Chapter 12

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

Antimicrobial Therapy

- **Ehrlich (1900’s)** – compound 606 to treat syphilis. Coined the term “selective toxicity”
- **Fleming (1928)** – discovered penicillin
- **Domagk (1930s)** – “prontosil” was modified in the body to an active compound (first sulfa drug!)

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.

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

The mechanism of action for different antimicrobial drug targets in bacterial cells

Cell wall synthesis

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

The mechanism of cell wall inhibition by penicillins and cephalosporins

Antibiotics weaken the cell wall, and cause the cell to lyse.

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?
- Not absorbed in the intestines!!!
- Penicillin V, ampicillin or other analogues may be used for oral administration
Penicillin

- *Penicillium 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 penicillins - \(\beta\)-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 penicillinas
- Broad-spectrum – inhibits cell wall synthesis
- 3rd generation drugs used to treat enteric bacteria, respiratory, skin, urinary and nervous system infections

II. 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

(a) purine
(b) purine analog
(c) pyrimidine
(d) pyrimidine analog

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

III. Protein synthesis

- Aminoglycosides
  - Binds the 30S ribosome → changes shape
  - 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

- Streptomyces and Micromonospora
- Broad-spectrum
- Commonly used to treat bubonic plague and sexually transmitted diseases
- Inhibits protein synthesis - binds 30S ribosomal subunit misreading of mRNA
Tetracycline

- *Streptomycetes*
- 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

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

Erythromycin

- *Streptomycetes*
- 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**

IV. 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.
  - Potentially toxic to humans!!

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
V. 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

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**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

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**The mode of action of sulfa drug**

The drug inhibits the synthesis of folic acid by interfering with the synthesis of dihydropteroic acid, a precursor to folic acid. This prevents the synthesis of nucleic acids, which is essential for the growth of the bacteria.

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**Other types of antimicrobials**

- **Antiprotozoan** – metronidazole - most are fairly toxic - black hairy tongue
  - Treat Giardia and amebiasis
- **Antimalarial** – Chlorquinine
  - malaria
- **Antihelminthic** – mebendazole
  - Tapeworms, roundworms

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**Flagyl**

*Figure 13.14. Black hairy tongue, a reaction to the drug metronidazole (Flagyl). The papillae on the tongue surface become elongated and filled with breakdown products of hemoglobin, which darken the tongue.*

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**Antiviral**

- Limited drugs available
- Difficult to maintain selective toxicity
- Effective drugs – target viral replication cycle (DNA Polymerase or RT in HIV)
  - Entry
  - Nucleic acid synthesis
  - Assembly/release (Amantidine – influenza)
- **Interferon** – artificial antiviral drug
Antimicrobial Resistance

- Resistance factors – R plasmids
  - Transformation, Conjugation, Transduction
  - Transposons
- 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

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 (synergism)
  - Phage therapy

Human Misuse of Antibiotics!!!

BAD!!!

GOOD!!!

Antibiotics!!!

β-lactamase

End of successful treatment
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
Antimicrobics have helped us deal with disease, but on the other hand, improper use of antimicrobics have created new difficulties.