a 12- to 22-carbon lactone ring linked to one or more sugars.
- Erythromycin is usually bacteriostatic and binds with the 23S rRNA of the 50S ribosomal subunit to inhibit peptide chain elongation during protein synthesis.
- Erythromycin is a relatively broad-spectrum antibiotic effective against gram-positive bacteria, mycoplasmas, and a few gram-negative bacteria.

- It is used with patients allergic to penicillins and in the treatment of whooping cough, diphtheria, diarrhea caused by *Campylobacter, and pneumonia from Legionella* or *Mycoplasma infections.*



Erythromycin, a Macrolide Antibiotic. The 14-member lactone ring is connected to two sugars.

Vancomycin and Teicoplanin

- Vancomycin is a glycopeptide antibiotic produced by *Streptomyces orientalis.*
- The antibiotic blocks peptidoglycan synthesis by inhibiting the transpeptidation step that cross-links adjacent peptidoglycan strands.
- The resulting peptidoglycan is mechanically weak and the cells osmotically lyse.
- Vancomycin's peptide portion binds specifically to the D-alanine-D-alanine terminal sequence on the pentapeptide portion of peptidoglycan. This complex blocks transpeptidase action.

- The antibiotic is bactericidal for Staphylococcus and some members of the genera *Clostridium, Bacillus, Streptococcus, and Enterococcus*.
- It is given both orally and intravenously, and has been particularly important in the treatment of antibiotic resistant *Staphylococcal* and *Enterococcal* infections.
- Vancomycin-resistant strains of *Enterococcus* have become widespread and recently a few cases of resistant *Staphylococcus aureus* have appeared.
- It is active against staphylococci, enterococci, streptococci, clostridia, *Listeria, and many other gram positive* pathogens.

Chloramphenicol

- Although chloramphenicol was first produced from cultures of *Streptomyces venezuelae, it is now made through* chemical synthesis.
- Like erythromycin, chloramphenicol binds to 23S rRNA on the 50S ribosomal subunit.
- It inhibits the peptidyl transferase and is bacteriostatic.
- This antibiotic has a very broad spectrum of activity but unfortunately is quite toxic.

- One may see allergic responses or neurotoxic reactions.
- The most common side effect is a temporary or permanent depression of bone marrow function, leading to aplastic anemia and a decreased number of blood leukocytes.
- Chloramphenicol is used only in life-threatening situations when no other drug is adequate.

Antifungal Drugs

- Treatment of fungal infections generally has been less successful than that of bacterial infections largely because eucaryotic fungal cells are much more similar to human cells than are bacteria.
- Many drugs that inhibit or kill fungi are therefore quite toxic for humans.
- In addition, most fungi have a detoxification system that modifies many antibiotics, probably by hydroxylation. As a result the added antibiotics are fungistatic only as long as repeated application maintains high levels of unmodified antibiotic.

- Despite their relatively low therapeutic index, a few drugs are useful in treating many major fungal diseases.
- Effective antifungal agents frequently either extract membrane sterols or prevent their synthesis.
- Fungal infections are often subdivided into infections of superficial tissues or superficial mycoses and systemic mycoses.

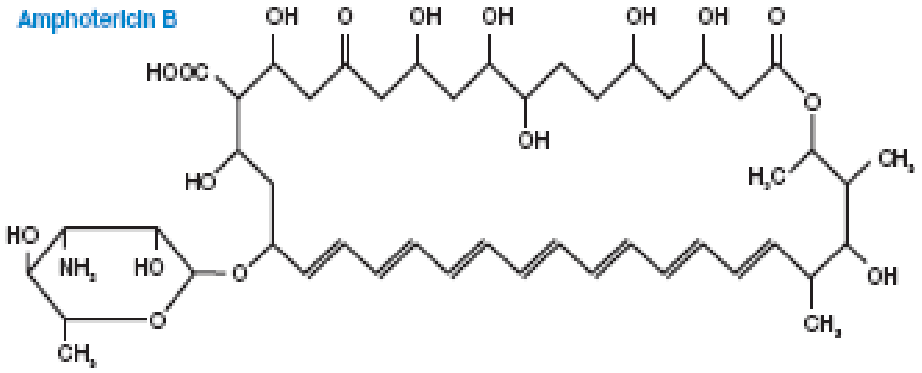
- Treatment for these two types of disease is very different. Several drugs are used to treat superficial mycoses.
- Three drugs containing imidazole—miconazole, ketoconazole, and clotrimazole—are broad-spectrum agents available as creams and solutions for the treatment of dermatophyte infections such as athlete’s foot, and oral and vaginal candidiasis.
- They are thought to disrupt fungal membrane permeability and inhibit sterol synthesis.
- Tolnaftate is used topically for the treatment of cutaneous infections, but is not as effective against infections of the skin and hair.

- Nystatin, a polyene antibiotic from *Streptomyces, is used to control Candida infections of the* skin, vagina, or alimentary tract.
- Griseofulvin, an antibiotic formed by *Penicillium, is given orally to treat chronic* dermatophyte infections.
- It is thought to disrupt the mitotic spindle and inhibit cell division; it also may inhibit protein and nucleic acid synthesis.
- Side effects of griseofulvin include headaches, gastrointestinal upset, and allergic reactions.

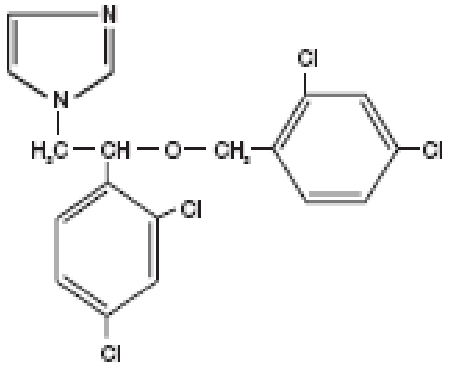
- Systemic infections are very difficult to control and can be fatal. Three drugs commonly used against systemic mycoses are amphotericin B, 5-flucytosine, and fluconazole.
- Amphotericin B from *Streptomyces spp.* binds to the sterols in fungal membranes, disrupting membrane permeability and causing leakage of cell constituents.
- The synthetic oral antimycotic agent 5-flucytosine (5-fluorocytosine) is effective against most systemic fungi, although drug resistance often develops rapidly.

- The drug is converted to 5-fluorouracil by the fungi, incorporated into RNA in place of uracil, and disrupts RNA function.
- Its side effects include skin rashes, diarrhea, nausea, aplastic anemia, and liver damage.
- Fluconazole is used in the treatment of candidiasis, cryptococcal meningitis, and coccidioidal meningitis.

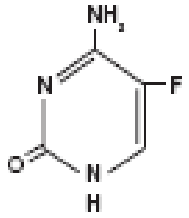
Amphotericin B



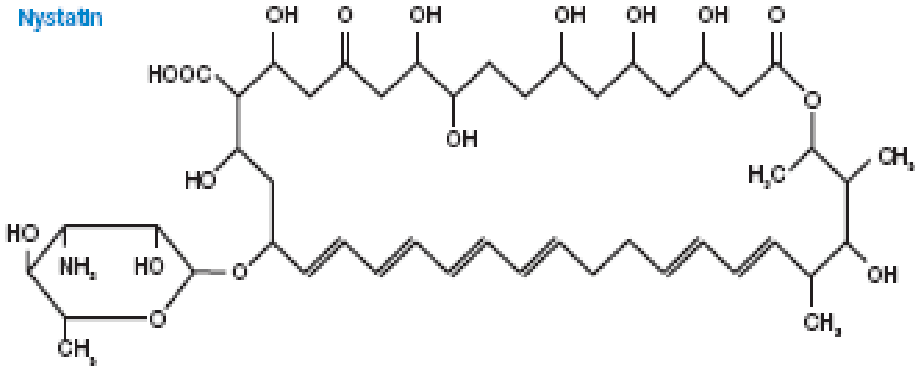
Miconazole



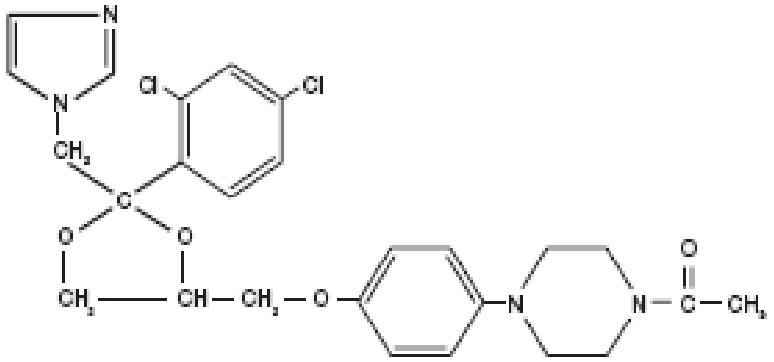
5-flucytosine



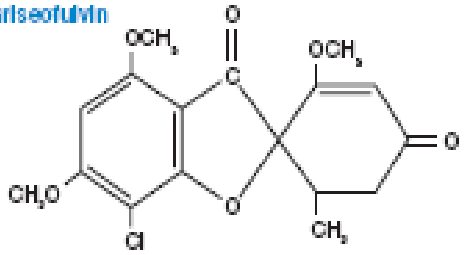
Nystatin



Ketoconazole



Griseofulvin



Antifungal Drugs. Six commonly used drugs are shown here.

Antiviral Drugs

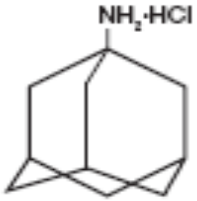
- For many years the possibility of treating viral infections with drugs appeared remote because viruses enter host cells and make use of host cell enzymes and constituents to a large extent.

- A drug that would block virus reproduction also was thought to be toxic for the host.

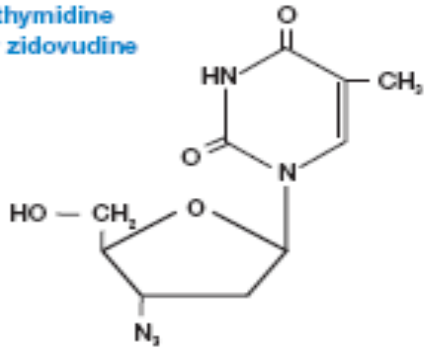
- Inhibitors of virus-specific enzymes and life cycle processes have now been discovered, and several drugs are used therapeutically.

Representative Antiviral Drugs.

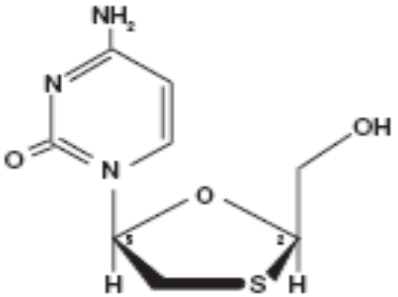
Amantadine



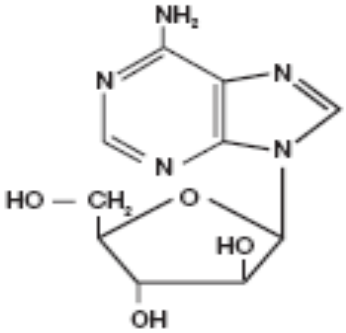
Azidothymidine (AZT) or zidovudine



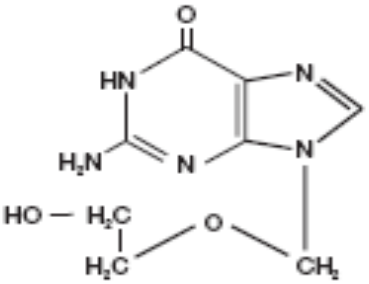
Lamivudine (3TC)



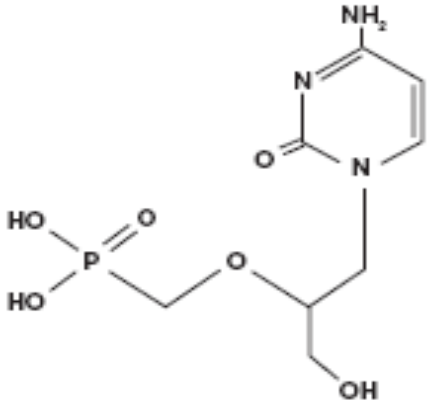
Adenine arabinoside (Ara-A, vidarabine)



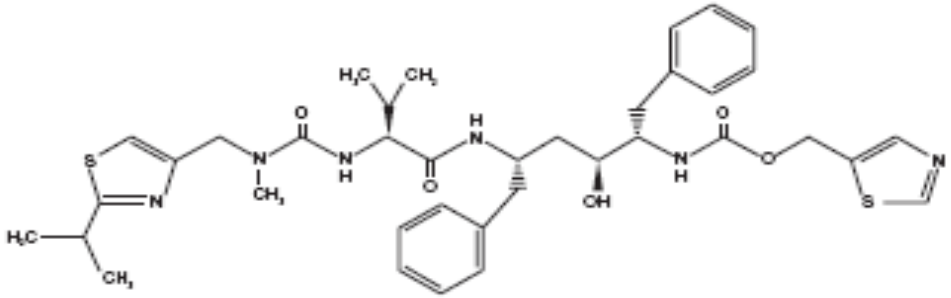
Acyclovir



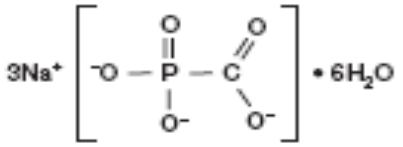
Cidofovir (HPMPC)



Ritonavir



Foscarnet



- Most antiviral drugs disrupt either critical stages in the virus life cycle or the synthesis of virus-specific nucleic acids.
- Amantadine and rimantadine can be used to prevent influenza A infections.
- When given in time, it will reduce the incidence of influenza by 50 to 70% in an exposed population.
- Amantadine blocks the penetration and uncoating of influenza virus particles.
- Adenine arabinoside or vidarabine disrupts the activity of DNA polymerase and several other enzymes involved in DNA and RNA synthesis and function. It is given intravenously or applied as an ointment to treat herpes infections.

- A third drug, acyclovir, is also used in the treatment of herpes infections. Upon phosphorylation, acyclovir resembles deoxy-GTP and inhibits the virus DNA polymerase.
- Ganciclovir, penciclovir, and its oral form famciclovir are effective in treatment of herpesviruses.
- Another kind of drug, foscarnet, inhibits the virus DNA polymerase in a different way. Foscarnet is an organic analogue of pyrophosphate that binds to the polymerase active site and blocks the cleavage of pyrophosphate from nucleoside triphosphate substrates. It is used in treating herpes and cytomegalovirus infections.

- Several broad-spectrum anti-DNA virus drugs have been developed.
- A good example is the drug HPMPC or cidofovir. It is effective against papo-viruses, adenoviruses, herpes viruses, irido-viruses, and poxviruses.

- Research on anti-HIV drugs has been particularly active. Many of the first drugs to be developed were reverse transcriptase inhibitors such as azidothymidine (AZT) or zidovudine, lamivudine (3TC), didanosine (ddI), zalcitabine (ddC), and stavudine (d4T).
- These interfere with reverse transcriptase activity and therefore block HIV reproduction.
- More recently HIV protease inhibitors have been developed. Three of the most used are saquinvir, indinavir, and ritonavir.
- These mimic the peptide bond that is normally attacked by the protease.

- The most successful treatment regimen involves a cocktail of agents given at high dosages to prevent the development of drug resistance.
- For example, the combination of AZT, 3TC, and ritonavir is very effective in reducing HIV plasma concentrations almost to zero.
- However, the treatment does not seem able to eliminate latent proviral HIV DNA that still resides in memory T cells, and possibly elsewhere.
- Probably the most publicized antiviral agents are interferons. These small proteins, produced by the host, inhibit virus replication and may be clinically useful in the treatment of influenza, hepatitis, herpes, and colds.