Antimicrobial Drugs

- Chemotherapy:
- Antimicrobial drugs: Interfere with the growth of microbes within a host.
- Antibiotic: A substance produced by a microbe that, in small amounts, inhibits another microbe.
- Selective toxicity: A drug that kills harmful microbes without damaging the host.

- 1928: Fleming discovered penicillin, produced by *Penicillium*.
- 1940: Howard Florey and Ernst Chain performed first clinical trials of penicillin.

The Action of Antimicrobial Drugs

- Broad-spectrum -
- Superinfection - growth of a pathogen (sometimes opportunistic) that is resistant to an antibiotic
- Bactericidal -
- Bacteriostatic - inhibits growth and reproduction of bacteria

Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis

- Penicillin
  - Natural penicillins
  - Semisynthetic penicillins

- Penicillin
  - Penicilinase-resistant penicillins
  - Extended-spectrum penicillins
  - Penicillins + β-lactamase inhibitors
    - Augmentin =

- Cephalosporins
  - 2nd, 3rd, and 4th generations more effective against gram-negatives

- Polypeptide antibiotics
  - Bacitracin
    -
    -
  - Vancomycin
    -
    - Important "last line" against antibiotic resistant *S. aureus*

- Antimycobacterial antibiotics
  - Isoniazid (INH)
    -
  - Ethambutol
    - Inhibits incorporation of mycolic acid

Antibacterial Antibiotics: Inhibitors of Protein Synthesis

- Chloramphenicol
  -
    - Binds 50S subunit, inhibits peptide bond formation

- Aminoglycosides
  - Streptomycin, neomycin, gentamycin
    -
      - Changes shape of 30S subunit

- Tetracyclines
  -
    - Interferes with tRNA attachment
- Erythromycin
  -
    - Binds 50S, prevents translocation

Antibacterial Antibiotics: Injury to the Plasma Membrane

- Polymyxin B
  -
  - Combined with bacitracin and neomycin in over-the-counter preparation.

Antibacterial Antibiotics: Inhibitors of Nucleic Acid Synthesis

- Rifamycin
  - Inhibits RNA synthesis
  -

- Quinolones and fluoroquinolones
  -
  - Inhibits DNA gyrase
  - Urinary tract infections

Antibacterial Antibiotics: Competitive Inhibitors

- Sulfonamides (sulfa drugs)
  - Inhibit folic acid synthesis
  -

Antifungal Drugs: Inhibition of Ergosterol Synthesis

- Polyenes
  - Amphotericin B
- Azoles
  - Miconazole
  - Triazoles

Antiviral Drugs: Nucleoside and Nucleotide Analogs

-
- acyclovir - used for herpes simplex, varicella-zoster (VZV) a.k.a. chickenpox
- guanine analogue -
- provides symptomatic relief, lessens duration of outbreak
- not a cure!

- AZT (zidovudine), DDI, DDC
- DNA nucleoside analogues
-
- inhibit reverse transcriptase
- symptomatic relief, not a cure, apparently not life extending

Antiviral Drugs: Enzyme Inhibitors

- Protease inhibitors
  - Indinavir
    -
- Inhibit attachment
  - Zanamivir
    -
- Inhibit uncoating
  - Amantadine
    -
- Interferons prevent spread of viruses to new cells
    -

- protease inhibitors -

- viral protease required for cleavage of viral polypeptide precursors

- promising results

- protease inhibitors in combination with other drugs (i.e., AZT) has reduced amount of virus below current limits of detection

Disk-Diffusion Test

- Method of in vitro testing antibiotic effectiveness.

Antibiotic Resistance

- A variety of mutations can lead to antibiotic resistance.
- Mechanisms of antibiotic resistance
  1.
  2. Prevention of penetration of drug.
  3. Alteration of drug's target site.
  4. Rapid ejection of the drug.
- Resistance genes are often on plasmids or transposons that can be transferred between bacteria
- Misuse of antibiotics selects for resistance mutants. Misuse includes:
  - Using outdated or weakened antibiotics.
  - Using antibiotics for the common cold and other inappropriate conditions.
  -
  - Failure to complete the prescribed regimen.
  - Using someone else's leftover prescription.

The Future of Chemotherapeutic Agents

- Antimicrobial peptides
  - Broad spectrum antibiotics from plants and animals
    - Squalamine (_____)
    - Protegrin (_____)
    - Magainin (_____)

- Antisense agents
  - Complementary DNA or peptide nucleic acids that binds to a pathogen's virulence gene(s) and prevents transcription.

Study Objectives

1. Define: chemotherapy, antimicrobial drug, antibiotic, selective toxicity, broad spectrum, narrow spectrum, bacteriocidial, and bacteriostatic.

2. Describe how antibacterial drugs inhibit/attack cell walls, membranes, protein synthesis, nucleic acid synthesis and give at least 2 examples.

3. Describe the mechanism of inhibition of sulfa drugs.

4. What organisms are killed by the following drugs: Polyenes, Miconazole.

5. Describe the antiviral activity of acyclovir, AZT, and protease inhibitors.

6. Describe the 4 mechanisms of antibiotic resistance.

7. Explain how the misuse of antibiotics selects for resistance mutants.