Chapter 33 Lecture Notes: Antimicrobial therapy

I. Chemotherapy

A. Definitions

1. Chemotherapy = treatment of a disease by a chemical compound selectively directed against invading microbes or abnormal cells
2. Antibiotic = a microbial product or its derivative that kills or inhibits growth of a susceptible organism
3. Antimicrobial = any agent that kills or inhibits growth of a susceptible organism

B. History

1. early 1900s: Paul Erlich -Concepts of magic bullet and selective toxicity
2. Duchesne (1896) and Fleming (1928) and Florey and Chain (1939) – penicillin
3. 1935: Gehard Domagk - sulfa drugs
4. 1944: Waksman - streptomycin

II. General characteristics of antimicrobial drugs

A. Selective toxicity – agent must kill or inhibit microbe while damaging the host as little as possible

1. balance between the
   a) therapeutic dose – drug level required for therapeutic treatment of an infection
   b) toxic dose – drug level that is toxic to host
2. therapeutic index – ratio of toxic dose to therapeutic dose (larger the number = better)

B. Range of effectiveness

1. Narrow-spectrum
2. Broad-spectrum

C. Classes based on target organisms that it effects

D. Cidal vs. static

III. Levels of activity of an antimicrobial drug

A. Values expressed as:

1. MIC (minimal inhibitory concentration) - lowest concentration of drug that prevents growth
2. MLC (minimal lethal concentration) - lowest concentration of drug that kills microbe

B. Tests for determining antimicrobial activity

1. Dilution susceptibility test - dilute antibiotic in 2-fold intervals and test for MIC
2. Disk diffusion test – see lab #10, Fig. 33-1, 33-2

3. Drug concentration in blood/body – via a variety of tests; important for verifying agent has reached blood or other bodily areas in therapeutic concentrations

C. Factors that influence effectiveness
   1. mode of administration
      a) oral – must survive acid
      b) topical
      c) parenteral – non-oral administration (i.e. injection)
   2. access of site of infection
   3. stability in body
   4. susceptibility of pathogen
   5. MIC – levels of drug at site must exceed MIC

IV. Mechanisms of action of antibacterial drugs

A. Cell wall synthesis inhibition
   1. Penicillins
      a) derivatives of 6-aminopenicillanic acid (ß-lactam ring is important structure) (Fig. 33-7)
      b) mechanism of action:
         (1) analogue of D-alanyl-D-alanine on peptide side chain of peptidoglycan → inhibits transpeptidase from crosslinking peptidoglycan
         (2) binds penicillin binding proteins → activation of autolysins
      c) bactericidal
      d) effective against gram + and gram -, depending on derivative
   2. Cephalosporins
      a) derivatives of 7-aminocephalosporanic acid (Fig. 33-8)
      b) similar mechanism of action as penicillins
      c) bactericidal
      d) broad spectrum
   3. Bacitracin
      a) peptide
      b) mechanism of action: inhibits dephosphorylation of bactoprenol pyrophosphate
      c) bactericidal
      d) mostly effective against gram +
   4. Vancomycin
      a) glycopeptide
      b) mechanism of action: prevents crosslinking of peptidoglycan by binding to the D-ala-D-ala portion of the cell wall precursor
      c) bactericidal
      d) gram +

B. Disruption of cell membranes
   1. see fungal drugs
   2. polymyxin B

a) basic polypeptides that act as detergents
b) mechanism of action: interact with phospholipids to increase permeability and decrease osmotic integrity → leakage on intracellular components
c) bactericidal
d) gram –

C. Interference with metabolism: Antimetabolites

Sufadrugs (sulfonamides)

a) structural analogues of p-aminobenzoic acid (Fig. 33-3, 33–4)
b) mechanism of action: competes with p-aminobenzoic acid for binding to the enzyme dihydropteroate synthetase → no folic acid synthesis → no nitrogenous base synthesis
c) bacteristatic
d) broad spectrum

D. Protein synthesis inhibition

1. Tetracycline
   a) 4-ring structure with side chains (Fig. 33-9)
   b) mechanism of action: reversible binding to the 30s subunit of ribosome → inhibits binding of aminoacyl tRNA to ribosome → inhibition of protein synthesis
   c) bacteriostatic
   d) broad spectrum
2. Aminoglycosides (streptomycin, kanamycin, gentamicin)
   a) group of antibiotics in which contain amino sugars and a cyclohexane ring (Fig. 33-10)
   b) mechanism: irreversible binding to the 30s subunit of ribosome → inhibits protein synthesis and causes misreading of mRNA
   c) bactericidal
   d) some are broad spectrum but mostly used against gram negatives
3. Macrolides (erythromycin)
   a) 12-22 carbon lactone ring linked to sugars (Fig. 33-11)
   b) mechanism (erythromycin): reversibly binds 23s rRNA of 50s subunit of the ribosome → inhibits translocation during protein synthesis
   c) bacteriostatic
   d) mostly gram +
4. Chloramphenicol
   a) Fig. 33-12
   b) mechanism: binds to 23S rRNA of 50s subunit of the ribosome → inhibits transpeptidation during protein synthesis
   c) bacteriostatic
   d) broad spectrum

E. Inhibition of nucleic acid synthesis

1. quinolones and fluoroquinolones

a) characterized by quinolone ring (Fig. 33-5)
b) mechanism of action: inhibits DNA gyrase → inhibition of DNA replication (Fig. 33-6)
c) bactericidal
d) broad spectrum

2. rifampin
a) macrocyclic compound
b) mechanism of action: inhibits RNAP → inhibition of RNA synthesis
c) bactericidal
d) mostly gram +, some gram negatives

V. Mechanisms of action of antifungal drugs
A. Selective toxicity problem
B. Polyenes
1. mechanism of action: inhibit synthesis of or interact with ergosterol → causes membrane permeability
2. fungicidal
C. Imidazoles
1. mechanism of action: disrupt fungal membrane synthesis and inhibit sterol synthesis
2. fungicidal
D. Others

VI. Mechanisms of action of antiviral drugs
A. Selective toxicity problem
B. Mechanisms of action based upon blocking critical steps in the virus life cycle

VII. Antimicrobial resistance
A. Molecular mechanisms
1. decreased drug accumulation
a) Prevention of entrance of drug into the cell
b) Pumping drug out of cell
2. enzymatic detoxification
3. bypass of antibiotic resistance step
4. altered target site
B. Origins of resistance
1. Inheritance from mother cell
2. Spontaneous mutation
3. Acquisition of plasmid (R plasmid) or transposon or phage with drug resistance gene
a) via conjugation or transformation (plasmid)
b) via transduction (phage)
C. Solutions
1. Effective use of antibiotics

    a) only for appropriate infections
    b) dual antibiotics
    c) completion of treatment
    d) narrow spectrum
2. Drug discovery
3. Rational drug design