College of dentist medicine
3rd year stage, pharmacology lecture.

Principles of Anti-microbial 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 have the ability to injure or kill an invading microorganism without harming the cells of the host.

Selection of Antimicrobial Agents
Selection of the most appropriate antimicrobial agent requires knowledge of **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 critically ill patients require empiric therapy-that is, immediate administration of drug(s) prior to bacterial identification and susceptibility testing.

Identification of the infecting organism
Characterization of the organism is central to selection of the proper drug. A rapid assessment of the nature of the pathogen can sometimes be made on the basis of the Gram stain, which is particularly useful in identifying the presence and morphologic features of microorganisms in body fluids. It is generally necessary to culture the infective organism to arrive at a conclusive diagnosis and to determine the susceptibility of the bacteria to antimicrobial agents.

Selecting a drug: The choice of drug in the absence of susceptibility data is influenced by the site of infection and the patient's history (for example, whether the infection was hospital- or community-acquired, whether the patient is immunocompromised, as well as the patient's travel record and age). Broad-spectrum therapy may be needed initially for serious infections when the identity of the organism is unknown or the site makes a polymicrobial infection likely.

Bacteriostatic vs. bactericidal drugs: Antimicrobial drugs are classified as either **bacteriostatic** or **bactericidal.**
Bacteriostatic drugs arrest the growth and replication of bacteria at serum levels achievable in the patient, thus limiting the spread of infection while the body's immune system attacks, immobilizes, and eliminates the pathogens. 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, these agents are often the drugs of choice in seriously ill patients.

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. For example, the endothelial cells comprising the walls of capillaries of many tissues have fenestrations (openings that act like windows) that allow most drugs not bound by

plasma proteins to penetrate. 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 tile-like 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 is particularly influenced by the following:

1- Lipid solubility of the drug: All compounds without a specific transporter must pass intracellularly from the blood to the CSF (through two endothelial cell membranes. The lipid solubility of a drug is therefore a major determinant of its ability to penetrate into the brain. For example, lipid-soluble drugs, such as the quinolones and metronidazole, have significant penetration into the CNS. In contrast, β-lactam antibiotics, such as penicillin, are ionized at physiologic pH and have low solubility in lipids.

2- Molecular 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.

3- Protein binding of the drug: A high degree of protein binding of a drug in the serum 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.

Patient factors

In selecting an antibiotic, attention must be paid to the condition of the patient.

1-Immune system: Elimination of infecting organisms from the body depends on an intact immune system. Antibacterial drugs decrease the microbial population (bactericidal) or inhibit further bacterial growth (bacteriostatic), but the host defense system must ultimately eliminate the invading organisms. Alcoholism, diabetes, infection with the human immunodeficiency virus, malnutrition, or advanced age can affect a patient's immunocompetence.

2- Renal dysfunction: Poor kidney function causes accumulation in the body of antibiotics that ordinarily are eliminated by this route. This may lead to serious adverse effects unless drug accumulation is controlled by adjusting the dose or the dosage schedule of the antibiotic.

3- Hepatic dysfunction: Antibiotics that are concentrated or eliminated by the liver (for example, erythromycin and tetracycline) are contraindicated in treating patients with liver disease.

4- Poor perfusion: Decreased circulation to an anatomic area, such as the lower limbs of a diabetic, reduces the amount of antibiotic that reaches that area, making infections notoriously difficult to treat.

5- 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, which affect bone growth.

6- Pregnancy: All antibiotics cross the placenta. Adverse effects to the fetus are rare, except the for tooth dysplasia and inhibition of bone growth encountered with the tetracyclines. Aminoglycosides should be avoided in pregnancy because of their ototoxic effect on the fetus.

7- Lactation: Drugs administered to a lactating mother may 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 enough to cause problems.

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. For example, isoniazid is active only against mycobacteria

B. Extended-spectrum antibiotics
Extended spectrum is the term applied to antibiotics that are 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 and chloramphenicol 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 of an organism such as Candida albicans.

Drug Resistance
Bacteria are said to be resistant to an antibiotic if the maximal level of that antibiotic that can be tolerated by the host does not halt their growth.

A. Genetic alterations leading to drug resistance
Acquired antibiotic resistance requires the temporary or permanent gain or 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.

Spontaneous mutations of DNA: Chromosomal alteration may occur by insertion, deletion, or substitution of one or more nucleotides within the genome. If the cell survives, it can replicate and transmit its mutated properties to progeny cells.

DNA transfer of drug resistance: Of particular clinical concern is resistance acquired due to DNA transfer from one bacterium to another. Resistance properties are usually encoded in extrachromosomal R factors (resistance plasmids). In fact, most resistance genes are plasmid mediated.

B. Altered expression of proteins in drug-resistant organisms

Drug resistance may be mediated by a variety of mechanisms, such as a **1-** lack of or an alteration in an antibiotic target site, **2-** lowered penetrability of the drug due to decreased permeability,**3-** increased efflux of the drug, or 4- presence of antibiotic-inactivating enzymes .

Prophylactic Antibiotics

Certain clinical situations require the use of antibiotics for the prevention rather than 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.

Complications of Antibiotic Therapy

Because the mechanism of action of a particular antibiotic is selectively toxic to an invading organism does not insure the host against adverse effects. For example, the drug may produce an allergic response or be toxic in ways unrelated to the drug's antimicrobial activity.

A. Hypersensitivity

Hypersensitivity 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, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria. These infections are often difficult to treat.

Sites of Antimicrobial Actions

Antimicrobial drugs can be classified in a number of ways. These include 1) by their chemical structure (for example, β-lactams or aminoglycosides), 2) by their mechanism of action (for example, cell wall synthesis inhibitors), or 3) by their activity against particular types of organisms (for example, bacteria, fungi, or viruses).