Chapter 12

Topics:
- Antimicrobial Therapy
- Selective Toxicity
- Survey of Antimicrobial Drug
- Microbial Drug Resistance
- Drug and Host Interaction

Antimicrobial Therapy

- Ideal drug
- Terminology
- Antibiotics

An ideal antimicrobial:
- soluble in body fluids,
- selectively toxic,
- nonallergenic,
- reasonable half life (maintained at a constant therapeutic concentration)
- unlikely to elicit resistance,
- has a long shelf life,
- reasonably priced.

There is no ideal antimicrobial

Selective Toxicity - Drugs that specifically target microbial processes, and not the human host’s.

Chemotherapy is the use of any chemical agent in the treatment of disease.

A chemotherapeutic agent or drug is any chemical agent used in medical practice.

An antibiotic agent is usually considered to be a chemical substance made by a microorganism that can inhibit the growth or kill microorganisms.

An antimicrobial or antimicrobial agent is a chemical substance similar to an antibiotic, but may be synthetic.

Antibiotics

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

Spectrum of antibiotics and targets

[Diagram showing various antibiotics and their targets]
5 General Mechanisms of Action for Antibiotics

- Inhibition of Cell Wall Synthesis
- Disruption of Cell Membrane Function
- Inhibition of Protein Synthesis
- Inhibition of Nucleic Acid Synthesis
- Anti-metabolic activity

Cell wall synthesis

- Bactericidal
- Vancomycin – hinders peptidoglycan elongation
- Penicillin and cephalosporins – binds and blocks peptidases involved in cross-linking the glycan molecules

Affect cell wall synthesis

Penicillin – Figure 13.11

Penicillin G - drug of choice for streptococci, meningococci, pneumococci, spirochetes, clostridia, aerobic gram-positive rods, treponemes - administered parenterally - other than by mouth - why?

Penicillin V, ampicillin or other analogues may be used for oral administration

Cephalosporins - similar to penicillins
Penicillin

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

Penicillin continued

- Resistance – if bacteria contain penicillinases - β-lactamase
- Inhibits cell wall synthesis
- Effective against Gram+ bacteria

Cephalosporin - beta lactam

- *Cephalosporium acremonium* (mold)
- Widely administered today
  - Diverse group (natural and semisynthetic- 4th generation!)
- Structure
  - similar to penicillin except
    - Main ring is different
    - Two sites for R groups

Cephalosporin continued...

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

- Chloroquine – binds and cross-links the double helix
- Other quinolones – inhibits DNA unwinding enzymes (gyrase) and block replication. Ciprofloxacin is an example
- Viruses
  - Analogs of purines and pyrimidines - sometimes considered antimetabolites

Rifampin - blocks transcription - can cause red man syndrome - a result of accumulation of metabolic products of the antimicrobial in secretions

“Red Man Syndrome”

Mostly seen with anti-viral agents

Examples of different antibiotics and their sites of inhibition on the prokaryotic ribosome
Protein synthesis

- **Aminoglycosides**
  - Binds the 30S ribosome
  - Misreads mRNA
- **Tetracyclines**
  - Binds the 30S ribosome
  - Blocks attachment of tRNA to A site
- **Chloramphenicol**
  - Binds to the 50S ribosome
  - Prevents peptide bond formation

Aminoglycosides

- **Streptomycyes and Micromonospora**
- Broad-spectrum
- Commonly used to treat bubonic plague and sexually transmitted diseases
- Inhibits protein synthesis - bind 30S ribosomal subunit

Tetracycline

- **Streptomycyes**
- Broad spectrum and low cost
- Commonly used to treat sexually transmitted diseases
- **Side effects** – gastrointestinal disruption, deposition in hard tissues
- Inhibits proteins synthesis - Binds the 30S ribosome and blocks attachment of tRNA

Chloramphenicol

- **Streptomycyes**
- Broad-spectrum
- Only made synthetically today
- Treat typhoid fever, brain abscesses
- **Side effects** – aplastic anemia
- Inhibits protein synthesis - binds 50S ribosome subunit - prevents peptide bond formation

Erythromycin

- **Streptomycyes**
- **Structure** – macrolide ring
- Broad-spectrum
- Commonly used as prophylactic drug prior to surgery
- **Side effects** - low toxicity
- Inhibits protein synthesis - bind to 50S ribosome subunit - prevents translocation
Cell membrane

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

- **Anti-fungal - Polyenes**
  - Amphotericin B and Nystatin - bind to sterols on cells membranes.

Polyenes

- Antifungal
- Commonly used for skin infections
- Targets the membrane - loss of selective permeability
- Polyenes – Amp B and Nystatin
- Amphotericin B - binds to ergosterol found in fungi and protozoa, but not in human cells - increases membrane permeability
- Side effects are numerous due to toxicity of the drug

ANTIMETABOLITES

Act either through competitive inhibition or erroneous incorporation – molecular mimicry

**Sulfonamides** - block synthesis of folic acid - and as a result, nucleic acid synthesis

Isoniazid - antimetabolite for two vitamins

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

The mode of action of sulfa drug

Other types of antimicrobials

- **Antiprotozoan** – metronidazole - most are fairly toxic - black hairy tongue
  - Treat Giardia and amebiasis
- **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

**Antimicrobial Resistance**

- Resistance factors – R plasmids
- 5 main mechanisms of resistance
- New approaches

**5 Mechanisms of Resistance**

1) Alteration of Targets – usually affects ribosomes
2) Alteration of Membrane Permeability - Change in the receptor that binds the drug
3) Development of Enzymes – β-lactamase
4) Efflux pumps – Membrane proteins many Gram negatives that pump out drug
5) Alteration of Metabolic Pathway – Development of alternate pathway

**Examples of mechanisms of acquired drug resistance**

- β-lactamase
- Membrane permeability
- Efflux pumps
- Alter targets
- Alternate metabolism

**Demonstration of how natural selection enables resistant strains to become dominant**
Human Misuse of Antibiotics!!!

Limiting Resistance

1) Constant exposure to high levels of antibiotic
2) Use of multiple antibiotics
3) Restricted use of antibiotics

New approaches

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

Drug and Host Interaction

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

Main Types of Side Effects Associated with Antimicrobial Treatment

1) Toxicity
2) Allergy – actual drug or breakdown products
3) Disruption of Normal Microflora
   Can Lead to SUPERINFECTIONS!!
Development of disease following broad spectrum antimicrobial therapy

Pseudomembranous colitis (antibiotic associated diarrhea) - often caused by Clostridium difficile

Yeast infection – after broad antibiotic use to treat UTI caused by *E. coli*

Effective drugs

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

An example of the Kirby-Bauer Test

The E-test is an alternative to the Kirby-Bauer procedure
Antimicrobics have helped us deal with disease, but on the other hand, improper use of antimicrobics have created new difficulties.