Chemical Control Methods

Chemotherapy
The Spectrum of Antimicrobial Activity

• = range of organisms affected by a drug

• Broad spectrum antibacterial drug affects both gram + and gram – organisms

• Narrow spectrum drug affects one or the other

• See table 20.2
Table 20.2  The Spectrum of Activity of Antibiotics and Other Antimicrobial Drugs

<table>
<thead>
<tr>
<th>Prokaryotes</th>
<th>Eukaryotes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mycobacteria</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
<td><strong>Fungi</strong>&lt;br&gt;Penicillin G&lt;br&gt;Streptomycin&lt;br&gt;Tetracycline&lt;br&gt;Isoniazid</td>
</tr>
<tr>
<td><strong>Gram-Negative Bacteria</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Gram-Positive Bacteria</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Chlamydias, Rickettsias</strong>&lt;sup&gt;†&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

*Growth of these bacteria frequently occurs within macrophages or tissue structures.<br>†Obligately intracellular bacteria.

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Broad vs. Narrow

- advantage of broad spectrum: more likely to affect an unidentified pathogen
- disadvantage of broad spectrum: more damage to beneficial normal flora; greater chance of superinfection (infection by a second pathogen)
- Competition, Predator/Prey Models
Concept of selective toxicity

• the obvious part: a drug must be more toxic to the pathogen than to the host

• HOW? Drug affects some aspect of the pathogen’s physiology that is not part of the host’s physiology
examples: block an enzyme that only the pathogen has; block formation of cell wall (we have none)

• some common actions:
Antimicrobial drugs function in one of the following five ways: inhibiting cell wall synthesis, inhibiting protein synthesis, inhibiting nucleic acid synthesis, injuring the plasma membrane, or inhibiting synthesis of essential metabolites.
1. Inhibitors of Cell Wall Synthesis

<table>
<thead>
<tr>
<th>Natural Penicillins</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G</td>
<td>Against gram-positive bacteria, requires injection</td>
</tr>
<tr>
<td>Penicillin V</td>
<td>Against gram-positive bacteria, oral administration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Semisynthetic Penicillins</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxacillin</td>
<td>Resistant to penicillinase</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Broad spectrum</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Broad spectrum; combined with inhibitor of penicillinase</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>A monobactam; effective for gram-negative bacteria, including Pseudomonas spp.</td>
</tr>
<tr>
<td>Imipenem</td>
<td>A carbapenem; very broad spectrum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cephalosporins</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalothin</td>
<td>First-generation cephalosporin; activity similar to penicillin; requires injection</td>
</tr>
<tr>
<td>Cefixime</td>
<td>Fourth-generation cephalosporin; oral administration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Polypeptide Antibiotics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacitracin</td>
<td>Against gram-positive bacteria; topical application</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>A glycopeptide type; penicillinase-resistant; against gram-positive bacteria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antitubercular Antibiotics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Inhibits synthesis of mycolic acid component of cell wall of Mycobacterium spp.</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Inhibits incorporation of mycolic acid into cell wall of Mycobacterium spp.</td>
</tr>
</tbody>
</table>
cell wall damage by antibiotic

- before antibiotic  after antibiotic
Remember the definition for antibiotic?

- A substance produced by microbes that in small amounts inhibits another microbe
- See table 20.1

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-Positive Rods</strong></td>
<td></td>
</tr>
<tr>
<td><em>Bacillus subtilis</em></td>
<td>Bacitracin</td>
</tr>
<tr>
<td><em>Paenibacillus polymyxa</em></td>
<td>Polymyxin</td>
</tr>
<tr>
<td><strong>Actinomycetes</strong></td>
<td></td>
</tr>
<tr>
<td><em>Streptomyces nodosus</em></td>
<td>Amphotericin B</td>
</tr>
<tr>
<td><em>Streptomyces venezuelae</em></td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td><em>Streptomyces aureofaciens</em></td>
<td>Chlortetracycline and tetracycline</td>
</tr>
<tr>
<td><em>Saccharopolyspora erythraea</em></td>
<td>Erythromycin</td>
</tr>
<tr>
<td><em>Streptomyces fradiae</em></td>
<td>Neomycin</td>
</tr>
<tr>
<td><em>Streptomyces griseus</em></td>
<td>Streptomycin</td>
</tr>
<tr>
<td><em>Micromonospora purpurea</em></td>
<td>Gentamicin</td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td></td>
</tr>
<tr>
<td><em>Cephalosporium</em> spp.</td>
<td>Cephalothin</td>
</tr>
<tr>
<td><em>Penicillum griseofulvum</em></td>
<td>Griseofulvin</td>
</tr>
<tr>
<td><em>Penicillum chrysogenum</em></td>
<td>Penicillin</td>
</tr>
</tbody>
</table>
Penicillin as an example

(a) Natural penicillins

Penicillin G (requires injection)

Penicillin V (can be taken orally)

(b) Semisynthetic penicillins

Oxacillin:
Narrow spectrum, only gram-positives, but resistant to penicillinase

Ampicillin:
Extended spectrum, many gram-negatives
Penicillinas (beta-lactamases)

- Bacterial enzymes that destroy natural penicillins
- Semisynthetic penicillins are made to resist penicillinas and have a broader spectrum of activity than natural (fungal made) penicillins

![Chemical structures of Penicillin and Penicilloic acid]

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2. Inhibitors of Protein Synthesis

- **Tetracyclines** as the example
  - Broad-spectrum antibiotics produced by *Streptomyces* spp.
  - 70S prokaryotic ribosome that tetracycline targets!
3. Competitive Inhibitors of bacterial enzyme function

- Let’s use sulfonamides (sulfa drugs) as the example
- First synthetic antimicrobial drugs used to treat microbial diseases

![Chemical structures of Sulfanilamide and p-aminobenzoic acid](image)
sulfonamide action

• in bacteria but not in people:

PABA  $\rightarrow$  Folic acid (vitamin)

enzyme: blocked by sulfonamide
Synergism and antagonism

• ___________: = combined effect of two drugs used at same time is greater than the sum of their individual effects: $2 + 2 = 8$ (next slide example)

• ___________: = combined effect of two drugs used at same time is less than the sum of their individual effects: $2 + 2 = 0$
  – E.g. Tetracycline is bacteriostatic and interferes with the action of penicillin….why?
TMP-SMZ : Sulfa drug synergism

1. Sulfamethoxazole, a sulfonamide that is a structural analog of PABA, competitively inhibits the synthesis of dihydrofolate acid from PABA.

2. Trimethoprim, a structural analog of a portion of dihydrofolate acid, competitively inhibits the synthesis of tetrahydrofolate acid.
-cidal vs -static

- cide or -cidal refers to killing, e.g.:
- stasis or -static refers to inhibition without killing, e.g.
- static effect often adequate: drug slows down pathogen; body defenses clean it up
Susceptibility testing

• done to determine which drugs might control an infection

• several methods. This is the Kirby-Bauer disk-diffusion method:
Kirby-Bauer: test to guide chemotherapy

Petri plate with pure culture of pathogen:

[Image of a Petri plate with antibiotic sensitivity test zones labeled A to G, showing a zone of inhibition around a susceptibility disk]
• Results reported as:
  – ___ (sensitive) = drug worked well
  – ___ (intermediate) or MS (moderately susceptible) = drug worked a little
  – ___ (resistant) = drug did not affect organism

• Simple and inexpensive but has limitations
Which Drug is the **most** effective?
A)  
B)  
C)  
D)  
E)
Which drug is NOT effective?
B)
C)
D)
E)
In general the bacteria growing on this plate are:
To drug “A”
A) S  
B) R  
C) I
Drug Resistance

• pathogen is not affected by a drug
  – opposite of susceptibility (a drug affects a pathogen)

• develops with every class of pathogen

• it is the PATHOGEN that changes: not the drug and not the host
  – we (hosts) may develop an allergy, but not a drug resistance
Drug resistance develops in the

• Pathogen

• The lack of susceptibility of a microbe to a chemotherapeutic agent
How Drug Resistance Develops

• a. selection & evolution: every time a drug dosage kills less than 100%, the survivors are the most drug resistant individuals (re: genetic variability in initial population)
• b. pathogen changes (mutations) so it is not affected by the drug
  – develops a way to inactivate the drug, such as penicillinase (beta-lactamase)
  – prevents the drug from reaching its target site within the pathogen
  – blocks entry of the drug into the cell
  – target site changes, e.g. a new enzyme appears that does same job but is not affected by the drug
  – Rapid efflux (ejection), which pumps the drug out of the cell before it can become effective
• If you are given an antibiotic and you do NOT finish taking your prescribed dosage of the antibiotic, which of the following is most likely to happen?
  
  A) That antibiotic will not be as effective for fighting future infections because you body will have adapted to the drug.
  
  B) That antibiotic will not be as effective in several weeks against that same infection (should you relapse) because the bacteria will be more resistant to the drug.
  
  C) The normal flora of microbes are more likely to evolve and become pathogens because of competition that results from stopping a drug before the initial infection was destroyed.
  
  D) Nothing will happen. As long as you are feeling better at the time in which you stop taking your antibiotic, your infection will be gone.
The four main mechanisms of microbial resistance to antimicrobial agents are blocking entry of the drug into the cell, inactivation of the drug by enzymes, alteration of the drug’s target sites, and efflux of the drug from the cell.
• c. recombination: drug resistance genes travel from pathogen to pathogen
Development of an antibiotic-resistant mutant during antibiotic therapy (fig. 20.21)
How to delay resistance

• probably can’t prevent, only delay resistance
• a. avoid unnecessary or inappropriate drug use
  – unnecessary: using drug for minor infection that the body defenses would clean up
  – inappropriate: using antibacterial drug for a viral infection
• b. when using a drug, use full dosage (to avoid leaving resistant survivors)
• c. in long-term use, rotate drugs
• d. minimize use of antibiotics in animal feed to promote growth