Drugs, Microbes, Host – The Elements of Chemotherapy

Supportive Therapies:
• Reduction in Stress
• Improvement in Diet
• Exercise
• Good Hygiene

Preventive Therapies:
- Prevent transmission of causal agents
  - Disinfection (inanimate objects)
  - Eradication of reservoirs
  - Elimination of vectors
  - Antisepsis
- Prevent infection
  - Restriction & localization by enforcing physical, chemical and biological barriers

Antimicrobial Chemotherapy
- Goal of antimicrobial chemotherapy: administer a drug to an infected person, which destroys the infective agent without harming the host’s cells
- Chemotherapeutic agents are described with regard to their origin, range of effectiveness, and whether they are naturally produced or chemically synthesized

TABLE 12.1 Characteristics of the Ideal Antimicrobial Drug
- Selectively toxic to the microbe but nontoxic to host cells
- Microbicidal rather than microbistatic
- Relatively soluble; functions even when highly diluted in body fluids
- Remains potent long enough to act and is not broken down or excreted prematurely
- Doesn’t lead to the development of antimicrobial resistance
- Complements or assists the activities of the host’s defenses
- Remains active in tissues and body fluids
- Readily delivered to the site of infection
- Reasonably priced
- Does not disrupt the host’s health by causing allergies or predisposing the host to other infections
Origins of Antimicrobial Drugs

- **Antibiotics** are secondary metabolic products of aerobic bacteria and fungi
  - Bacteria: *Streptomycetes* and *Bacillus*
  - Molds: *Penicillium* and *Cephalosporium*
- Chemists have created new generations of drugs by altering the structure of naturally occurring antibiotics (semi-synthetic drugs)
- Researchers continue to search for new antimicrobial compounds also in organisms other than bacteria and fungi (bioprospecting)

Interactions between Drug & Microbe

- **Goal** of antimicrobial and antiviral drugs:
  - Disrupt cellular processes or structures of bacteria, fungi, and protozoa
  - Inhibit virus replication
- Most antimicrobial and antiviral drugs
  - Interfere with the function of enzymes required to synthesize or assemble macromolecules or
  - Destroy structures already formed in the cell
- Antimicrobial drugs should be **selectively toxic** in that they destroy or inhibit microbial cells without damaging host tissues.

Major Mechanisms of Drug Action

- Inhibition of synthesis and interference with structure and function of **nucleic acids**
- Inhibition of synthesis and interference with structure and function of **proteins**
- Inhibition of **cell wall** synthesis
- Interference with **cell membrane structure or function**
- Inhibition of specific **metabolic pathways** such as folic acid synthesis

Antimicrobial Drugs that affect Nucleic Acid Synthesis

- Block synthesis of nucleotides
- Inhibit replication (DNA synthesis)
- Inhibit (prevent or stop) transcription (RNA synthesis)
**Antimicrobial Drugs that block Protein Synthesis**

- Inhibit translation by reacting with the ribosome-mRNA complex
- Selective effect is possible because bacterial ribosomes are different from eukaryotic ribosomes

**Antimicrobial Drugs that Affect the Bacterial Cell Wall**

- Active cells with a cell wall must constantly synthesize new NAM-NAG units, transport them across the plasma membrane to the proper place and incorporate them into the existing peptidoglycan layer in the cell envelope
- Penicillins and cephalosporins react with one or more of the enzymes required to complete this process (PBPs)
  
  ===> Bactericidal antibiotics

**Antimicrobial Drugs that Disrupt Cell Membrane Function**

- Damaged cell membranes invariably result in death from elimination of gradients or lysis
- Specificity is possible because particular microbial groups have differences in the types of lipids in their cell membranes
Antimicrobial Drugs that Inhibit Folic Acid Synthesis

- Sulfonamides and trimethoprim act via competitive inhibition
- Supplied to cells in high concentrations to make sure enzyme is constantly occupied with the metabolic analog inhibitor rather than the true substrate

Major Antimicrobial Drug Groups

- About 260 different antimicrobial drugs
- Classified in 20 drug families
- Largest number of antimicrobial drugs are used to combat bacterial infections

Antibacterial Drugs Targeting the Cell Wall

- Penicillin group
  - Most end in the suffix -cillin
  - Can obtain natural penicillin through microbial fermentation
  - All consist of three parts: a thiazolidine ring, a beta-lactam ring, and a variable side chain
Subgroups and Uses of Penicillins

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Characteristics of Action</th>
<th>Uses, Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Penicillin G</td>
<td>Broad-spectrum</td>
<td>Can be hydrolyzed by penicillinases</td>
<td>Allergic reactions</td>
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<tr>
<td>Penicillin V</td>
<td>Narrow-spectrum</td>
<td>Good absorption</td>
<td>None</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Broad-spectrum</td>
<td>Resistant to most penicillinases (PBPs)</td>
<td>Fewer allergic reactions</td>
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<td>Four generations exist based on antibacterial activity</td>
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The Cephalosporin Group of Drugs

- Newer than penicillins
- Currently account for the majority of all antibiotics administered

Other Beta-Lactam Antibiotics

- **Imipenem**
  - Activity against Pseudomonas aeruginosa and the Enterococcus species.
  - Not active against methicillin-resistant Staphylococcus aureus (MRSA)

- **Aztreonam**
  - Strong activity against susceptible Gram-negative bacteria, including Pseudomonas aeruginosa. It has no useful activity against Gram-positive bacteria or anaerobic bacteria

Other Drugs Targeting the Cell Wall

- **Bacitracin**
  - Interferes with bactoprenol, which exports "pre-fabricated" NAM-NAG units across the bacterial plasma membrane

- **Isoniazid**
  - Activated by KatG to form isonicotinic acyl radical; react with a NADH to form isonicotinic acyl-NADH complex. This complex will inhibit the synthesis of mycolic acid in the mycobacterial cell wall.

- **Vancomycin**
  - For the treatment of serious, life-threatening infections by Gram-positive bacteria which are unresponsive to other less toxic antibiotics.

- **Fosfomycin trimethamine**
  - Treatment of urinary tract infections, where it is usually administered as a single dose
Antibacterial Drugs
Targeting Protein Synthesis

• Aminoglycoside Drugs
  – Products of various species of soil actinomycetes in the genera Streptomyces and Micromonospora
  – Relatively broad spectrum because they inhibit protein synthesis
  – Most used to combat aerobic Gram-negative rods and certain gram-positive bacteria:
    • Streptomycin: Bubonic plague and tularemia and good antituberculosis agent
    • Gentamicin: Less toxic and used for gram-negative rods

Tetracycline Antibiotics

• Bind to ribosomes and block protein synthesis
• Broad-spectrum
• Used to combat aerobic and anerobic Gram-positive and Gram-negative rods and cocci
  – Mycoplasmas, rickettsias, and spirochetes
  – STDs, Rocky Mountain spotted fever, Lyme disease, typhus, Mycoplasma pneumonia, cholera, leptospirosis, acne (Doxycline and minocycline)
  – some protozoa

Chloramphenicol

• Unique nitrobenzene structure
• Entirely chemosynthetic
• Blocks peptide bond formation and protein synthesis ==&gt; Broad-spectrum
• Very toxic to human cells so its uses are restricted

Erythromycin and Clindamycin

• Erythromycin
  – Large lactone ring with sugars attached
  – Relatively broad-spectrum
  – Fairly low toxicity
  – Blocks protein synthesis by attaching to the ribosome
  – Mycoplasma pneumonia, legionellosis, Chlamydia infections, pertussis, diphtheria

• Clindamycin (derived from lincomycin)
  – Broad-spectrum
  – Causes adverse reactions in the GI tract, so applications are limited. Often used against oral cavity infections.

Synercid and Oxazolidones

• Synercid
  – Combined antibiotic from the streptogramin group
  – Effective against Staphylococcus and Enterococcus species and against resistant strains of Streptococcus
  – Binds to sites on the 50S ribosome, inhibiting translation

• Oxazolidones
  – Inhibit the initiation of protein synthesis
  – Not found in nature ==&gt; Hope that drug resistance among bacteria will be slow to develop
  – Used to treat infections caused by two of the most difficult clinical pathogens: methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE)

Antibacterial Drugs
Targeting Folic Acid Synthesis

• Sulfonamides, Trimethoprim, and Sulfones
  – Sulfonamides ("Sulfa drugs")
    • First modern synthetic antimicrobial drug
    • Used to combat shigellosis, acute UTIs, certain protozoan infections
  – Trimethoprim
    • Inhibits the enzymatic step immediately following the step inhibited by sulfonamides in the synthesis of folic acid
    • Often given in combination with sulfamethoxazole
    • One of the primary treatments for pneumonia caused in AIDS patients by Pneumocystis carinii (and P. jiroveci), called PCP
  – Sulfones
    • Chemically related to sulfonamides
    • Lack their broad-spectrum effects
    • Key drugs in treating leprosy (Hansen's disease)
Antibacterial Drugs Targeting DNA or RNA synthesis

- Fluoroquinolones
- High potency and broad spectrum
- Inhibit a wide variety of Gram-positive and Gram-negative bacteria even at low concentrations of bacteria

Norfloxacin and Ciprofloxacin

- UTIs, STDs, gastrointestinal infections, osteomyelitis, respiratory infections (anthrax!), soft tissue infections

Sparfloxacin and Levofloxacin

- Pneumonia, bronchitis sinusitis

Rifampi(ci)n

- Product of the genus *Streptomyces*
- Limited in spectrum
- Mainly for infections by several Gram-positive rods and cocci (a few Gram-negative bacteria)
- In particular, used against mycobacterial infections such as tuberculosis and leprosy
- Usually given in combination with other drugs

Antibacterial Drugs Targeting Cell Membranes

- Polymyxins: narrow-spectrum peptide antibiotics
  - From *Bacillus polymyxa*
  - Limited by their toxicity to the kidney
  - Some can be used to treat drug-resistant *Pseudomonas aeruginosa*
- Daptomycin
  - Lipopeptide made by *Streptomyces*
  - Most active against Gram-positive bacteria

Agents to Treat Fungal Infections

- Fungal cells are eukaryotic, so present special problems
  - Majority of chemotherapeutic drugs are designed to act on bacteria and are ineffective for fungal infections
  - Similarities between fungal and human cells-toxicity to humans
- Four main groups
  - Macrolide polyene antibiotics, Griseofulvin, Synthetic azoles, Fluocytosine

Antiparasitic Chemotherapy

- Antimalarial Drugs: Quinine and its derivatives
  - Quinine: extracted from the bark of the cinchona tree
  - Replaced by synthesized quinolines (chloroquine and primaquine), which have less toxicity to humans
- Chemotherapy for Other Protozoan Infections
  - Metronidazole (Flagyl) - *Amoebicide*
    - treating intestinal infections by *Entamoeba histolytica*
    - Orally applied also suited to combat infections by *Giardia lamblia* and *Trichomonas vaginalis*
  - Quincline, sulfonamides, tetracyclines
Antihelminthic Drug Therapy

- Flukes, tapeworms, and roundworms have greater similarities to human physiology
  - Using drugs to block their reproduction is usually not successful in eradicating adult worms
  - Most effective drugs immobilize, disintegrate, or inhibit the metabolism of all stages of the life cycle

Antiviral Chemotherapeutic Agents

- Selective toxicity is almost impossible to achieve because the same metabolic system is responsible for the well-being of both virus & host
- Several antiviral drugs have been developed that target specific points in the infectious cycle of viruses
  - Three major modes of action:
    - Prevent attachment & penetration of the virus into the host cell
    - Blocking the transcription & translation of viral macromolecules
    - Preventing the maturation of viral particles

Interferon (IFN): An Alternative to Artificial Drugs

- Glycoprotein produced by fibroblasts and leukocytes in response to various immune stimuli
- Produced also using recombinant DNA technologies
- Known therapeutic benefits:
  - Reducing the time of healing and some of the complications in certain infections
  - Preventing or reducing some symptoms of cold and HPV
  - Slowing the progress of certain cancers
  - Treating hairy-cell leukemia (a rare cancer), hepatitis C, genital warts, and Kaposi’s sarcoma in AIDS patients
  - Often results in serious side effects

Interactions Between Microbes and Drugs: The Acquisition of Drug Resistance

- **Drug resistance**: an adaptive response in which microorganisms begin to tolerate an amount of drug that would ordinarily be inhibitory
- Can be intrinsic or acquired
- Microbes become newly resistant to a drug after
  - Spontaneous mutations in critical chromosomal genes
  - Acquisition of new genes or sets of genes via transfer from another species (i.e., via plasmids) called resistance factors

![Interactions Between Microbes and Drugs: The Acquisition of Drug Resistance](image-url)
New Approaches to Antimicrobial Therapy

- Often researchers try to find new targets in the bacterial cell and custom-design drugs that aim for processes such as:
  - iron-scavenging capabilities of bacteria
  - genetic control mechanisms in bacteria referred to as riboswitches
- **Probiotics and prebiotics, Lantibiotics**

Problems with Chemotherapy:

**Toxicity to Organs**

- Liver, kidneys, gastrointestinal tract, cardiovascular system and blood-forming tissue, nervous system, respiratory tract, skin, bones, and teeth, etc.

Allergic Responses to Drugs

- **Allergy**: heightened sensitivity
- The drug acts as an antigen and stimulates an allergic response
- Reactions such as skin rash, respiratory inflammation, and rarely anaphylaxis

Superinfection

- When certain beneficial species (natural flora) are destroyed, microbes that were once kept in check can begin to overgrow and cause disease, called then a **superinfection**
  - Using a broad-spectrum cephalosporin for UTI destroys lactobacilli in the vagina; without the lactobacilli, *Candida albicans* can proliferate and cause a yeast infection
  - Oral therapy with tetracyclines, clindamycin, and broad-spectrum penicillins and cephalosporins is associated with antibiotic-associated colitis

Selecting an Antimicrobial Drug

- Three factors must be known
  - The nature of the microorganism causing the infection
  - The degree of the microorganism’s susceptibility to various drugs
  - The overall medical condition of the patient
- Identifying the Agent
  - Direct examination of body fluids, sputum, or stool is a rapid initial method
  - The choice of drug will be based on experience with drugs that are known to be effective against the microbe: the “informed best guess”
- Testing for the Drug Susceptibility of Microorganisms

The MIC and Therapeutic Index

- **MIC**: minimum inhibitory concentration: the smallest concentration (highest dilution) of drug that visibly inhibits bacterial growth
- Once therapy has begun, it is important to observe the patient’s clinical response