Chapter 12
The Elements of Chemotherapy

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

Antimicrobial Therapy

Ideal drug:
- selectively toxic (specifically target microbial processes)
- microbicidal (not microbistatic)
- soluble and functional when diluted
- long acting (not removed or broken down too quickly)
- no resistance development
- works together with body defenses
- easily delivered to site
- $$$$
- no allergies or predisposition to other diseases

Terms Related to Chemotherapy

<table>
<thead>
<tr>
<th>TABLE 12.2</th>
<th>Terminology of Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapeutic drug</strong></td>
<td>Any chemical used in the treatment, relief, or prevention of disease</td>
</tr>
<tr>
<td><strong>Prophylaxis</strong></td>
<td>Use of a drug to prevent a disease</td>
</tr>
<tr>
<td><strong>Antimicrobial chemotherapy</strong></td>
<td>Use of drugs to control infection</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td>Naturally produced by the natural microbe, process or organism that can inhibit or destroy other microorganisms</td>
</tr>
<tr>
<td><strong>Semisynthetic drugs</strong></td>
<td>Drugs which are chemically modified or elaborated in the laboratory after being isolated from natural sources</td>
</tr>
<tr>
<td><strong>Synthetic drugs</strong></td>
<td>The use of chemical reactions to synthesize antimicrobial compounds in the laboratory</td>
</tr>
<tr>
<td><strong>Narrow spectrum (labeled spectrum)</strong></td>
<td>Antibacterial effective against a limited array of microorganisms, examples: drugs effective against green-pseudococcus bacteria, effective against a single type of microorganism for example, a drug effective against both gram-positive and gram-negative bacteria</td>
</tr>
<tr>
<td><strong>Broad spectrum (unlabeled spectrum)</strong></td>
<td>Include a broad range of microorganisms, examples: penicillin, effective against a wide variety of microorganisms, gram-negative bacteria</td>
</tr>
</tbody>
</table>

Antibiotics

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

- Mechanism of action
- Bacterial cell wall
- Nucleic acid synthesis
- Protein synthesis
- Cell membrane
- Folic acid synthesis

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
  - Asidothymidine (AZT)
  - Analogs of purines and pyrimidines

Protein synthesis

- Aminoglycosides
  - 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
- Anit-fungal
  - Amphoterin B
  - Forms complexes with sterols in the membrane
  - Leakage
  - Can affect human cell membranes (toxicity)
Folic acid synthesis

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

Survey of Antimicrobial Drugs

- Penicillin
- Cephalosporins
- Streptomycin
- Tetracycline
- Sulfomides
- Polyenes
- Antiviral
Chemotherapeutic agents to treat infectious fungal and protozoan diseases

Chemotherapeutic agents used to treat infectious helminthic and viral diseases

### 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)

- **Penicillin (cont.)**
  - 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 semisynthetic)
- Structure
  - Similar to penicillin except
    - Main ring is different
    - Two sites for R groups

Cephalosporin (cont.)

- 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

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
Streptomycin structure - amino sugars and 6-carbon ring (aminocyclitol) = characteristics of streptomycin

Streptomyces:
synthesizes many different antibiotics such as aminoglycosides, tetracycline, chloramphenicol, and erythromycin.

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 proteins synthesis

Chloramphenicol
- *Streptomyces*
- Structure - nitrobenzene structure
- Broad-spectrum
- Only made synthetically today
- Treat typhoid fever, brain abscesses
- Side effects – 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

Versatility of sulfonamides
(due to different R groups attached to main structural nucleus)
Polyenes

- Antifungal
- Structure - large complex steroidal structure
- Include polyenes, azoles, and flucytosine
- Some toxicity to humans
- Commonly used for skin infections
- Targets the membrane - loss of selective permeability

Other 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

Antiviral drug structures and their mode of action
Antimicrobial Resistance

- Resistance factors
- New enzymes
- Permeability
- Alter receptors
- Change metabolic patterns
- Natural selection
- New approaches

Spread of resistance factors
Mechanisms commonly associated with drug resistance

Resistance natural selection enables resistant strains to become dominant

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
Tetracycline treatments can cause teeth discoloration.

Disrupting the microflora in the intestine can result in superinfections.

Effective drugs

- Identify infectious agent
- Sensitivity testing (Kirby-Bauer, E-test)
- Minimum Inhibitory Concentration (MIC) → The lower the MIC, the more effective the drug is toward combating the bacterium.
Sensitivity tests like Kirby-Bauer Test can determine drug effectiveness by zone of inhibition.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptibility (%)</th>
<th>Resistance (%)</th>
<th>Actual Result (mm) for Staphylococcus aureus</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>&gt;10</td>
<td>&lt;32</td>
<td>15</td>
<td>S</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>&gt;30</td>
<td>&lt;32</td>
<td>20</td>
<td>S</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>&gt;30</td>
<td>&lt;32</td>
<td>15</td>
<td>I</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;30</td>
<td>&lt;32</td>
<td>16</td>
<td>S</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>&gt;30</td>
<td>&lt;32</td>
<td>20</td>
<td>S</td>
</tr>
<tr>
<td>Neomycin</td>
<td>&gt;30</td>
<td>&lt;32</td>
<td>12</td>
<td>R</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>&gt;30</td>
<td>&lt;32</td>
<td>10</td>
<td>R</td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>&gt;30</td>
<td>&lt;32</td>
<td>10</td>
<td>R</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>&gt;30</td>
<td>&lt;32</td>
<td>11</td>
<td>R</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>&gt;30</td>
<td>&lt;32</td>
<td>15</td>
<td>S</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>&gt;30</td>
<td>&lt;32</td>
<td>25</td>
<td>S</td>
</tr>
</tbody>
</table>

R = resistant, I = intermediate, S = sensitive

The dilution test - an effective method of determining the MIC.

The lower the MIC, the more effective the drug is in combating the bacterium.

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Penicillin G</th>
<th>Ampicillin</th>
<th>Sulfamethoxazole</th>
<th>Tetracycline</th>
<th>Cefalexin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>4.0</td>
<td>0.05</td>
<td>3.0</td>
<td>0.3</td>
<td>4.0</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
<td>5.6</td>
<td>1.6</td>
<td>10.0</td>
<td>0.3</td>
<td>40.0</td>
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<tr>
<td>Neisseria gonorrhoea</td>
<td>0.15</td>
<td>0.3</td>
<td>5.0</td>
<td>0.8</td>
<td>2.0</td>
</tr>
<tr>
<td>E. coli</td>
<td>10.0</td>
<td>12.0</td>
<td>3.0</td>
<td>6.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>&gt;30.0</td>
<td>&gt;30.0</td>
<td>NA</td>
<td>&gt;10.0</td>
<td>NA</td>
</tr>
<tr>
<td>Salmonella species</td>
<td>2.0</td>
<td>4.0</td>
<td>3.0</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>0.36</td>
<td>NA</td>
<td>NA</td>
<td>3.0</td>
<td>12.0</td>
</tr>
</tbody>
</table>

*Not = not available*