Chapter 12

Drugs, Microbes, Host – The Elements of Chemotherapy
Principles of Antimicrobial Therapy

• Administer a drug to an infected person that destroys the infective agent without harming the host’s cells.

• Antimicrobial drugs are produced naturally or synthetically.
<table>
<thead>
<tr>
<th>Characteristics of the Ideal Antimicrobial Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Selectively toxic to the microbe but nontoxic to host cells</td>
</tr>
<tr>
<td>• Microbicidal rather than microbistatic</td>
</tr>
<tr>
<td>• Relatively soluble; functions even when highly diluted in body fluids</td>
</tr>
<tr>
<td>• Remains potent long enough to act and is not broken down or excreted prematurely</td>
</tr>
<tr>
<td>• Doesn’t lead to the development of antimicrobial resistance</td>
</tr>
<tr>
<td>• Complements or assists the activities of the host’s defenses</td>
</tr>
<tr>
<td>• Remains active in tissues and body fluids</td>
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<tr>
<td>• Readily delivered to the site of infection</td>
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<tr>
<td>• Reasonably priced</td>
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<tr>
<td>• Does not disrupt the host’s health by causing allergies or predisposing the host to other infections</td>
</tr>
</tbody>
</table>
Origins of Antimicrobial Drugs

• **Antibiotics** are common metabolic products of aerobic bacteria and fungi
  – Bacteria in genera *Streptomyces* and *Bacillus*
  – Molds in genera *Penicillium* and *Cephalosporium*

• By inhibiting the other microbes in the same habitat, antibiotic producers have less competition for nutrients and space
Streptomyces
Interactions Between Drug and Microbe

- Antimicrobial drugs should be **selectively toxic** - drugs should kill or inhibit microbial cells without simultaneously damaging host tissues.
- As the characteristics of the infectious agent become more similar to the vertebrate host cell, complete selective toxicity becomes more difficult to achieve and more side effects are seen.
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Chemotherapeutic drug</td>
<td>Any chemical used in the treatment, relief, or prophylaxis of a disease</td>
</tr>
<tr>
<td>Prophylaxis*</td>
<td>Use of a drug to prevent potential for infection of a person at risk</td>
</tr>
<tr>
<td>Antimicrobial chemotherapy*</td>
<td>The use of chemotherapeutic drugs to control infection</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>All-inclusive term for any antimicrobial drug, regardless of its origin</td>
</tr>
<tr>
<td>Antibiotics*</td>
<td>Substances produced by the natural metabolic processes of some microorganisms that can inhibit or destroy other microorganisms</td>
</tr>
<tr>
<td>Semisynthetic drugs</td>
<td>Drugs that are chemically modified in the laboratory after being isolated from natural sources</td>
</tr>
<tr>
<td>Synthetic drugs</td>
<td>The use of chemical reactions to synthesize antimicrobial compounds in the laboratory.</td>
</tr>
<tr>
<td>Narrow spectrum (limited spectrum)</td>
<td>Antimicrobials effective against a limited array of microbial types—for example, a drug effective mainly on gram-positive bacteria</td>
</tr>
<tr>
<td>Broad spectrum (extended spectrum)</td>
<td>Antimicrobials effective against a wide variety of microbial types—for example, a drug effective against both gram-positive and gram-negative bacteria</td>
</tr>
</tbody>
</table>

*prophylaxis (proh"-fih-lak’-sis) Gr. prophylassein, to keep guard before. A process that prevents infection or disease in a person at risk.

*chemotherapy (kee"-moh-ther’-uh-pee) Gr. cheimeia, chemistry, and therapeia, service to the sick. Use of drugs to treat disease.

*antibiotic (an-tee’-by-aw”-tik) Gr. anti, against, and bios, life.
Mechanisms of Drug Action

1. Inhibition of cell wall synthesis
2. Disruption of cell membrane structure or function
3. Inhibition of nucleic acid synthesis, structure or function
4. Inhibition of protein synthesis
5. Blocks on key metabolic pathways
<table>
<thead>
<tr>
<th>Infectious Agent</th>
<th>Drug Groups/Examples</th>
<th>General Targets</th>
<th>Outcome of Drug Action on the Microbe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td>Penicillins</td>
<td>Cell wall synthesis</td>
<td>Lysis of cells</td>
</tr>
<tr>
<td></td>
<td>Penicillin, ampicillin</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Cephalosporins</td>
<td>Cell wall synthesis</td>
<td>Lysis of cells</td>
</tr>
<tr>
<td></td>
<td>Keflex, cefotaxime</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Bacitracin</td>
<td>Cell wall</td>
<td>Lysis of cells</td>
</tr>
<tr>
<td></td>
<td>Aminoglycosides</td>
<td>Prokaryotic</td>
<td>Inhibit protein synthesis</td>
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<tr>
<td></td>
<td>Streptomycin</td>
<td>ribosomes</td>
<td></td>
</tr>
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<td></td>
<td>Gentamicin</td>
<td></td>
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<tr>
<td></td>
<td>Macrolides</td>
<td>Various targets</td>
<td>Inhibit protein synthesis</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>Ribosomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>Cell wall</td>
<td>Lysis of cells</td>
</tr>
<tr>
<td></td>
<td>Tetracyclines</td>
<td>Prokaryotic</td>
<td>Inhibit protein synthesis</td>
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<tr>
<td></td>
<td>Doxycycline</td>
<td>ribosomes</td>
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</tr>
<tr>
<td></td>
<td>Chloramphenicol</td>
<td>Ribosomes</td>
<td>Inhibits protein synthesis</td>
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<tr>
<td></td>
<td>Fluoroquinolones</td>
<td>DNA gyrase</td>
<td>Block replication of DNA</td>
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<td></td>
<td>Ciprofloxacin</td>
<td>RNA polymerase</td>
<td>Stops mRNA synthesis</td>
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<tr>
<td></td>
<td>Levofloxacin</td>
<td>Metabolic pathway</td>
<td></td>
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<tr>
<td></td>
<td>Rifampin</td>
<td>Metabolic pathway</td>
<td>Inhibit folic acid formation</td>
</tr>
<tr>
<td></td>
<td>Sulfur drugs</td>
<td>Metabolic pathway</td>
<td>Inhibits folic acid formation</td>
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<td></td>
<td>Sulfasaxazole</td>
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<td></td>
<td>Trimethoprim</td>
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<tr>
<td><strong>Fungi</strong></td>
<td>Macrolides</td>
<td>Fungal cell</td>
<td>Loss of selective permeability</td>
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<tr>
<td></td>
<td>Amphotericin B</td>
<td>membrane</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Azoles</td>
<td>Fungal cell</td>
<td>Loss of selective permeability</td>
</tr>
<tr>
<td></td>
<td>Micronazole</td>
<td>membrane</td>
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<td></td>
<td>Fluconazole</td>
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<td></td>
<td>Fluetoxyne</td>
<td>Fungal DNA and</td>
<td>Stops cell reproduction</td>
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<tr>
<td></td>
<td></td>
<td>RNA synthesis</td>
<td></td>
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<tr>
<td><strong>Protozoa</strong></td>
<td>Quinines</td>
<td>Nutrition of the</td>
<td>Buildup of toxic wastes in the parasite's cells</td>
</tr>
<tr>
<td></td>
<td>Chloroquine</td>
<td>malaria parasite</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mefloquine</td>
<td>Anaerobic cells</td>
<td>Buildup of toxic free radicals</td>
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<tr>
<td></td>
<td>Toxoplasmose</td>
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<tr>
<td><strong>Helminthes</strong></td>
<td>Benzathones</td>
<td>Microtubules</td>
<td>Inhibit glucose metabolism</td>
</tr>
<tr>
<td></td>
<td>Dichlokarbamidine</td>
<td>Unknown</td>
<td>Kills larval forms</td>
</tr>
<tr>
<td></td>
<td>Piperazine</td>
<td>Worm muscles</td>
<td>Worm is expelled</td>
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<tr>
<td></td>
<td>Niclosamide</td>
<td>ATP formation</td>
<td>Loosens worm hold</td>
</tr>
<tr>
<td></td>
<td>Ivermectin</td>
<td>Nerve transmission</td>
<td>Worm is expelled</td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td>Amantidinie</td>
<td>Host cell membrane</td>
<td>Blocks entry, fusion</td>
</tr>
<tr>
<td></td>
<td>Cyclovirins</td>
<td>DNA synthesis</td>
<td>Stop virus replication</td>
</tr>
<tr>
<td></td>
<td>Azidothymidine</td>
<td>Reverse transcriptase</td>
<td>Blocks DNA formation</td>
</tr>
</tbody>
</table>
The Spectrum of an Antimicrobial Drug

- Spectrum – range of activity of a drug
  - narrow-spectrum – effective on a small range of microbes
    - target a specific cell component that is found only in certain microbes
  - broad-spectrum – greatest range of activity
    - target cell components common to most pathogens
1. Drugs that affect the bacterial cell wall

- Most bacterial cell walls contain a rigid girdle of peptidoglycan.
- **Penicillin and cephalosporin** block synthesis of peptidoglycan, causing the cell wall to lyse.
- Penicillins do not penetrate the outer membrane and are less effective against gram-negative bacteria.
- Broad spectrum penicillins and cephalosporins can cross the cell walls of gram-negative bacteria.
Peptidoglycan (cell wall)

Exposure to cephalosporin (or penicillin)

Weak points lacking peptidoglycan

Exposure to hypotonic environment

Membrane bulges out as water diffuses into cell.

Membrane breaks.

Cell lyses.
2. **Drugs that disrupt cell membrane function**

- A cell with a damaged membrane dies from disruption in metabolism or lysis.
- These drugs have specificity for a particular microbial group, based on differences in types of lipids in their cell membranes.
- **Polymyxins** interact with phospholipids and cause leakage, particularly in gram-negative bacteria.
- **Amphotericin B** and nystatin form complexes with sterols on fungal membranes which causes leakage.
2. Drugs that disrupt cell membrane function
3. Drugs That Inhibit Nucleic Acid Synthesis

- May block synthesis of nucleotides, inhibit replication, or stop transcription.
- Chloroquine binds and cross-links the double helix; quinolones inhibit DNA helicases.
- Antiviral drugs that are analogs of purines and pyrimidines insert in viral nucleic acid, preventing replication.
4. Drugs That Block Protein Synthesis

- Ribosomes of eucaryotes differ in size and structure from procaryotes; antimicrobics usually have a selective action against procaryotes; can also damage the eucaryotic mitochondria.
- Aminoglycosides (streptomycin, gentamycin) insert on sites on the 30S subunit and cause misreading of mRNA.
- Tetracyclines block attachment of tRNA on the A acceptor site and stop further synthesis.
4. Drugs that block protein synthesis

FIGURE 12.5
Sites of inhibition on the procaryotic ribosome and major antibiotics that act at these sites. All have the general effect of blocking protein synthesis. Blockage actions are indicated by X.
5. Drugs that Affect Metabolic Pathways

- Sulfonamides and trimethoprim block enzymes required for tetrahydrofolate synthesis needed for DNA and RNA synthesis.

- **Competitive inhibition** – drug competes with normal substrate for enzyme’s active site

- **Synergistic effect** – an additive effect, achieved by multiple drugs working together, requiring a lower dose of each
Survey of Major Antimicrobial Drug Groups

- Antibacterial drugs
  - antibiotics
  - synthetic drugs
- Antifungal drugs
- Antiprotozoan drugs
- Antiviral drugs

About 260 different antimicrobial drugs are classified in 20 drug families.
Antibacterial antibiotics

- Penicillins
- Cephalosporins
- Other beta-lactam antibiotics
- Aminoglycosides
- Tetracycline antibiotics
- Chloramphenicol
- Other *Streptomyces* antibiotics
- The *Bacillus* antibiotics
- New classes
• Beta-lactam antimicrobials - all contain a highly reactive 3 carbon, 1 nitrogen ring
• Primary mode of action is to interfere with cell wall synthesis.
• Greater than ½ of all antimicrobial drugs are beta-lactams.
• Penicillins and cephalosporins most prominent beta-lactams
Penicillins

R Group

Nucleus

Nafcillin

CH – CO

COONa

Ticarcillin

Cl

CO

N

CH

O

Cloxacillin

CH – CO

COONa

Carbenicillin
# TABLE 12.5

## Characteristics of Selected Penicillin Drugs

<table>
<thead>
<tr>
<th>Name</th>
<th>Spectrum of Action</th>
<th>Uses, Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G</td>
<td>Narrow</td>
<td>Best drug of choice when bacteria are sensitive; low cost; low toxicity</td>
<td>Can be hydrolyzed by penicillinase; allergies occur; requires injection</td>
</tr>
<tr>
<td>Penicillin V</td>
<td>Narrow</td>
<td>Good absorption from intestine; otherwise, similar to penicillin G</td>
<td>Hydrolysis by penicillinase; allergies</td>
</tr>
<tr>
<td>Oxacillin, dicloxacillin</td>
<td>Narrow</td>
<td>Not susceptible to penicillinase; good absorption</td>
<td>Allergies; expensive</td>
</tr>
<tr>
<td>Methicillin, nafcillin</td>
<td>Narrow</td>
<td>Not usually susceptible to penicillinase</td>
<td>Poor absorption; allergies; growing resistance</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Broad</td>
<td>Works on gram-negative bacilli</td>
<td>Can be hydrolyzed by penicillinase; allergies; only fair absorption</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Broad</td>
<td>Gram-negative infections; good absorption</td>
<td>Hydrolysis by penicillinase; allergies</td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>Broad</td>
<td>Same as ampicillin</td>
<td>Poor absorption; used only parenterally</td>
</tr>
<tr>
<td>Azlocillin, mezlocillin ticarcillin</td>
<td>Very broad</td>
<td>Effective against <em>Pseudomonas</em> species; low toxicity compared with aminoglycosides</td>
<td>Allergies, susceptible to many beta-lactamases</td>
</tr>
</tbody>
</table>
• Penicillins G and V most important natural forms
• Penicillin is the drug of choice for gram-positive cocci (streptococci) and some gram-negative bacteria (meningococci and syphilis spirochete)
• Semisynthetic penicillins – **ampicillin**, carbenicillin & amoxicillin have broader spectra – gram negative enterics rods
• **Penicillinase-resistant** – **methicillin, nafcillin, cloxacillin**
• Primary problems – allergies and resistant strains of bacteria
Cephalosporins

- Account for majority of all antibiotics administered
- Isolated from *Cephalosporium acremonium* mold
- Beta-lactam ring that can be altered
- Relatively broad-spectrum, resistant to most penicillinases, & cause fewer allergic reactions
- Some are given orally, many must be administered parenterally
- Generic names have root – *cef*, *ceph*, or *kef*. 
Cephalosporins

- 4 generations exist: each group more effective against Gram-negatives than the one before with improved dosing schedule and fewer side effects
  - **first generation** – cephalothin, cefazolin – most effective against Gram-positive cocci and few Gram-negative
  - **second generation** – cefaclor, cefonacid – more effective against Gram-negative bacteria
  - **third generation** – cephalexin, ceftriaxone – broad-spectrum activity against enteric bacteria with beta-lactamases
  - **fourth generation** – cefepime – widest range; both Gram-negative and Gram-positive
<table>
<thead>
<tr>
<th>R Group 1</th>
<th>Basic Nucleus</th>
<th>R Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical Structure 1" /></td>
<td>Cephalothin (first generation*)</td>
<td><img src="image2.png" alt="Chemical Structure 2" /></td>
</tr>
<tr>
<td><img src="image3.png" alt="Chemical Structure 3" /></td>
<td>Cefotiam (second generation)</td>
<td><img src="image4.png" alt="Chemical Structure 4" /></td>
</tr>
<tr>
<td><img src="image5.png" alt="Chemical Structure 5" /></td>
<td>Moxalactam (third generation)</td>
<td><img src="image6.png" alt="Chemical Structure 6" /></td>
</tr>
<tr>
<td><img src="image7.png" alt="Chemical Structure 7" /></td>
<td>Cefepime (fourth generation)</td>
<td><img src="image8.png" alt="Chemical Structure 8" /></td>
</tr>
</tbody>
</table>

*New improved versions of drugs are referred to as new “generations.”
Additional Beta-lactam Drugs

• Carbapenems
  – imipenem – broad-spectrum drug for infections with aerobic and anaerobic pathogens; low dose, administered orally with few side effects

• Monobactams
  – aztreonam – newer narrow-spectrum drug for infections by Gram-negative aerobic bacilli; may be used by people allergic to penicillin
Non Beta-lactam Cell Wall Inhibitors

- **vancomycin** – narrow-spectrum, most effective in treatment of Staphylococcal infections in cases of penicillin and methicillin resistance or if patient is allergic to penicillin; toxic and hard to administer; restricted use

- **bacitracin** – narrow-spectrum produced by a strain of *Bacillus subtilis*; used topically in ointment

- **isoniazid** (INH) – works by interfering with mycolic acid synthesis; used to treat infections with *Mycobacterium tuberculosis*; oral doses in combination with other antimicrobials such as rifampin, ethambutol
Drugs That Interfere with Protein Synthesis

- **Aminoglycosides** – composed of 2 or more amino sugars and an aminocyclitol (6C) ring; binds ribosomal subunit
  - Products of various species of soil actinomycetes in genera *Streptomyces* and *Micromonospora*
  - **Broad-spectrum**, inhibit protein synthesis, especially useful against aerobic Gram-negative rods and certain gram-positive bacteria
    - *streptomycin* – bubonic plague, tularemia, TB
    - *gentamicin* – less toxic, used against Gram-negative rods
    - newer – *tobramycin* and *amikacin* Gram-negative bacteria
Tetracycline Antibiotics

- **Broad-spectrum**, block protein synthesis by binding ribosomes
- **Aureomycin**, **terramycin**, **tetracycline**, **doxycycline** and **minocycline** – low cost oral drugs; side effects are a concern
- **Treatment for STDs**, Rocky Mountain spotted fever, Lyme disease, typhus, acne and protozoa
Figure 12.10 (a)

(a) Tetracyclines
Chloramphenicol

- Isolated from \textit{Streptomyces venezuelae}
- Potent broad-spectrum drug with unique nitrobenzene structure
- Blocks peptide bond formation
- No longer derived from natural source
- Very toxic, restricted uses, can cause irreversible damage to bone marrow
- Typhoid fever, brain abscesses, rickettsial & chlamydial infections
Figure 12.10 (b)
Drugs that Act on DNA or RNA

• Fluoroquinolones – work by binding to DNA gyrase and topoisomerase IV
  – Broad spectrum effectiveness

• Concerns have arisen regarding the overuse of quinoline drugs
  – CDC is recommending careful monitoring of their use to prevent ciprofloxacin-resistant bacteria
Drugs That Interfere with Protein Synthesis

• Aminoglycosides – composed of one or more amino sugars and an aminocyclitol (6C) ring; binds ribosomal subunit
• Products of various species of soil actinomycetes in genera *Streptomyces* and *Micromonospora*
• Broad-spectrum, inhibit protein synthesis, especially useful against aerobic gram-negative rods and certain gram-positive bacteria
  – Streptomycin – bubonic plague, tularemia, TB
  – Gentamicin – less toxic, used against gram-negative rods
  – Newer – tobramycin and amikacin gram-negative bacteria
Macrolides and Related Antibiotics

- Erythromycin – large lactone ring with sugars; attaches to ribosomal 50s subunit
- **Broad-spectrum**, fairly low toxicity
- Taken orally for Mycoplasma pneumonia, legionellosis, Chlamydia, pertussis, diphtheria and as a prophylactic prior to intestinal surgery
- For penicillin-resistant – gonococci, syphilis, acne
- Newer semi-synthetic macrolides – clarithromycin, azithromycin
Figure 12.10 (c)

(c) Erythromycin
Drugs that Affect Metabolic Pathways

• Sulfonamides and trimethoprim block enzymes required for tetrahydrofolate synthesis needed for DNA and RNA synthesis.

• **Competitive inhibition** – drug competes with normal substrate for enzyme’s active site

• **Synergistic effect** – an additive effect, achieved by multiple drugs working together, requiring a lower dose of each
Drugs That Block Metabolic Pathways

- Most are synthetic; most important are sulfonamides, or sulfa drugs - first antimicrobial drugs
- Narrow-spectrum; block the synthesis of folic acid by bacteria
  - sulfisoxazole – shigellosis, UTI, protozoan infections
  - silver sulfadiazine – burns, eye infections
  - trimethoprim – given in combination with sulfamethoxazole – UTI, PCP
Figure 12.11 Structure of sulfonamides
Newly Developed Classes of Antimicrobials

• Formulated from pre-existing drug classes
• Three new drug types:
  – Fosfomycin trimethamine – a phosphoric acid effective as alternate treatment for UTIs; inhibits cell wall synthesis
  – Synercid – effective against *Staphylococcus* and *Enterococcus* that cause endocarditis and surgical infections; used when bacteria is resistant to other drugs; inhibits protein synthesis
  – Daptomycin – directed mainly against gram-positive; disrupts membrane function
Newly Developed Classes of Antimicrobials

• Ketolides – telitromycin (Ketek), new drug with different ring structure from Erythromycin; used for infection when resistant to macrolides

• Oxazolidinones – linezolid (Zyvox); synthetic antimicrobial that blocks the interaction of mRNA and ribosome
  – Used to treat methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *Enterococcus* (VRE)
Agents to Treat Fungal Infections

- Fungal cells are eukaryotic; a drug that is toxic to fungal cells also toxic to human cells
- Five antifungal drug groups:
  - Macrolide polyene
    - Amphotericin B – mimic lipids, most versatile and effective, topical and systemic treatments
    - Nystatin – topical treatment
  - Griseofulvin – stubborn cases of dermatophyte infections, nephrotoxic
  - Synthetic azoles – broad-spectrum; ketoconazole, clotrimazole, miconazole
  - Flucytosine – analog of cytosine; cutaneous mycoses or in combination with amphotericin B for systemic mycoses
  - Echinocandins – damage cell walls; capsofungin
Antiparasitic Chemotherapy

- Antimalarial drugs – quinine, chloroquine, primaquine, mefloquine
- Antiprotozoan drugs – metronidazole (Flagyl), quinicrine, sulfonamides, tetracyclines
- Antihelminthic drugs – immobilize, disintegrate, or inhibit metabolism
  - Mebendazole, thiaabendazole – broad-spectrum – inhibit function of microtubules, interferes with glucose utilization and disables them
  - Pyrantel, piperazine – paralyze muscles
  - Niclosamide – destroys scolex
Antiviral Chemotherapeutic Agents

- Selective toxicity is almost impossible due to obligate intracellular parasitic nature of viruses
- Block penetration into host cell
- Block replication, transcription, or translation of viral genetic material
  - Nucleotide analogs
    - Acyclovir – herpesviruses
    - Ribavirin – a guanine analog – RSV, hemorrhagic fevers
    - AZT – thymine analog – HIV
- Prevent maturation of viral particles
  - Protease inhibitors – HIV
<table>
<thead>
<tr>
<th><strong>ACTION</strong></th>
<th><strong>DESCRIPTION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Inhibition of Virus Entry or Release</strong></td>
<td></td>
</tr>
<tr>
<td>1. Fusozon</td>
<td>Polypeptide of 30 amino acids (trade name) blocks HIV infection by preventing binding of viral gp41 receptors to cell receptor, thereby preventing fusion of virus with cell</td>
</tr>
<tr>
<td>2. Amanitidine and relatives</td>
<td>Also blocks entry of influenza virus by interfering with fusion of virus with cell membrane (also release)</td>
</tr>
<tr>
<td>3. Tamiflu, Relenza</td>
<td>Stop the actions of influenza neuraminidase, required for entry of virus into cell</td>
</tr>
<tr>
<td><strong>II. Inhibition of Nucleic Acid Synthesis</strong></td>
<td></td>
</tr>
<tr>
<td>5. Acyclovir, other 'cytoviris'</td>
<td>Terminates DNA replication in herpesviruses</td>
</tr>
<tr>
<td>6. Nucleotide analog reverse transcriptase (RT) inhibitors (zidovudine – AZT)</td>
<td>Stop the action of reverse transcriptase in HIV, blocking viral DNA production</td>
</tr>
<tr>
<td>7. Non-nucleoside reverse transcriptase inhibitors (nevirapine)</td>
<td>Attach to HIV RT binding site, stopping its action</td>
</tr>
<tr>
<td><strong>III. Inhibition of Effective Viral Assembly/Release</strong></td>
<td></td>
</tr>
<tr>
<td>8. Normal HIV binding and replication</td>
<td>for comparison with 5, 7, and 9.</td>
</tr>
<tr>
<td>9. Protease inhibitors</td>
<td>Saquinavir (Fortovase) Ritonavir (Norvir) These insert onto HIV protease, an enzyme that clips viral proteins into functional pieces. Viruses are defective and unable to infect other cells</td>
</tr>
</tbody>
</table>

*Details of viral cycle are omitted for ease in observing drug effects.
Drugs for Treating Influenza

- Amantadine, rimantidine – restricted almost exclusively to influenza A viral infections; prevent fusion of virus with cell membrane
- Relenza and tamiflu – slightly broader spectrum; blocks neuraminidase in influenza A and B
Antiherpes Drugs

• Many antiviral agents mimic the structure of nucleotides and compete for sites on replicating DNA
  – Acyclovir – Zovirax
  – Valacyclovir – Valtrex
  – Famiciclovir – Famvir
  – Peniciclovir – Denavir

• Oral and topical treatments for oral and genital herpes, chickenpox, and shingles
Drugs for Treating HIV Infections and AIDS

- Retrovirus offers 2 targets for chemotherapy:
  - Interference with viral DNA synthesis from viral RNA using nucleoside reverse transcriptase inhibitors (nucleotide analogs)
  - Interference with synthesis of DNA using nonnucleoside reverse transcriptase inhibitors

Azidothymidine (AZT) – first drug aimed at treating AIDS, thymine analog
Interferons (INF)

- Human-based glycoprotein produced primarily by fibroblasts and leukocytes
- Therapeutic benefits include:
  - Reduces healing time and some complications of infections
  - Prevents or reduces symptoms of cold and papillomavirus
  - Slows the progress of certain cancers, leukemias, and lymphomas
  - Treatment of hepatitis C, genital warts, Kaposi’s sarcoma
12.4 The Acquisition of Drug Resistance

- Adaptive response in which microorganisms begin to tolerate an amount of drug that would ordinarily be inhibitory; due to genetic versatility or variation; intrinsic and acquired

- Acquired resistance:
  - Spontaneous mutations in critical chromosomal genes
  - Acquisition of new genes or sets of genes via transfer from another species
    - Originates from resistance factors (plasmids) encoded with drug resistance, transposons
Mechanisms of Drug Resistance

• Drug inactivation by acquired enzymatic activity – penicillinases

• Decreased permeability to drug or increased elimination of drug from cell – acquired or mutation

• Change in drug receptors – mutation or acquisition

• Change in metabolic patterns – mutation of original enzyme
1. **Drug inactivation**

   ![Diagram of drug inactivation]

   - **Active penicillin**
   - **Inactive penicillin**

   Inactivation of a drug like penicillin by penicillinase, an enzyme that cleaves a portion of the molecule and renders it inactive.

2. **Decreased permeability**

   ![Diagram of decreased permeability]

   - **Drug**
   - **Cell surface of microbe**
   - **Normal receptor**
   - **Different receptor**

   2. The receptor that transports the drug is altered, so that the drug cannot enter the cell.

3. **Activation of drug pumps**

   ![Diagram of activation of drug pumps]

   - **Drug**
   - **Inactive drug pump**
   - **Active drug pump**

   3. Specialized membrane proteins are activated and continually pump the drug out of the cell.

4. **Change in drug binding site**

   ![Diagram of change in drug binding site]

   - **Drug binding site on target (ribosome)**

   4. Binding site on target (ribosome) is altered so drug has no effect.

5. **Use of alternate metabolic pathway**

   ![Diagram of alternate metabolic pathway]

   - **Drug acts**
   - **A → B → C → D → Product**
   - **C₁ → D₁**

   5. The drug has blocked the usual metabolic pathway (green), so the microbe circumvents it by using an alternate, unblocked pathway that achieves the required outcome (red).
Natural Selection and Drug Resistance

• Large populations of microbes likely to include drug resistant cells due to prior mutations or transfer of plasmids – no growth advantage until exposed to drug.
• If exposed, sensitive cells are inhibited or destroyed while resistance cells will survive and proliferate.
• Eventually population will be resistant – selective pressure - **natural selection**.
• Worldwide indiscriminate use of antimicrobials has led to explosion of drug resistant microorganisms.
Selection for drug resistance

(a) Population of microbial cells

(b) Sensitive cells (●) eliminated by drug; resistant mutants survive

(c) All cells are now resistant
Side effects of drugs

1. Toxicity to organs
2. Allergic responses
3. Suppression and alteration of microflora