General Principles of Antimicrobial Therapy

Microorganisms of medical importance fall into four categories: bacteria, viruses, fungi, and parasites.

The first broad classification of antibiotics follows this classification closely, so that we have:

1. Antibacterial
2. Antiviral
3. Antifungal
4. antiparasitic agents

However, there are many antibiotics that work against more than one category of microbes.

Antimicrobial molecules should be viewed as ligands whose receptors are microbial proteins.

The microbial proteins targeted by the antibiotic are essential components of biochemical reactions in the microbes, and interference with these physiological pathways kills the microorganisms.

Selection of Antimicrobial Agents

Selection of the most appropriate antimicrobial agent requires knowledge of

1) the identity of the organism,
2) the susceptibility of the organism to a particular agent,
3) the site of the infection,
4) patient factors,
5) the safety and efficacy of the agent, and
6) the cost of therapy.

However, most patients require empiric therapy (immediate administration of drug(s) prior to bacterial identification and susceptibility testing).

Bacteriostatic versus bactericidal drugs

Antimicrobial drugs are commonly classified as either bacteriostatic or bactericidal.

Bactericidal agents: They kill or destroy bacteria.

Bacteriostatic drugs : only arrest the growth and replication of bacteria at drug levels achievable in the patient.

At high concentration, some of the ‘static’ drugs may produce ‘cidal’ effect.

Patient factors In selecting an antibiotic

attention must be paid to the condition of the patient. For example, the status of the immune system, kidneys, liver, circulation, and age must be considered. In women, pregnancy or breast-feeding also affects selection of the antimicrobial agent.

1. **Immune system**: Elimination of infecting organisms from the body is highly dependent on an intact immune system, and the host defense system must ultimately eliminate the invading organisms. Alcoholism, diabetes, HIV infection, malnutrition, autoimmune diseases, pregnancy, advanced age, and immunosuppressive drugs can affect immunocompetence. High doses of bactericidal agents or longer courses of treatment may be required to eliminate infective organisms in these individuals.

2. **Renal dysfunction:** Poor kidney function may cause accumulation of certain antibiotics. Dosage adjustment prevents drug accumulation and adverse effects. Serum creatinine levels are frequently used as an index of renal function for adjustment of drug regimens. However, direct monitoring of serum levels of some antibiotics (for example, vancomycin, aminoglycosides) is preferred to identify maximum and/or minimum values and prevent potential toxicities. [Note: The number of functional nephrons decreases with age. Thus, elderly patients are particularly vulnerable to accumulation of drugs eliminated by the kidneys, even with normal serum creatinine levels.]

3. **Hepatic dysfunction:** Antibiotics that are concentrated or eliminated by the liver (for example, erythromycin and doxycycline) must be used with caution when treating patients with liver dysfunction.

4. **Poor perfusion:** Decreased circulation to an anatomic area, such as the lower limbs of a diabetic patient, reduces the amount of antibiotic that reaches that site of infection, making it more difficult to treat. Decreased perfusion of the gastrointestinal tract may result in reduced absorption, making attainment of therapeutic concentrations more difficult with enteral routes.

5. **Age:** Renal or hepatic elimination processes are often poorly developed in newborns, making neonates particularly vulnerable to the toxic effects of agents such as chloramphenicol and sulfonamides. Young children should not be treated with tetracyclines or quinolones, which affect bone growth and joints, respectively. Elderly patients may have decreased renal or liver function, which may alter the pharmacokinetics of certain antibiotics.

6. **Pregnancy and lactation:** Many antibiotics cross the placental barrier or enter the nursing infant via the breast milk. Prescribers should consult the product labeling of an antibiotic to review the risk summary and clinical considerations for use in pregnancy and lactation. Although the concentration of an antibiotic in fetal circulation or in breast milk is usually low, the total dose to the infant may be sufficient to produce detrimental effects. For example, congenital abnormalities have been reported after administration of tetracyclines to pregnant women, and these agents should be generally be avoided in pregnancy due to the risk to the fetus.

7. **Risk factors for multidrug-resistant organisms:** Infections with multidrug-resistant pathogens need broader antibiotic coverage when initiating empiric therapy. Common risk factors for infection with these pathogens include prior antimicrobial therapy in the preceding 90 days, hospitalization for greater than 2 days within the preceding 90 days, current hospitalization exceeding 5 days, admission from a nursing home, high frequency of resistance in the community or local hospital unit (assessed using hospital antibiograms), and immunosuppressive diseases and/or therapies.

Route of Administration The oral route of administration is appropriate for mild infections that can be treated on an outpatient basis. Parenteral administration is used for drugs that are poorly absorbed from the GI tract and for treatment of patients with serious infections who require maintenance of higher serum concentrations of antimicrobial agents. In hospitalized patients requiring intravenous (IV) therapy, the switch to oral agents should occur as soon as possible. Switching patients from IV to oral therapy when clinically stable has been shown to decrease health care costs, shorten length of stay, and decrease complications from IV catheters. However, some antibiotics, such as vancomycin and aminoglycosides, are poorly absorbed from the gastrointestinal (GI) tract and do not achieve adequate serum levels via oral administration.

Chemotherapeutic Spectra:

A. **Narrow-spectrum antibiotics** Chemotherapeutic agents acting only on a single or a limited group of microorganisms are said to have a narrow spectrum.

B. **Extended-spectrum antibiotics** Extended spectrum is the term applied to antibiotics that are modified to be effective against gram-positive organisms and also against a significant number of gram-negative bacteria. For example, ampicillin.

C. **Broad-spectrum antibiotics** Drugs such as tetracycline, fluoroquinolones and carbapenems affect a wide variety of microbial species and are referred to as broad-spectrum antibiotics. Administration of broad-spectrum antibiotics can drastically alter the nature of the normal bacterial flora and precipitate a superinfection due to organisms such as Clostridium difficile, the growth of which is normally kept in check by the presence of other colonizing microorganisms.

Antibiotic Resistance: is defined as the unresponsiveness of a microorganism to an antimicrobial agent.

•The natural resistance is genetically determined.

- In acquired resistance, microbes that initially respond to an antimicrobial agent later develop resistance to the same agent by mutation or gene transfer.

Classification of Antimicrobial Agents by their site of action:

1. Cell wall inhibitors.
2. Protein synthesis inhibitors.
3. Cell membrane function inhibitors.
4. Metabolism inhibitors.
5. Nucleic acid function or synthesis inhibitors.