Chapter 9. Controlling Microbial Growth in Vivo
Using Antimicrobial Agents

• Chapter 9 Outline
  • Characteristics of an Ideal Antimicrobial Agent
  • How Antimicrobial Agents Work
  • Antibacterial Agents
  • Antifungal Agents
  • Antiprotozoal Agents
  • Antiviral Agents
  • Drug Resistance
  • Some Strategies in the War Against Drug Resistance
  • Undesirable Effects of Antimicrobial Agents

• Introduction
  • Chemotherapy is the use of any chemical (drug) to treat any disease or condition.
  • A chemotherapeutic agent is any drug used to treat any condition or disease.
  • An antimicrobial agent is any chemical (drug) used to treat an infectious disease, either by inhibiting or killing pathogens in vivo. Some antimicrobial agents are antibiotics.

• Introduction, cont.
  • Drugs used to treat bacterial diseases are called antibacterial agents; those used to treat fungal diseases, antifungal agents; protozoal diseases, antiprotozoal agents; viral diseases, antiviral agents.

• Characteristics of an Ideal Antimicrobial Agent
  • The ideal antimicrobial agent should:
    – Kill or inhibit the growth of pathogens
    – Cause no damage to the host
    – Cause no allergic reaction in the host
    – Be stable when stored in solid or liquid form

  • How Antimicrobial Agents Work
  • The 5 most common mechanisms of action of antimicrobial agents are:
    – Inhibition of cell wall synthesis
    – Damage to cell membranes
    – Inhibition of nucleic acid synthesis (either DNA or RNA synthesis)
    – Inhibition of protein synthesis
    – Inhibition of enzyme activity

• Antibacterial Agents
  • Bacteriostatic drugs inhibit growth of bacteria, whereas bactericidal drugs kill bacteria.
  • Sulfonamide drugs inhibit production of folic acid (a vitamin) in those bacteria that require p-aminobenzoic acid to synthesize folic acid; without folic acid bacteria cannot produce certain essential proteins and die.
    – Sulfa drugs are competitive inhibitors; they are bacteriostatic.

• Antibacterial Agents, cont.
  • Colistin and nalidixic acid destroy only Gram-negative bacteria; they are referred to as narrow-spectrum antibiotics.
  • Antibiotics that are destructive to both Gram-positive and Gram-negative bacteria are called broad-spectrum antibiotics (examples: ampicillin, chloramphenicol and tetracycline).

• Multidrug therapy
  – Sometimes one drug is not sufficient; 2 or more drugs may be used simultaneously, as in the treatment of tuberculosis.

• Some Major Categories of Antibacterial Agents
  • Penicillins: bactericidal; interfere with cell wall synthesis
  • Cephalosporins: bactericidal; interfere with cell wall synthesis
• Tetracyclines: bacteriostatic; inhibit protein synthesis
• Aminoglycosides: bactericidal; inhibit protein synthesis
• Macrolides: bacteriostatic at lower doses; bactericidal at higher doses; inhibit protein synthesis
• Fluoroquinolones: bactericidal; inhibit DNA synthesis
• Antibacterial Agents, cont.
  • Synergism Versus Antagonism
    – Synergism is when 2 antimicrobial agents are used together to produce a degree of pathogen killing that is greater than that achieved by either drug alone. Synergism is a good thing!
      – $2 + 2 = 6$
    – Antagonism is when 2 drugs actually work against each other. The extent of pathogen killing is less than that achieved by either drug alone. Antagonism is a bad thing!
      – $2 + 2 = 1$
• Antifungal Agents
• Most antifungal agents work in one of 3 ways:
  • http://www.doctorfungus.org/thedrugs/antif_pharmac.php
    – By binding with cell membrane sterols (e.g., nystatin and amphotericin B)
    – By interfering with sterol synthesis (e.g., clotrimazole and miconazole)
    – By blocking mitosis or nucleic acid synthesis (e.g., griseofulvin and 5-flucytosine)
• Antifungal agents and antiprotozoal agents tend to be more toxic to the patient because, like the infected human, they are eucaryotic organisms.
• Antiviral Agents
• Antiviral agents are the newest weapons in antimicrobial methodology.
• Difficult to develop these agents because viruses are produced within host cells.
• Some drugs have been developed that are effective in certain viral infections, but not others; they work by inhibiting viral replication within cells.
• Antiviral agent “cocktails” (several drugs that are administered simultaneously) are being used to treat HIV infection.
• Drug Resistance
  “Superbugs”
• Superbugs are microbes (mainly bacteria) that have become resistant to one or more antimicrobial agent. Infections caused by superbugs are difficult to treat!
• Bacterial superbugs include:
  – methicillin-resistant *Staphylococcus aureus* (MRSA)
  – vancomycin-resistant *Enterococcus* spp. (VRE)
  – multidrug-resistant *Mycobacterium tuberculosis* (MDRTB)
  – multidrug-resistant strains of *Acinetobacter*, *Burkholderia*, *E. coli*, *Klebsiella*, *Pseudomonas*, *Stenotrophomonas*, *Salmonella*, *Shigella*. and *N. gonorrhoaeae*;
  – β-lactamase-producing strains of *Streptococcus pneumoniae*
  – *Haemophilus influenzae*; carbapenemase-producing *Klebsiella pneumoniae*.
• Drug Resistance
  How Bacteria Become Resistant to Drugs
• Some bacteria are naturally resistant = intrinsic resistance
  – They lack the specific target site for the drug
  – The drug is unable to cross the organism’s cell wall or cell membrane and thus, cannot reach its site of action.
• Acquired resistance = bacteria that were once susceptible to a particular drug become resistant.
• Before a drug enters a bacterial cell it must first bind to proteins on the surface of the cell; these proteins are called drug-binding sites. A chromosomal mutation that affects the structure of a drug-binding site can prevent the drug from binding, resulting in drug resistance.
• Drug Resistance
  How Bacteria Become Resistant to Drugs, cont.
• To enter a bacterial cell, a drug must be able to pass through the cell wall and cell membrane
  – Chromosomal mutations may alter the structure of the cell membrane, thus preventing the drug from entering the cell; this results in drug resistance.
• Bacteria can develop the ability to produce an enzyme that destroys or inactivates a drug.
  – Many bacteria have become resistant to penicillin because they have acquired the gene for penicillinase production during conjugation.
  – A plasmid that contains multiple genes for drug resistance is known as a resistance factor (R-factor).
How Bacteria Become Resistant to Drugs, cont.

Bacteria can also become resistant to drugs by developing the ability to produce multidrug-resistance (MDR) pumps (also known as MDR transporters or efflux pumps).

- An MDR pump enables the cell to pump out drugs before they can damage or kill the cell.

Summary: Bacteria can acquire resistance to antimicrobial agents by chromosomal mutation or by the acquisition of new genes by transduction, transformation, and, most commonly, by conjugation.

Drug Resistance

β-Lactamases

Every penicillin and cephalosporin molecule contains a β-lactam ring.

Some bacteria produce enzymes, β-lactamases, that destroy this ring; when the β-lactam ring is destroyed, the drug no longer works.

- 2 types of β-lactamases - penicillinases and cephalosporinases; some bacteria produce both types.

Drug companies have developed special drugs that combine a β-lactam antibiotic with a β-lactamase inhibitor.

Some Strategies in the War Against Drug Resistance

- Education of healthcare professionals and patients

Patients should stop demanding antibiotics every time they are, or their child is, sick

- Physicians should not be pressured by patients and should prescribe drugs only when warranted

- Clinicians should prescribe a narrow-spectrum drug if lab results indicate that it kills the pathogen

- Patients should destroy any excess or out-dated medications

- Antibiotics should not be used in a prophylactic manner

- Healthcare professionals should practice good infection control

- Patients should take drugs in manner prescribed

Undesirable Effects of Antimicrobial Agents

- Reasons why antimicrobial agents should not be used indiscriminately:
  - Organisms susceptible to the agent will die, but resistant ones will survive; this is known as selecting for resistant organisms.
- The patient may become allergic to the agent.
- Many agents are toxic to humans and some are very toxic.
- With prolonged use, a broad-spectrum antibiotic may destroy the normal flora, resulting in an overgrowth of bacteria known as a superinfection.