Chapter 20:
Antimicrobial Drugs
Antimicrobial Drugs:

**Antibiotic**: Substance produced by a microorganism that in small amounts inhibits the growth of another microbe.

Antibiotic producing microbes include:

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

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

- **Actinomycetes**:
  - *Streptomyces venezuelae*: Chloramphenicol
  - *Streptomyces griseus*: Streptomycin
  - *Streptomyces nodosus*: Amphotericin B
  - *Micromonospora purpurea*: Gentamycin
Penicillium Colony Inhibits Bacterial Growth
• **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: Tetracyclin

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

- Inhibition of cell wall synthesis: penicillins, cephalosporins, bacitracin, vancomycin
- Inhibition of protein synthesis: chloramphenicol, erythromycin, tetracyclines, streptomycin
- Inhibition of nucleic acid replication and transcription: quinolones, rifampin
- Injury to plasma membrane: polymyxin B
- Inhibition of synthesis of essential metabolites: sulfanilamide, trimethoprim
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 (β-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

Common nucleus
\[ \text{Common nucleus} \]
\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{CH} & \quad \text{CH} \\
\text{CH} & \quad \text{CH} \\
\text{COOH} & \quad \text{COOH}
\end{align*}
\]

\[ \beta\text{-lactam ring} \]
Penicillinate and Penicillin Resistance

$\beta$-lactam ring

Penicillin

Penicilloic acid

Copyright © 2007 Pearson Education, Inc., publishing as Benjamin Cummings.
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.
Chloramphenicol and Tetracycline Inhibit Protein Synthesis

![Chemical structures of Chloramphenicol and Tetracycline]
Chloramphenicol Inhibits Protein Synthesis

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

50S portion

Protein synthesis site

Growing polypeptide

Messenger RNA

30S portion

70S prokaryotic ribosome

Translation

Direction of ribosome movement

Tetracyclines
Interfere with attachment of tRNA to mRNA-ribosome complex

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

(b) In the diagram the black arrows indicate the different points at which chloramphenicol, the tetracyclines, and streptomycin exert their activities.
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.
  - May be toxic to human cells.
  - E.g.: Rifampin and quinolones.
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. Sulfa Drugs Inhibit Folic Acid Synthesis (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.

Precursors of proteins, DNA, RNA → DNA RNA

Copyright © 2007 Pearson Education, Inc., publishing as Benjamin Cummings.
Safety Concerns with the Use of Antimicrobials:

- **Toxicity**
  - Kidney damage
  - Liver damage
  - Bone marrow (Chloramphenicol and aplastic anemia)

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

- **Hypersensitivity reactions**
  - Anaphylactic reactions to penicillin
  - Triple antibiotic ointment (rashes & neomycin B)

- **Fetal damage/risk to pregnant women**
  - Tetracycllin causes discoloration of teeth in children and may cause liver damage in pregnant women
  - Fluoroquinolones may cause cartilage damage.

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

- **Antibiotic Resistance**: Multiple antibiotic resistant is becoming a huge problem. MRSA= Methicillin Resistant *Staphylococcus aureus.*
Fluoroquinolone Resistant *Campylobacter jejuni* in U.S.