Take Two and Call Me In the Morning
Drugs, Microbes, Host - The Elements of Chemotherapy

Antibiotics

- Naturally occurring antimicrobials
  - Metabolic products of bacteria and fungi
  - Reduce competition for nutrients and space
- Bacteria
  - *Streptomyces, Bacillus*
- Molds
  - *Penicillium, Cephalosporium*

Selective Toxicity

- Drugs that specifically target microbial processes, and not the human host cellular processes.

Cell wall synthesis

- Bactericidal
- Cycloserine – inhibits the formation of the basic peptidoglycan subunits
- Vancomycin – hinders peptidoglycan elongation
- Penicillin and cephalosporins – binds and blocks peptidases involved in cross-linking the glycan molecules

Nucleic acid synthesis

- Chloroquine – binds and cross-links the double helix
- Other quinolones – inhibits DNA unwinding enzymes
- Viruses
  - Azidothymidine (AZT)
  - Analogs of purines and pyrimidines

Protein synthesis

- Aminoglycosides (streptomycin, gentamycin)
  - Binds the 30S ribosome
  - Misreads mRNA
- Tetracyclines
  - Blocks attachment of tRNA
- Chloramphenicol
  - Binds to the 50S ribosome
  - Prevents peptide bond formation

Cell membrane

- Polymyxins
  - Interact with membrane phospholipids
  - Distorts the cell surface
  - Leakage of proteins and nitrogen bases
- Anti-fungal

  - Amphotericin B
  - Forms complexes with sterols in the membrane
  - Leakage
  - Can affect human cell membranes (toxicity)

Folic acid synthesis

- Sulfonamides (sulfa drugs) and trimethoprim
  - Analogs
  - Competitive inhibition
  - Prevents the metabolism of DNA, RNA, and amino acid

Penicillin

- *Penicillin chrysogenum*
- A diverse group (1st, 2nd , 3rd generations)
  - Natural (penicillin G and V)
  - Semisynthetic (ampicillin)
- Structure
  - Thiazolidine ring
  - *Beta-lactam* ring
  - Variable side chain (R group)

- Resistance – if bacteria contain penicillinases
- Inhibits cell wall synthesis
- Treat streptococci, meningococci, and spirochete infections

Cephalosporin

- *Cephalosporium acremonium* (mold)
- Widely administered today
  - Diverse group (natural and semi-synthetic)
- Structure
  - similar to penicillin except
    - Main ring is different
    - Two sites for R groups

- Resistant to most pencillinases
- Broad-spectrum – inhibits cell wall synthesis
- 3rd generation drugs used to treat enteric bacteria, respiratory, skin, urinary and nervous system infections

Aminoglycosides

- *Streptomyces* and *Micromonospora*
- Structure
  - Amino sugars and an aminocyclitol ring
- Broad-spectrum
- Commonly used to treat bubonic plague and sexually transmitted diseases
- Inhibits protein synthesis

Tetracycline

- *Streptomyces*
- Structure
  - Diverse
  - complex series of rings
- Broad spectrum and low cost
- Commonly used to treat sexually transmitted diseases
- Side effects – gastrointestinal disruption
- Inhibits protein synthesis

Chloramphenicol

- *Streptomyces*
- Structure - nitrobenzene structure
- Broad-spectrum
- Only made synthetically today
- Treat typhoid fever, brain abscesses
- Side effects – Toxicity leading to aplastic anemia
- Inhibits protein synthesis

Erythromycin

- *Streptomyces*
- Structure – macrolide ring
- Broad-spectrum
- Commonly used as prophylactic drug prior to surgery
- Side effects - low toxicity
- Inhibits protein synthesis

Sulfonamides (sulfa drugs)

- Synthetic drug
- Based on sulfanilamides
- Used in combination with other synthetics such as trimethoprim
- Commonly used to treat pneumonia in AIDS patients
- Inhibits folic acid synthesis

Polyenes

- Antifungal
- Structure – large complex steroidal structure
- Some toxicity to humans
- Commonly used for skin infections
- Targets the membrane - lost of selective permeability

Other types of antimicrobials

- Antiprotozoan – metronidazole
  - Treat giardia
- Antimalarial – Quinine

  - malaria
- Antihelminthic – mebendazole
  - Tapeworms, roundworms

Antiviral

- Limited drugs available
- Difficult to maintain selective toxicity
- Effective drugs – target viral replication cycle
  - Entry
  - Nucleic acid synthesis
  - Assembly/release
- Interferon – artificial antiviral drug

New approaches

- Increase drug resistance requires new approaches for developing effective antimicrobials
  - Prevent iron –scavenging capabilities
  - Inhibit genetic controls (riboswitches)
  - Probiotics and prebiotics

Drug and Host Interaction

- Toxicity to organs
- Allergic reactions
- Suppress/alter microflora
- Effective drugs

Effective drugs

- Identify infectious agent
- Sensitivity testing
- Minimum Inhibitory Concentration (MIC)