Drugs and Microbes

"Early" Antimicrobial Drugs
- Arsenic - Ehrlich
- Silver nitrate - Creede
- Sulfonamide - Dye Industry
- Penicillin - Fleming

Antibiotics
- Substances produced by organisms that inhibit or kill other organisms
- Can be broad range or very specific
- Resistance to many in their native form occurs naturally; synthetic derivatives may circumvent this temporarily

Targeting of Drugs to Microbes
- Antimicrobial drugs should be selectively toxic - drugs should kill or inhibit microbial cells without simultaneously damaging host tissues
- As the characteristics of the infectious agent become more similar to the vertebrate host cell, complete selective toxicity becomes more difficult to achieve and more side effects are seen!

Targets of Drug Action
- Cell wall synthesis
- Cell membrane structure/function
- Protein synthesis
- DNA/RNA functions
Cell Wall Drugs
- Penicillin and derivatives (derivatives have broader activity towards Gram -)
- Cephalosporins
- Monobactams
- Vancomycin

Cell Membrane Agents
- Polymixin is most widely used

Protein Synthesis Blocks
- Tetracycline
- Chloramphenicol
- Erythromycin
- Clindamycin

Nucleic Acid Metabolism Agents
- Sulfonamide derivatives block nucleotide synthesis
- Rifampin blocks mRNA synthesis
- Ciprofloxacin inhibits DNA replication

Agents to Treat Eukaryotic Pathogens
- Fungi – amphotericin, miconazole, flucytosine, Nikkomycin Z (in trials)
- Malaria – quinine, chloroquine, primaquine, mefloquine, artemisinin
- Protozoans – metronidazole, quinocide, sulfonamides
Antivirals
- Uptake blockers – Amantidine, Tamiflu
- Nucleic acid synthesis inhibitors – Acyclovir, AZT
- Assembly inhibitors – Saquinavir
- Interferons - human-based glycoproteins produced primarily by fibroblasts and leukocytes; reduce healing time and some complications of infections

Antibiotic Resistance: an Evolutionary Response to Selective Pressure

Some Forms of Resistance
- Detoxification
- Genetic alteration of target
- Reduced uptake
- Active efflux

A few Antibiotics and their Detoxification Enzymes
- Ampicillin – β-lactamase
- Chloramphenicol – Chloramphenicol Acetyl Transferase
- Neomycin – Neomycin Phosphotransferase

Genetic Alteration of Target
Tetracycline and erythromycin resistance can be conferred by alterations in ribosomal components

Reduced Uptake
Resistance to methicillin has been reported as the result of a mutation in the mec gene product causing it to poorly bind methicillin
Active Efflux

Resistance to multiple antibiotics has been reported as the result of an energy-requiring pump protein.

Antibiotic Resistance is Genetically Determined

Mechanisms by Which Bacteria Acquire New DNA

- Transformation – cells pick up DNA in their environment
- Conjugation – one bacteria directly transfers DNA to another
- Transduction – a defective virus transfers DNA from one bacteria to another

Antibiotic Resistance as a Public Health Problem

There are strains of most pathogenic bacteria which are resistant to nearly all conventional antibiotics.

How did this problem occur?

- Over-prescription of antibiotics
- Failure in patient compliance
- Non-targeted uses in agriculture
Possible Solutions

- Develop new antibiotics that counter resistance or attack other pathways
- Target the resistance mechanisms
- Appropriate prescribing procedures for currently effective antibiotics
- Combinatorial therapy
- Educate patients in proper use
- Limit use in meat and fruit production

Host Reactions to Drug Therapy

~5% of population experiences an adverse reaction to an antimicrobial

Some Types of Adverse Reactions

- Organ/tissue toxicity
- Allergic reactions
- Superinfection after loss of normal GI flora

Factors to Consider in Antimicrobial Therapy

- Nature of the organism
- Degree of microbe's susceptibility to a range of drugs; may need in vitro testing
- Patient's condition

The Kirby-Bauer Disk-Diffusion System Assesses Microbial Susceptibility and Gives an Estimate of Minimum Inhibitory Concentration

KB Disc System

- Plate lawn of test bacteria
- Add antibiotic discs with range of doses
- Incubate
- Look for zones of clearing around discs
- Disc with minimum concentration of antibiotic that produces clearing is MIC
Therapeutic Index

Ratio of toxic dose to minimum effective dose