Chemotherapeutic Drugs
Principles of Antimicrobial Therapy

Antimicrobial therapy takes advantage of the biochemical differences that exist between microorganisms and human beings. Antimicrobial drugs are effective in the treatment of infections because of their selective toxicity; that is, they can injure or kill an invading microorganism without harming the cells of the host. In most instances, the selective toxicity is relative rather than absolute, requiring that the concentration of the drug be carefully controlled to attack the microorganism, while still being tolerated by the host.

SELECTION OF ANTIMICROBIAL AGENTS

Selection of the most appropriate antimicrobial agent requires knowing:

1) the organism's identity, 2) the organism's susceptibility to a particular agent, 3) the site of the infection, 4) patient factors, 5) the safety of the agent, and 6) the cost of therapy.
   However, some patients require empiric therapy (immediate administration of drug(s) prior to bacterial identification and susceptibility testing).

A- Identification of the infecting organism

Characterizing the organism is central to selection of the proper drug. This process can be conducted using different techniques; however, the direct microscopic visualization and cultivation and identification are the most common techniques are used.

Empiric therapy prior to identification of the organism

Ideally, the antimicrobial agent used to treat an infection is selected after the organism has been identified and its drug susceptibility established. However, in the critically ill patient, such a delay could prove fatal, immediate empiric therapy is indicated.

Timing: Acutely ill patients with infections of unknown origin—for example, a neutropenic patient (one who is predisposed to infections due to a reduction in neutrophils) or a patient with meningitis (acute inflammation of the membranes covering the brain and spinal cord)—require immediate treatment. If possible, therapy should be initiated after specimens for laboratory analysis have been obtained but before the results of the culture and sensitivity are available.

Selecting a drug: Drug choice in the absence of susceptibility data is influenced by the site of infection and the patient's history (for example, previous infections, age, recent travel history, recent antimicrobial therapy, immune status, and whether the infection was hospital- or community-acquired). Broad-spectrum therapy may be indicated initially when the organism is unknown or polymicrobial infections are likely. The choice of agent(s) may also be guided by known association of particular organisms in a given clinical setting.

For example, gram-positive cocci in the spinal fluid of a new-born infant is unlikely to be Streptococcus pneumoniae and most likely to be Streptococcus agalactiae (a group B streptococci), which is sensitive to *penicillin G*.
By contrast, gram-positive cocci in the spinal fluid of a 40-year-old patient are most likely to be S. pneumoniae. This organism is frequently resistant to *penicillin G* and often requires treatment with a high-dose third generation cephalosporin (such as *ceftriaxone*) or *vancomycin*.

Determining antimicrobial susceptibility of infective organisms
After a pathogen is cultured, its susceptibility to specific antibiotics serves as a guide in choosing antimicrobial therapy. Some pathogens, such as Streptococcus pyogenes and Neisseria meningitidis, usually have predictable susceptibility patterns to certain antibiotics. In contrast, most gram-negative bacilli, enterococci, and staphylococcal species often show unpredictable susceptibility patterns and require susceptibility testing to determine appropriate antimicrobial therapy.

Bacteriostatic versus bactericidal drugs:

- **Bacteriostatic drugs** arrest the growth and replication of bacteria, thus limiting the spread of infection until the immune system attacks, immobilizes, and eliminates the pathogen. If the drug is removed before the immune system has scavenged the organisms, enough viable organisms may remain to begin a second cycle of infection.
- **Bactericidal drugs** kill bacteria at drug serum levels achievable in the patient. Because of their more aggressive antimicrobial action, bactericidal agents are often the drugs of choice in seriously ill and immunocompromised patients.
- Although practical, this classification may be too simplistic because it is possible for an antibiotic to be bacteriostatic for one organism and bactericidal for another. For example, *linezolid* is bacteriostatic against Staphylococcus aureus and enterococci but is bactericidal against most strains of S. pneumoniae.

Minimum inhibitory concentration (MIC) is the lowest antimicrobial concentration that prevents visible growth of an organism after 24 hours of incubation.
Minimum bactericidal concentration (MBC): is the lowest concentration of antimicrobial agent that results in a 99.9% decline in colony count after overnight broth dilution incubations.

B- Effect of the site of infection on therapy: the blood–brain barrier
Adequate levels of an antibiotic must reach the site of infection for the invading microorganisms to be effectively eradicated. Capillaries with varying degrees of permeability carry drugs to the body tissues.
Natural barriers to drug delivery are created by the structures of the capillaries of some tissues, such as the prostate, testes, placenta, the vitreous body of the eye, and the central nervous system (CNS).

Of particular significance are the capillaries in the brain, which help to create and maintain the blood–brain barrier. This barrier is formed by the single layer of endothelial cells fused by tight junctions that impede entry from the blood to the brain of virtually all molecules, except those that are small and lipophilic. The penetration and concentration of an antibacterial agent in the CSF (cerebrospinal fluid) are particularly influenced by the following:

a- Lipid solubility of the drug: The lipid solubility of a drug is a major determinant of its ability to penetrate into the brain. Lipids soluble drugs, such as *chloramphenicol* and *metronidazole*, have significant penetration into the CNS, whereas β-lactam antibiotics, such as *penicillin*, are ionized at physiologic pH and have low solubility in lipids and They therefore have limited penetration through the intact blood–brain barrier under normal circumstances.

b- **Weight of the drug:** A compound with a low molecular weight has an enhanced ability to cross the blood–brain barrier, whereas compounds with a high molecular weight (for example, *vancomycin*) penetrate poorly, even in the presence of meningeal inflammation.

c- **Protein binding of the drug:** A high degree of protein binding of a drug restricts its entry into the CSF. Therefore, the amount of free (unbound) drug in serum, rather than the total amount of drug present, is important for CSF penetration.

C- **Patient factors**

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

a- Immune system: Elimination of infecting organisms from the body depends on an intact immune system, and the host defence system must ultimately eliminate the invading organisms. For example, Alcoholism, diabetes or advanced age can affect a patient's immunocompetence, as can immunosuppressive drugs. High doses of bactericidal agents or longer courses of treatment may be required to eliminate infective organisms in these individuals.

b- Renal dysfunction: Poor kidney function may cause accumulation of certain antibiotics. Dosage adjustment prevents drug accumulation and therefore adverse effects. So, the direct monitoring of serum levels of some antibiotics (for example, *vancomycin*, aminoglycosides) is preferred to identify maximum and/or minimum values to prevent potential toxicities.

c- 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.

d- **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 area, making these infections difficult to treat.

e- **Age:** Renal or hepatic elimination processes are often poorly developed in newborns, making neonates particularly vulnerable to the toxic effects of *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.

f- **Pregnancy and lactation:** Many antibiotics cross the placental barrier or enter the nursing infant via the breast milk. Although the concentration of an antibiotic in breast milk is usually low, the total dose to the infant may be sufficient to produce detrimental effects.

D- **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, high frequency of resistance in the community or local hospital unit, and immunosuppressive diseases and/or therapies.

E- **Safety of the agent**

Antibiotics such as the penicillins are among the least toxic of all drugs because they interfere with a site or function unique to the growth of microorganisms. Other antimicrobial agents (for example, *chloramphenicol*) have less specificity and are reserved for life-threatening infections because of the potential for serious toxicity to the patient. [Note: Safety is related not only to the inherent nature of the drug but also to patient factors that can predispose to toxicity.]

8- Cost of therapy

Often several drugs may show similar efficacy in treating an infection but vary widely in cost.

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, for whom it is necessary to maintain higher serum concentrations of antimicrobial agents. For example, some antibiotics, such as *vancomycin*, the aminoglycosides, and *amphotericin B* are so poorly absorbed from the gastrointestinal (GI) tract that adequate serum levels cannot be obtained by oral administration.

DETERMINANTS OF RATIONAL DOSING

Rational dosing of antimicrobial agents is based on their pharmacodynamics (the relationship of drug concentrations to antimicrobial effects) and pharmacokinetic properties (the absorption, distribution, metabolism, and elimination of the drug). Three important properties that have a significant influence on the frequency of dosing are concentration dependent killing, time-dependent killing, and post-antibiotic effect (PAE).

A. Concentration-dependent killing

Certain antimicrobial agents, including aminoglycosides and *daptomycin*, show a significant increase in the rate of bacterial killing as the concentration of antibiotic increases. So, giving drugs that exhibit this concentration-dependent killing by a once-a-day bolus infusion achieves high peak levels, favoring rapid killing of the infecting pathogen.

B. Time-dependent (concentration-independent) killing

In contrast, β-lactams, glycopeptides, macrolides, *clindamycin*, and *linezolid* do not exhibit concentration-dependent killing. The clinical efficacy of these antimicrobials is best predicted by the percentage of time that blood concentrations of a drug remain above the MIC. This effect is sometimes called concentration-independent or time-dependent killing.

C. Postantibiotic effect

The PAE is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC. Antimicrobial drugs exhibiting a long PAE (for example, aminoglycosides and fluoroquinolones) often require only one dose per day, particularly against gram-negative bacteria.

CHEMOTHERAPEUTIC SPECTRA

The clinically important bacteria have been organized into eight groups based on Gram stain, morphology, and biochemical or other characteristics. The ninth section of the list is labelled "Other," and it is used to represent any organism not included in one of the other eight categories. The list is used to illustrate the spectra of bacteria for which a particular class of antibiotics is therapeutically effective.

A. Narrow-spectrum antibiotics

Chemotherapeutic agents acting only on a single or a limited group of microorganisms are said to have a narrow spectrum. For example, *isoniazid* is active only against Mycobacterium tuberculosis.

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* is considered to have an extended spectrum because it acts against gram-positive and some gram-negative bacteria.

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.

COMBINATIONS OF ANTIMICROBIAL DRUGS

It is therapeutically advisable to treat patients with a single agent that is most specific to the infecting organism. This strategy reduces the possibility of superinfections, decreases the emergence of resistant organisms, and minimizes toxicity. However, some situations require combinations of antimicrobial drugs. For example, the treatment of tuberculosis benefits from drug combinations.

A. Advantages of drug combinations

Certain combinations of antibiotics, such as β-lactams and aminoglycosides, show synergism; that is, the combination is more effective than either of the drugs used separately. Because such synergism among antimicrobial agents is rare, multiple drugs used in combination are only indicated in special situations (for example, when an infection is of unknown origin or in the treatment of enterococcal endocarditis).

B. Disadvantages of drug combinations

A number of antibiotics act only when organisms are multiplying. Thus, coadministration of an agent that causes bacteriostasis plus a second agent that is bactericidal may result in the first drug interfering with the action of the second. For example, bacteriostatic tetracycline drugs may interfere with the bactericidal effects of penicillins and cephalosporins. Another concern is the risk of selection pressure and the development of antibiotic resistance by giving unnecessary combination therapy.

DRUG RESISTANCE

- Bacteria are considered resistant to an antibiotic if the maximal level of that antibiotic that can be tolerated by the host does not halt their growth. Drug resistance can be occurred by two mechanisms:

1- **Genetic alterations leading to drug resistance:** Acquired antibiotic resistance requires the temporary or permanent alteration of bacterial genetic information. Resistance develops due to the ability of DNA to undergo spontaneous mutation or to move from one organism to another.

2- **Altered expression of proteins in drug-resistant organisms**: can be represented by different mechanisms, which are:*1) Modification of target sites 2) Decreased accumulation and 3) Enzymatic inactivation.*

PROPHYLACTIC USE OF ANTIBIOTICS

Certain clinical situations, such as dental procedures and surgeries, require the use of antibiotics for the prevention rather than for the treatment of infections. Because the indiscriminate use of antimicrobial agents can result in bacterial resistance and superinfection, prophylactic use is restricted to clinical situations in which the benefits outweigh the potential risks. The duration of prophylaxis should be closely observed to prevent the unnecessary development of antibiotic resistance. In dental practice, a prophylactic treatment can be prescribed for patients with heart problems such as implanted prosthetic heart valves and rheumatic heart disease.

COMPLICATIONS OF ANTIBIOTIC THERAPY

Even though antibiotics are selectively toxic to an invading organism, it does not protect the host against adverse effects. For example, the drug may produce an allergic response or may be toxic in ways unrelated to the antimicrobial activity.

A. Hypersensitivity

Hypersensitivity or immune reactions to antimicrobial drugs or their metabolic products frequently occur. For example, the penicillins, despite their almost absolute selective microbial toxicity, can cause serious hypersensitivity problems, ranging from urticaria (hives) to anaphylactic shock.

B. Direct toxicity

High serum levels of certain antibiotics may cause toxicity by directly affecting cellular processes in the host (for example, aminoglycosides can cause ototoxicity).

C. Superinfections

Drug therapy, particularly with broad-spectrum antimicrobials or combinations of agents, can lead to alterations of the normal microbial flora of the upper respiratory, oral, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria. These infections usually require secondary treatments using specific anti-infective agents.

SITES OF ANTIMICROBIAL ACTIONS

Antimicrobial drugs can be classified in a number of ways:

1) by their chemical structure (for example, β-lactams or aminoglycosides)
2) by their mechanism of action (for example, cell wall synthesis inhibitors (Figure 1).
3) by their activity against particular types of organisms (for example, bacteria, fungi, or viruses).

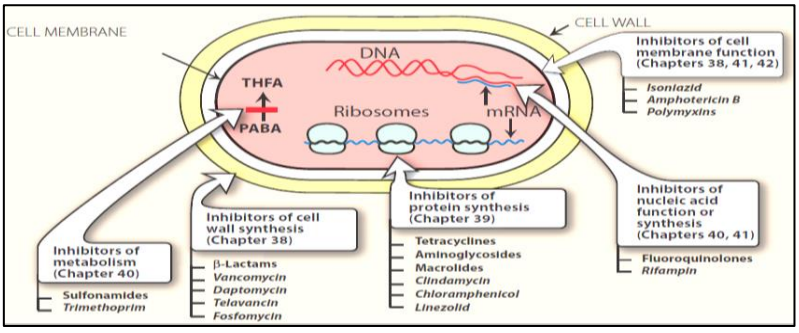

Figure 1: Classification of some antimicrobial agents by their sites of action. (THFA = tetrahydrofolic acid; PABA = *p*-aminobenzoic acid.)