Chapter 10 Controlling Microbial Growth in the Body: Antimicrobial Drugs
The History of Antimicrobial Agents

• Drugs
  • Chemicals that affect physiology in any manner

• Chemotherapeutic agents
  • Drugs that act against diseases

• Antimicrobial agents (antimicrobials)
  • Drugs that treat infections
The History of Antimicrobial Agents

- Paul Ehrlich
  - "Magic bullets"
    - Arsenic compounds that killed microbes
- Alexander Fleming
  - Penicillin released from *Penicillium*
- Gerhard Domagk
  - Discovered *sulfanilamide*
- Selman Waksman
  - Antibiotics
    - Antimicrobial agents produced naturally by organisms
Figure 10.1 Antibiotic effect of the mold *Penicillium chrysogenum*.

*Staphylococcus aureus* (bacterium)

*Penicillium chrysogenum* (fungus)

Zone where bacterial growth is inhibited
The History of Antimicrobial Agents

- **Semisynthetics**
  - Chemically altered antibiotics that are more effective, longer lasting, or easier to administer than naturally occurring ones

- **Synthetics**
  - Antimicrobials that are completely synthesized in a lab
Mechanisms of Antimicrobial Action

• Successful chemotherapy requires **selective toxicity**
• Antibacterial drugs constitute largest number and diversity of antimicrobial agents
• Fewer drugs to treat eukaryotic infections
• Antiviral drugs limited
Chemotherapeutic Agents: Modes of Action

- Inhibition of DNA & RNA Synthesis
- Inhibition of Protein Synthesis
- Inhibition of Metabolic Pathway
- Inhibition of Cell Wall Synthesis
- Disruption of Plasma Membrane
Figure 10.3c-e Bacterial cell wall synthesis and the inhibitory effects of beta-lactams on it.

(c) β-lactam ring

Penicillin G (natural)

Imipenem (semisynthetic)

Cephalothin (natural)

Methicillin (semisynthetic)

Penicillins

Carbapenems

Cephalosporins

(d) New cross-links inhibited by beta-lactam

Previously formed crossbridge

Growth

Beta-lactam interferes with the linking enzymes, and NAM subunits remain unattached to their neighbors. However, the cell continues to grow as it adds more NAG and NAM subunits.

(e) The cell bursts from osmotic pressure because the integrity of peptidoglycan is not maintained.
Mechanisms of Antimicrobial Action

• **Inhibition of Cell Wall Synthesis**
  • Inhibition of Synthesis of Bacterial Walls
    • Semisynthetic derivatives of beta-lactams
      • More stable in acidic environments
      • More readily absorbed
      • Less susceptible to deactivation
      • More active against more types of bacteria
Mechanisms of Antimicrobial Action

- **Inhibition of Protein Synthesis**
  - Prokaryotic ribosomes are 70S (30S and 50S)
  - Eukaryotic ribosomes are 80S (40S and 60S)
  - Drugs can selectively target translation
  - Mitochondria of animals and humans contain 70S ribosomes
    - Can be harmful
Incorrect amino acids
Ribosome
Some aminoglycosides, for example streptomycin, cause change in 30S shape, so mRNA is misread.

Lincosamides or macrolides bind to 50S subunit, blocking proper mRNA movement through ribosome. Synthesis stops.

Tetracycline and some aminoglycosides block docking site of tRNA.

Antisense nucleic acid

Chloramphenicol blocks peptide bond formation.

Oxazolidinone

Figure 10.4 The mechanisms by which antimicrobials target prokaryotic ribosomes to inhibit protein synthesis.
Mechanisms of Antimicrobial Action

• Disruption of Cytoplasmic Membranes
  • Some drugs form channel through cytoplasmic membrane and damage its integrity
  • Amphotericin B attaches to ergosterol in fungal membranes
    • Humans somewhat susceptible because cholesterol similar to ergosterol
    • Bacteria lack sterols; not susceptible
Mechanisms of Antimicrobial Action

• Disruption of Cytoplasmic Membranes
  • Azoles and allylamines inhibit ergosterol synthesis
  • Polymyxin disrupts cytoplasmic membranes of Gram-negative bacteria
    • Toxic to human kidneys
  • Some parasitic drugs act against cytoplasmic membranes
Mechanisms of Antimicrobial Action

• **Inhibition of Metabolic Pathways**
  
  • *Antimetabolic agents* can be effective when pathogen and host metabolic processes differ
    
    • *Atovaquone* interferes with electron transport in protozoa and fungi
    
    • Heavy metals inactivate enzymes
    
    • Agents that disrupt tubulin polymerization and glucose uptake by many protozoa and parasitic worms
    
    • Drugs that block activation of viruses
    
    • Metabolic antagonists
Figure 10.6 The antimetabolic action of sulfonamides in inhibiting nucleic acid synthesis.

(a) Para-aminobenzoic acid (PABA) and some of its structural analogs, the sulfonamides

(b) Role of PABA in folic acid synthesis in bacteria and protozoa

(c) Inhibition of folic acid synthesis by sulfonamide
Mechanisms of Antimicrobial Action

• **Inhibition of Metabolic Pathways**
  • Antiviral agents can target unique aspects of viral metabolism
    • Amantadine, rimantadine, and weak organic bases prevent viral uncoating
  • Protease inhibitors interfere with an enzyme that HIV needs in its replication cycle
Mechanisms of Antimicrobial Action

- **Inhibition of Nucleic Acid Synthesis**
  - Several drugs block DNA replication or RNA transcription
  - Drugs often affect both eukaryotic and prokaryotic cells
  - Not normally used to treat infections
  - Used in research and perhaps to slow cancer cell replication
Mechanisms of Antimicrobial Action

• **Inhibition of Nucleic Acid Synthesis**
  • **Nucleotide or nucleoside analogs**
    • Interfere with function of nucleic acids
    • Distort shapes of nucleic acid molecules and prevent further replication, transcription, or translation
    • Most often used against viruses
    • Effective against rapidly dividing cancer cells
Figure 10.7 Nucleosides and some of their antimicrobial analogs.
Mechanisms of Antimicrobial Action

- **Inhibition of Nucleic Acid Synthesis**
  - Quinolones and fluoroquinolones
    - Act against prokaryotic DNA gyrase
  - Inhibitors of RNA polymerase
  - *Reverse transcriptase inhibitors*
    - Act against an enzyme HIV uses in its replication cycle
    - Do not harm people because humans lack reverse transcriptase
Mechanisms of Antimicrobial Action

• Prevention of Virus Attachment, Entry, or Uncoating
  • *Attachment antagonists* block viral attachment or receptor proteins
  • New area of antimicrobial drug development
  • *Pleconaril* blocks viral attachment
  • *Arildone* prevents viral uncoating
Resistance to Antimicrobial Drugs

• The Development of Resistance in Populations
  • Some pathogens are naturally resistant
  • Resistance by bacteria acquired in two ways:
    • New mutations of chromosomal genes
    • Acquisition of R plasmids via transformation, transduction, and conjugation.
Figure 10.15  The development of a resistant strain of bacteria.

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

transducing phage
(bacterial DNA)

resistant cell
Resistance to Antimicrobial Drugs

- **Mechanisms of Resistance**
  - At least seven mechanisms of microbial resistance
    - Production of enzyme that destroys or deactivates drug
    - Slow or prevent entry of drug into the cell
    - Alter target of drug so it binds less effectively
    - Alter their own metabolic chemistry
    - Pump antimicrobial drug out of the cell before it can act
    - Bacteria in biofilms can resist antimicrobials
    - *Mycobacterium tuberculosis* produces MfpA protein
      - Binds DNA gyrase, preventing the binding of fluoroquinolone drugs
Resistance to Antimicrobial Drugs

- **Multiple Resistance and Cross Resistance**
  - Pathogen can acquire resistance to more than one drug
  - Common when R plasmids exchanged
  - Develop in hospitals and nursing homes
    - Constant use of drugs eliminates sensitive cells
  - **Multiple-drug-resistant** pathogens are resistant to at least three antimicrobial agents
- **Cross resistance**
Resistance to Antimicrobial Drugs

• **Retarding Resistance**
  - Maintain high concentration of drug in patient for sufficient time
    - Inhibit the pathogen so immune system can eliminate
  - Use antimicrobial agents in combination
    - **Synergism** versus *antagonism*
Figure 10.17 An example of synergism between two antimicrobial agents.

Disk with semisynthetic amoxicillin-clavulanic acid

Disk with semisynthetic aztreonam
Resistance to Antimicrobial Drugs

- **Retarding Resistance**
  - Use antimicrobials only when necessary
  - Develop new variations of existing drugs
    - *Second-generation drugs*
    - *Third-generation drugs*
  - Search for new antibiotics, semisynthetics, and synthetics
    - *Bacteriocins*
  - Design drugs complementary to the shape of microbial proteins to inhibit them