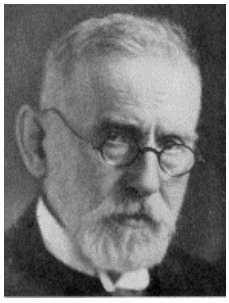
Antimicrobial Drugs

Antimicrobial Drugs

- Chemotherapy: The use of drugs to treat a disease
- Antimicrobial drugs: Interfere with the growth of microbes within a host
- Antibiotic: Substance produced by a microbe that, in small amounts, inhibits another microbe
- Selective toxicity: A drug that kills harmful microbes without damaging the host
  - It is easier to find agents toxic to prokaryotic cells that do not harm eukaryotic hosts than to eukaryotic pathogens (fungi, parasites,etc)

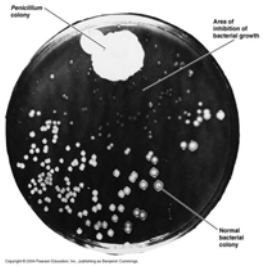
The dawn of antibiotics

- Paul Erlich (1910)
  - Wanted to find the "magic bullet" for syphilis
  - proposed the idea of the blood brain barrier
  - Worked at staining tissues and first to come up with the idea behind "selective toxicity"
  - Nobel Prize in 1908



Alexander Fleming

- A physician who studied bacterial action of blood and antisepsis
- Discovered and named Lysozyme
- Discovered mold growing on an agan plate(1928)
- 1945 Nobel Prize in Physiology or Medicine along with Chain and Florey



Chain and Florey

- 1940 developed a system for growing *Penicillium* and purifying the drug
- Tested the drug in mice, passed all trials
- Received the Nobel Prize in 1945 with Alexander Fleming for their work

Antibiotics

- A substance produced by a microorganism that inhibits or kills other microbes
- Bacteriostatic
- Bacteriocidal

- Theraputic index: toxicity; lowest dose toxic to patient divided by dose used for therapy (if high→less toxic)

Microbes that produce antibiotics

TABLE 20.1 Representative Sources of Antibiotics

Microorganism	Antibiotic
Gram-Positive Rods	
Bacillus subtilis	Bacitracin
Bacillus polymyxa	Polymyxin
Actinomycetes	
Streptomyces nodosus	Amphotericin B
Streptomyces venezuelae	Chloramphenicol
Streptomyces aureofaciens	Chlortetracycline and tetracycline
Streptomyces erythraeus	Erythromycin
Streptomyces fradiae	Neomycin
Streptomyces griseus	Streptomycin
Micromonospora purpureae	Gentamicin
Fungi	
Cephalosporium spp.	Cephalothin
Penicillium griseofulvum	Griseofulvin
Penicillium notatum	Penicillin

Range of activity

- Narrow range: target one group of microbes
- Broad range: target a wide group of different microbes
- Which one is the best?
- Superinfection
  - Clostridia difficile: Antibiotic Associated Colitis
  - Yeast

Spectrum of activity

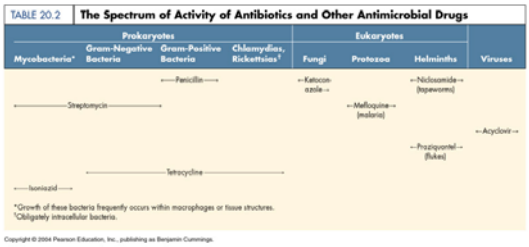


TABLE 20.2 The Spectrum of Activity of Antibiotics and Other Antimicrobial Drugs

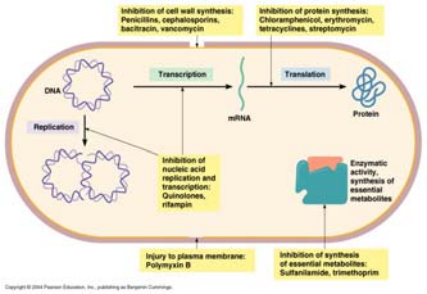
Prokaryotes				Eukaryotes			
Mycobacteria*	Gram-Negative Bacteria	Gram-Positive Bacteria	Chlamydias, Rickettsias†	Fungi	Protozoa	Helminths	Viruses
	←Penicillin→			←Ketoconazole→		←Niclosamide→ (tapeworms)	
←Streptomycin→					←Mefloquine→ (malaria)		←Acyclovir→
						←Praziquantel→ (flukes)	
	←Tetracycline→						
←Isoniazid→							

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

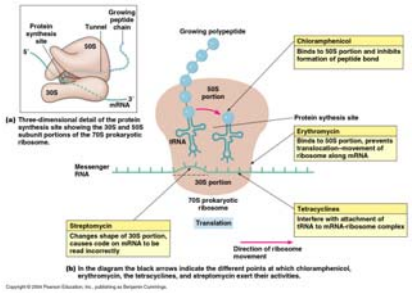
Targets of antibiotics

- Inhibition of cell wall synthesis: peptidoglycan
- Inhibition of protein synthesis: ribosomes
- Injures plasma membrane: changes permeability
- Inhibits nucleaic acid synthesis: interfere with replication and transcription
- Inhibits synthesis of essential metabolites: competitively inhibited by similar substance

Targets of antimicrobial drugs



Some drugs target protein synthesis



(a) Three-dimensional detail of the protein synthesis site showing the 30S and 50S subunit portions of the 70S prokaryotic ribosome.

(b) In the diagram the black arrows indicate the different points at which chloramphenicol, erythromycin, the tetracyclines, and streptomycin exert their activities.

How does penicillin work?

- Inhibits formation of tetrapeptide side chains….which means….
- What happens if you put a cell in a solution with penicillin?

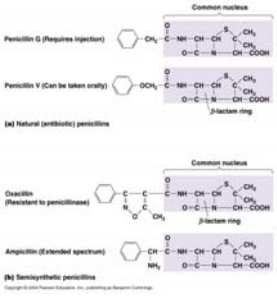
Penicillin weakens the cell wall

(a) (b)

Antibacterial Antibiotics Inhibitors of Cell Wall

- Penicillin
  - Penicilinase-resistant penicillins
  - Extended-spectrum penicillins
  - Penicillins + β-lactamase inhibitors
  - Carbapenems
  - Monobactam

Penicillins



How organisms degrade penicillins

Inhibitors of cell wall synthesis

- Cephalosporins
  - 2nd, 3rd, and 4th gene against gram-negati

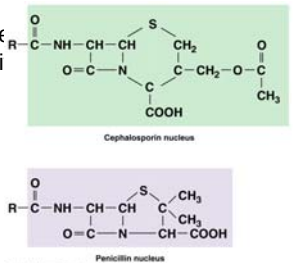


Figure 20.9

Inhibitors of Cell Wall Synthesis

- Polypeptide antibiotics
  - Bacitracin
    - Topical application
    - Against gram-positives
  - Vancomycin
    - Glycopeptide
    - Important "last line" against antibiotic resistant *S. aureus*

Antibiotics for *Mycobacterium*

- Antimycobacterium antibiotics
  - Isoniazid (INH)
    - Inhibits mycolic acid synthesis
  - Ethambutol
    - Inhibits incorporation of mycolic acid

Inhibitors of Protein Synthesis

- Chloramphenicol
  - Broad spectrum
    - Binds 50S subunit, inhibits peptide bond formation
- Aminoglycosides
  - Streptomycin, neomycin, gentamycin
    - Broad spectrum
      - Changes shape of 30S subunit

Inhibitors of Protein Synthesis

- Tetracyclines
  - Broad spectrum
    - Interferes with tRNA attachment
- Macrolides
  - Gram-positives
    - Binds 50S, prevents translocation
- Erythromycin
  - Gram-positives
    - Binds 50S, prevents translocation

Inhibitors of Protein Synthesis

- Streptogramins
  - Gram-positives
    - Binds 50S subunit, inhibits translation
- Synercid
  - Gram-positives
    - Binds 50S subunit, inhibits translation
- Oxazolidinones
  - Linezolid
    - Gram-positives
      - Binds 50S subunit, prevents formation of 70S ribosome

Injury to the Plasma Membrane

- Polymyxin B
  - Topical
  - Combined with bacitracin and neomycin in over-the-counter preparation

Inhibitors of Nucleic Acid Synthesis

- Rifamycin
  - Inhibits RNA synthesis
  - Antituberculosis
- Quinolones and fluoroquinolones
  - Ciprofloxacin
  - Inhibits DNA gyrase
  - Urinary tract infections

Sulfonamides (sulfa drugs)

- First synthetic drugs to treat microbial infections
- Used to treat urinary tract infections (UTIs)
- Combination of trimethoprim and sulfamethoxazole (TMP-SMZ) example of synergism

Competitive Inhibitors

- Sulfonamides (Sulfa drugs)
  - Inhibit folic acid synthesis
  - Broad spectrum

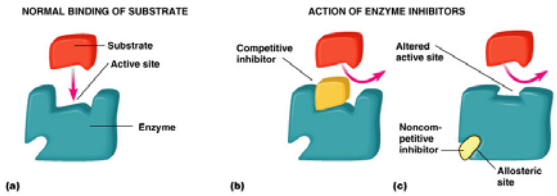
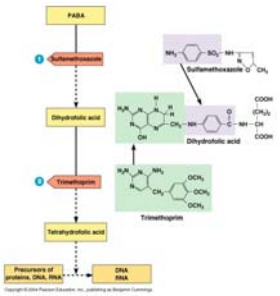


Figure 5.7

TMP-SMZ



Tests for microbial sensitivity

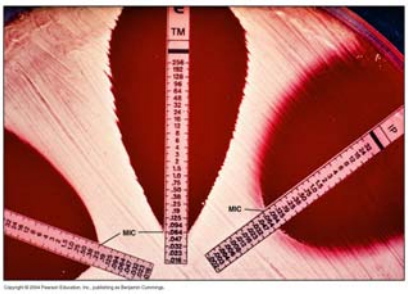
- MIC Minimal inhibitory concentration
- MBC Minimal bactericidal concentration

Tests for microbial sensitivity

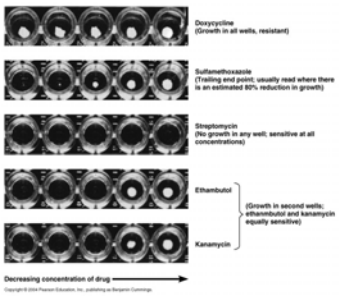
- Kirby-Bauer (disk diffusion method)
  - We did this in lab
- E test -determines the minimum inhibitory concentration (MIC
- Dilution tests for MIC

Kirby-Bauer tests for sensitivity

E-test for MIC



MIC testing



Effects of Combinations of Drugs

- Synergism occurs when the effect of two drugs together is greater than the effect of either alone.
- Antagonism occurs when the effect of two drugs together is less than the effect of either alone.

Effects of Combinations of Drugs

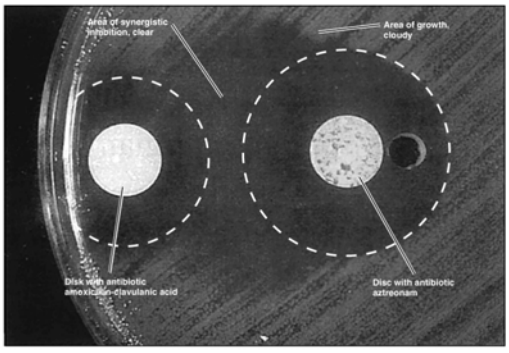
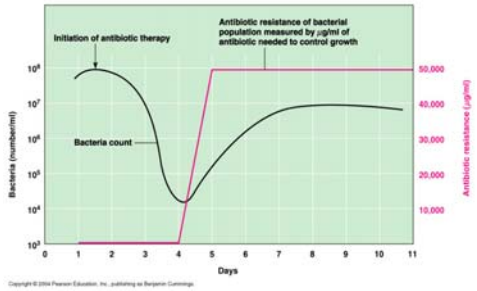


Figure 20.22

Development of antibiotic resistant bacteria



Drug resistance

- Destruction or inactivation of the drug
- Prevention of penetration to target site
- Alteration of target site (mutation)
- Pumping of the drug out of the bacterial cell: rapid ejection of drug
- Resistance genes are often on plasmids or transposons that can be transferred between bacteria.

Examples of resistant bacteria

- *Neisseria gonorrhoeae*
- Enterococcus: VRE (vancomycin resistant enterococci)
- *Staphylococcus aureus*:
  - MRSA (methicillin resistant Staph aureus)
  - VISA(vancomycin intermediate Staph aureus)
- *Streptococcus pneumoniae*
- *Mycobacterium tuberculosis*