Chapter 10: Controlling Microbial Growth in the Body: Antimicrobial Drugs
Antimicrobial Drugs:

Antibiotic: Term coined by Fleming to describe an antimicrobial substance produced naturally by a microorganism. Today term is used for antibacterial agents (not antiviral or antifungal). May be natural, semi-synthetic or synthetic.

Antibiotic producing microbes include:

◆ **Gram-Positive Rods:**
  ◆ *Bacillus subtilis*: Bacitracin
  ◆ *Bacillus polymyxa*: Polymyxin

◆ **Fungi**
  ◆ *Penicillium notatum*: Penicillin
  ◆ *Cephalosporium spp.*: Cephalothin

◆ **Streptomyces:**
  ◆ *Streptomyces erythraeus*: Erythromycin
  ◆ *Streptomyces venezuelae*: Chloramphenicol
  ◆ *Streptomyces griseus*: Streptomycin
  ◆ *Streptomyces nodosus*: Amphotericin B
Penicillium Colony Inhibits Bacterial Growth

Staphylococcus aureus

Penicillium chrysogenum
• **Antibacterials:** Relatively easy to develop and find with low toxicity because procaryotic cells are very different from host cells.

• **Antihelminthic, antiprotozoan, and antifungal drugs:** More difficult to develop because eucaryotic cells resemble human cells.

• **Antivirals:** Most difficult to develop because virus reproduces using host cell enzymes and machinery.

**Spectrum of Antimicrobial Activity**

◆ **Broad Spectrum:** Effective against many different types of bacteria (e.g.: both gram positive and negative). Examples: Tetracycllin

◆ **Narrow Spectrum Antibiotics:** Effective against a subset of bacteria (either gram positive and negative). Examples: Penicillin, Isoniazid *(Mycobacteria only)*
### Spectrum of Action for Selected Antimicrobials

#### The Spectrum of Activity of Antibiotics and Other Antimicrobial Drugs

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Mechanisms of Action of Antibiotics

Inhibition of cell wall synthesis
- Penicillins
- Cephalosporins
- Vancomycin
- Bacitracin
- Isoniazid
- Ethambutol
- Echinocandins (antifungal)

Inhibition of pathogen’s attachment to, or recognition of, host
- Arildone
- Pleconaril

Inhibition of DNA or RNA synthesis
- Actinomycin
- Nucleotide analogs
- Quinolones
- Rifampin

Inhibition of general metabolic pathway
- Sulfonamides
- Trimethoprim
- Dapsone

Inhibition of protein synthesis
- Aminoglycosides
- Tetracyclines
- Chloramphenicol
- Macrolides

Disruption of cytoplasmic membrane
- Polymyxins
- Polyenes (antifungal)
Antimicrobial Mechanisms of Action

- **Inhibition of Cell Wall Synthesis:** Interfere with peptidoglycan synthesis.
  - Result in cell lysis.
  - Low toxicity.
  - E.g.: Penicillin and vancomycin.

Other antibiotics in the penicillin family (B-lactams):
- Ampicillin, Methicillin, and Oxacillin
Structure of Penicillin and Related Antibiotics

(a) Natural penicillins

Penicillin G (Requires injection)

Penicillin V (Can be taken orally)

(b) Semisynthetic penicillins

Oxacillin
Narrow spectrum, only gram-positives, but resistant to penicillinase

Ampicillin
Extended spectrum, many gram-negatives
Antimicrobial Mechanisms of Action

◆ Inhibition of Protein Synthesis: Interfere with procaryotic (70S) ribosomes, also found in mitochondria.

◆ Most have broad spectrum of activity
◆ Tetracyclin, chloramphenicol, erythromycin, and streptomycin.
◆ May cause toxicity to active cells of liver and bone marrow.
Chloramphenicol and Tetracycline Inhibit Protein Synthesis

Chloramphenicol

Tetracycline

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Chloramphenicol Inhibits Protein Synthesis

Chloramphenicol
Binds to 50S portion and inhibits formation of peptide bond

Protein synthesis site

30S portion

50S portion

Growing polypeptide

Messenger RNA

tRNA

70S prokaryotic ribosome

Streptomycin
Changes shape of 30S portion, causes code on mRNA to be read incorrectly

Translation

Direction of ribosome movement

Tetracyclines
Interfere with attachment of tRNA to mRNA-ribosome complex

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

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Antimicrobial Mechanisms of Action

- **Injury to the Plasma Membrane:** Cause changes in membrane permeability.
  - Result in loss of metabolites and/or cell lysis.
  - Many polypeptide antibiotics.
  - E.g.: Polymyxin B (antibacterial) or miconazole (antifungal).

- **Inhibition of Nucleic Acid (DNA/RNA) Synthesis:**
  - Interfere with DNA replication and transcription.
  - Many are nucleotide analogs, may be toxic to human cells.
  - Rifampin (tuberculosis) and quinolones (bacteria).
  - Reverse transcriptase inhibitors used against HIV.
Disruption of Cell Membranes by Antifungal Amphotericin B
Nucleosides Inhibit DNA or RNA Synthesis

- Tenofovir
- Dideoxyinosine (ddI)
- Ribavirin
- Penciclovir
- Adenosine arabinoside
- Adenosine
- Guanosine
- Acyclovir (ACV)
- Ganciclovir
- Stavudine (d4T)
- Azidothymidine (AZT)
- Thymidine
- Cytidine
- Dideoxycytidine (ddC)
- Lamivudine
- Iododeoxyuridine
- Trifluridine
Antimicrobial Mechanisms of Action

◆ Inhibition of Synthesis of Essential Metabolites: Involve competitive inhibition of key enzymes.
  ◆ Closely resemble substrate of enzyme.
  ◆ E.g.: Sulfa drugs inhibit the synthesis of folic acid which is necessary for DNA and RNA synthesis.
Sulfa Drugs Inhibit Folic Acid Synthesis

1. Sulfamethoxazole, a sulfonamide that is a structural analog of PABA, competitively inhibits the synthesis of dihydrofolate acid from PABA.

2. Trimethoprim, a structural analog of a portion of dihydrofolate acid, competitively inhibits the synthesis of tetrahydrofolate acid.
Antimicrobial Mechanisms of Action

**Inhibition of Virus Attachment:** Binding of viruses can be blocked by peptide and sugar analogs of attachment or receptor proteins.

- Arildone (Pleconaril): Blocks poliovirus and some cold viruses
Safety Concerns with the Use of Antimicrobials:

- **Toxicity**
  - Kidney damage: Polymyxin, Bacitracin, Streptomycin
  - Liver damage: Isoniazid, Tetracylin
  - Bone marrow: Chloramphenicol can cause aplastic anemia
  - Neurological: Aminoglycosides, Chloramphenicol, Vancomycin
  - Other: Hairy black tongue (Metronidazole) harmless, temporary condition.

- **Fetal damage/risk to pregnant women**
  - Tetracycllin causes discoloration and malformation of teeth and skull in children. May cause liver damage in pregnant women
  - Sulfonamides: Can cause mental retardation of fetus if given in last trimester.

- **Interactions with other medications**
  - May neutralize effectiveness of contraceptive pills

- **Hypersensitivity reactions**
  - Anaphylactic reactions to penicillin: Seen in 0.1% of Americans
  - Triple antibiotic ointment (rashes & neomycin B)
Side Effects from Toxicity of Antimicrobial Agents

Black Hairy Tongue  Discoloration of teeth enamel
Flagyl (Metronidazole)  Tetracycline
Safety Concerns with the Use of Antimicrobials:

- **Dysbiosis**: Host’s normal beneficial flora killed off, causing various symptoms such as diarrhea, digestive problems (constipation, gas), yeast infections (oral thrush, vaginitis), etc. Probiotics and antifungals can help.

- **Antibiotic Resistance**: Multiple antibiotic resistant is becoming a growing problem with many pathogens.
  - MRSA= Methicillin Resistant *Staphylococcus aureus*
  - *Mycobacterium tuberculosis*
  - *Plasmodium spp.*
  - *Pseudomonas aeruginosa*
  - *Neisseria gonnorhoeae*
Penicillinase and Penicillin Resistance

Lactam ring

β-lactamase (penicillinase) breaks this bond

Inactive penicillin
Development of Antibiotic Resistant Strains of Bacteria

(a) Population of microbial cells
(b) Sensitive cells inhibited by exposure to drug
(c) Most cells now resistant

Drug-sensitive cell
Drug-resistant mutant
Exposure to drug
Remaining population grows over time
Fluoroquinolone Resistant *Campylobacter jejuni* in U.S.
Prevention of Antimicrobial Resistance:

- Take all medication prescribed to kill sensitive cells and allow body’s defenses to kill all remaining cells.
- Use a combination of two or more antimicrobials.
  - Synergism: One drug enhances another (Penicillin + Streptomycin)
  - Antagonism: One drug inhibits another
- Limit use of antimicrobials to necessary cases.
  - 30% of ear infections and 50% of sore throats are viral
- Develop new drugs and variations of existing drugs.