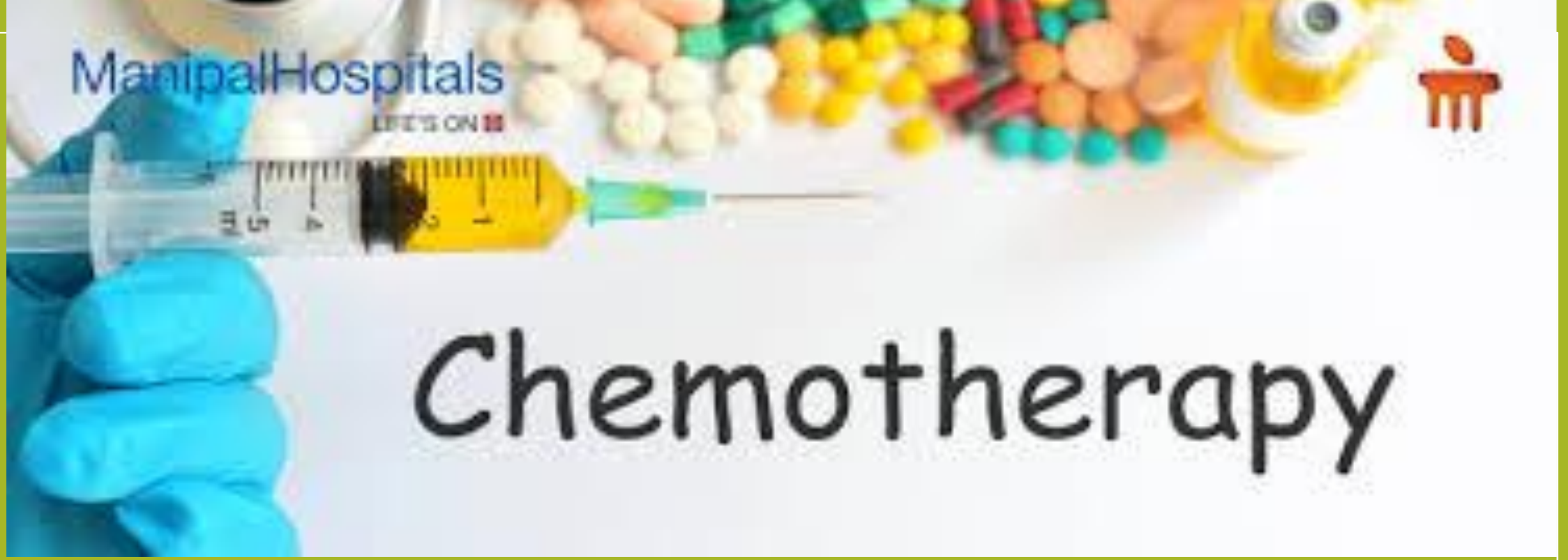

Lecture 5 by

Dr. Omar Dawood Salman

Department of Pharmacology / College of Medicine / University of Diyala

Principles of Chemotherapy

Chemotherapy is the term originally used to describe the use of drugs that are:-

- **"Selectively toxic"** to invading microorganisms while having minimal effects on the host (these called antibiotics).
- **The term also covers** the use of drugs that target tumors. Chemotherapy is specifically associated with those side effects such as loss of hair, nausea and vomiting.

Antimicrobial therapy

1. Takes advantage of the biochemical differences that exist between microorganisms and human beings.

2. These 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.

3. The selective toxicity is relative rather than absolute, requiring that the concentration of the drug **must 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 knowledge of :-

1) The organism's identity.
2) Some critically ill patients require empiric therapy.
3) The organism's susceptibility to a particular agent.
4) The site of the infection.
5) Patient factors (age, liver and kidney status .etc.)
6) The safety of the agent.
7) The cost of therapy.

Bacteriostatic vs. bactericidal drugs:

- Antimicrobial drugs are classified as either bacteriostatic or bactericidal. **Bacteriostatic drug**s 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 stopped 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. This classification may be too simplistic, because it is possible for an antibiotic to be bacteriostatic for one organism and bactericidal for another.

D-Effect of the site of infection on therapy: The blood-brain barrier

- Adequate levels of an antibiotic must reach the site of infection for 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.
- However, natural barriers to drug delivery are created by the structures of the capillaries of some tissues, such as the prostate, the vitreous body of the eye, and the central nervous system (CNS).

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, B-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.

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.

- 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.

Pregnancy and lactation

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

- 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.

Determinants of Rational Dosing

- Rational dosing of antimicrobial agents is based on their pharmacodynamics (the relationship of drug concentrations to antimicrobial effects) as well as their pharmacokinetic properties (the absorption, distribution, and elimination of the drug by the body).
- Three important properties that have a significant influence on the frequency of dosing are:
- A - concentration-dependent killing.
- B - time-dependent killing.
- C - post antibiotic effect.
- Utilizing these properties to optimize antibiotic dosing regimens will improve clinical outcomes and possibly decrease the development of resistance.

A-Concentration-dependent killing

- Certain antimicrobial agents, including aminoglycosides, fluoroquinolones, and carbapenems show a significant increase in the rate of bacterial killing as the concentration of antibiotic increases from 4- to 64-fold the MIC of the drug for the infecting organism
- 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

- **B-lactams, glycopeptides, macrolides, clindamycin, and linezolid do not exhibit this property; that is, increasing the concentration of antibiotic to higher multiples of the MIC does not significantly increase the rate of kill .**
- **The clinical efficacy of antimicrobials that have a non significant, dose-dependent killing effect 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. For example,**

- penicillin's and cephalosporins, dosing schedules that ensure blood levels greater than the MIC 60 to 70 percent of the time have been demonstrated to be clinically effective.

- Some experts therefore suggest that some severe infections are best treated by continuous infusion of these agents rather than by intermittent dosing.

C. Post antibiotic effect

The post antibiotic effect (PAE) is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC.

Chemotherapeutic Spectra

- the clinically important bacteria have been organized into eight groups based on Gram stain, morphology, and biochemical or other characteristics.
- Depending on the obove criteria antibiotic divided into:-

•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, the growth of which is normally kept in check by the presence of other microorganisms.

Combinations of Antimicrobial Drugs

It is therapeutically advisable to treat patients with the single agent that is most specific for the infecting organism. This strategy reduces the possibility of super- infection, decreases the emergence of resistant organisms , and minimizes toxicity.

Advantages of drug combinations

- Certain combinations of antibiotics such as B-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.

Disadvantages of drug combinations

- A number of antibiotics act only when organisms are multiplying. Thus, co- administration of an agent that causes bacteriostatic 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 effect of penicillins and cephalosporins

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. Some organisms are inherently resistant to an antibiotic. For example, gram-negative organisms are inherently resistant to vancomycin.
- **Prophylactic Antibiotics**
- Certain clinical situations require the use of antibiotics for the prevention rather than the treatment of infections. Because the haphazard use of antimicrobial agents can result in bacterial resistance and super-infection, prophylactic use is restricted to clinical situations in which the benefits outweigh the potential risks. The duration of prophylaxis is dictated by the duration of the risk of infection.

Complications of Antibiotic Therapy

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 by interfering with membrane function in the hair cells of the organ of Corti.

C. **Super-infections** 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 sites of action can be classified by their mechanism of action into:-

Mechanism of Action	Antimicrobial Agents
Inhibition of bacterial cell-wall synthesis	Penicillins, cephalosporins, imipenem/ meropenem, aztreonam, vancomycin
Inhibition of bacterial protein synthesis	Aminoglycosides, chloramphenicol, macrolides, tetracyclines, streptogramins, linezolid
Inhibition of nucleic synthesis	Fluoroquinolones, rifampin
Inhibition of folic acid synthesis	Sulfonamides, trimethoprim, pyrimethamine

Cell Wall Inhibitors

- Some antimicrobial drugs selectively interfere with synthesis of the bacterial cell wall structure that mammalian cells do not possess.
- The cell wall is composed of a polymer called **peptidoglycan** that consists of glycan units joined to each other by peptide cross-links.
- To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms; they have little or no effect on bacteria that are not growing and dividing.
- The most important members of this group of drugs are the B-lactam antibiotics (named after the B-lactam ring that is essential to their activity) and vancomycin.

Penicillins

- The penicillins are among the most widely effective antibiotics and also the least toxic drugs known, but increased resistance has limited their use.
- The nature of this side chain affects the antimicrobial spectrum, stability to stomach acid, and susceptibility to bacterial degradative enzymes (B -lactamases).

Penicillins

- The penicillins interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage), resulting in exposure of the osmotically less stable membrane.
- Cell lysis can then occur, either through osmotic pressure or through the activation of autolysins.
- These drugs are thus bactericidal.

- The success of a penicillin antibiotic in causing cell death is related to the;-

  A-antibiotic's size, B-charge, and C-hydrophobicity.

- Penicillins are only effective against rapidly growing organisms that synthesize a peptidoglycan cell wall. Consequently, they are inactive against organisms devoid of this structure, such as mycobacteria, protozoa, fungi, and viruses.
- Gram-negative microorganisms have an outer lipopolysaccharide membrane (envelope) surrounding the cell wall that presents a barrier to the water-soluble penicillins.
- However, gram-negative bacteria have proteins inserted in the lipopolysaccharide layer that act as water-filled channels (called porins) to permit transmembrane entry
- . [Note: Pseudomonas aeruginosa lacks porins, making these organisms intrinsically resistant to many antimicrobial agents.]

1-Natural penicillins

- These penicillins, which include those classified as antistaphylococcal, are obtained from fermentations of the mold Penicillium chrysogenum.
- Other penicillins, such as ampicillin, are called semisynthetic, because the different R groups are attached chemically to the 6 aminopenicillanic acid nucleus obtained from fermentation broths of the mold

➢ Penicillin G (benzylpenicillin) is the cornerstone of therapy for infections caused by a number of gram-positive and gram-negative cocci, gram-positive bacilli, and spirochetes .

➢ Penicillin G is susceptible to inactivation by B-lactamases (penicillinases).

❖ Penicillin V has a spectrum similar to that of penicillin G, but it is not used for treatment of bacteremia because of its higher minimum bactericidal concentration (the minimum amount of the drug needed to eliminate the infection)

❖ Penicillin V is more acid-stable than penicillin G. It is often employed orally in the treatment of infections, where it is effective against some anaerobic organisms.

2-Antistaphylococcal penicillins

- Methicillin , nafcillin , oxacillin , and dicloxacillin are penicillinase-resistant penicillins.
- Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci.
- Because of its toxicity, methicillin is not used clinically except to identify resistant strains of S. aureus].
- these drugs are destroyed in the acidic environment. Therefore, they must be administered 30 to 60 minutes before meals or 2 to 3 hours postprandially.

3-Extended-spectrum penicillins

- Ampicillin and amoxicillin have an antibacterial spectrum similar to that of penicillin G but are more effective against gram-negative bacilli. They are therefore referred to as extended-spectrum penicillins.
- These agents are also widely used in the treatment of respiratory infections, and amoxicillin is employed prophylactically by dentists for patients with abnormal heart valves who are to undergo extensive oral surgery. Resistance to these antibiotics is now a major clinical problem because of inactivation by plasmid-mediated penicillinase.
- Escherichia coli and Haemophilus influenzae are frequently resistant.
- Formulation with a B-lactamase inhibitor, such as clavulanic acid or sulbactam, protects amoxicillin or ampicillin, respectively, from enzymatic hydrolysis and extends their antimicrobial spectrum.

4-Antipseudomonal penicillins

- Carbenicillin , ticarcillin , and piperacillin are called antipseudomonal penicillins because of their activity against P. aeruginosa .

- Piperacillin is the most potent of these antibiotics. They are effective against many gram-negative bacilli, but not against klebsiella, because of its constitutive penicillinase.

- Formulation of ticarcillin or piperacillin with clavulanic acid or tazobactam, respectively, extends the antimicrobial spectrum of these antibiotics to include penicillinase-producing organisms

5-Penicillins and aminoglycosides

- The antibacterial effects of all the B-lactam antibiotics are synergistic with the aminoglycosides. Because cell wall synthesis inhibitors alter the permeability of bacterial cells, these drugs can facilitate the entry of other antibiotics (such as aminoglycosides) that might not ordinarily gain access to intracellular target sites.

✓This can result in enhanced antimicrobial activity. [Note: Although the combination of a penicillin plus an aminoglycoside is used clinically, these drug types should never be placed in the same infusion fluid, because on prolonged contact, the positively charged aminoglycosides form an inactive complex with the negatively charged penicillins.]

Causes of resistance to B- Lactam

1- B-Lactamase activity

This family of enzymes hydrolyzes the cyclic amide bond of the B-lactam ring, which results in loss of bactericidal activity .They are the major cause of resistance to the penicillins and are an increasing problem.

- B-Lactamases are either constitutive or, more commonly, are acquired by the transfer of plasmids.
- Some of the B-lactam antibiotics are poor substrates for B-lactamases and resist cleavage, thus retaining their activity against B-lactamase producing organisms.

Note: Certain organisms may have chromosome-associated B-lactamases that are inducible by B-lactam antibiotics (for example, cefoxitin).]

- Gram-positive organisms secrete b-lactamases extracellularly, whereas gram-negative bacteria confine the enzymes in the periplasmic space between the inner and outer membranes.

2-Decreased permeability to the drug.

- ❑ Decreased penetration of the antibiotic through the outer cell membrane prevents the drug from reaching the target PBPs.
- These penicillin-binding proteins (PBPs) are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of the morphologic features of the bacterium.
- Exposure to these antibiotics can therefore not only prevent cell wall synthesis but also lead to morphologic changes or lysis of susceptible bacteria.

- ❑ The presence of an efflux pump can also reduce the amount of intracellular drug.

Causes of resistance to B- Lactam

3-Altered PBPs

- ✓ Modified PBPs have a lower affinity for B-lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect inhibition of bacterial growth.
- ✓ This mechanism may explain MRSA, although it does not explain its resistance to non-B -lactam antibiotics like erythromycin, to which they are also refractory.

Adverse reactions

1-Hypersensitivity. This is the most important adverse effect of the penicillins. The major antigenic determinant of penicillin hypersensitivity is its metabolite, penicilloic acid, which reacts with proteins and serves as a hapten to cause an immune reaction.

2-Diarrhea. This effect, which is caused by a disruption of the normal balance of intestinal microorganisms, is a common problem. It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum. As with some other antibiotics, pseudomembranous colitis[2] may occur

3-Nephritis; All penicillins, but particularly methicillin, have the potential to cause acute interstitial nephritis.

[Methicillin is therefore no longer available.]

4-Neurotoxicity: The penicillins are irritating to neuronal tissue, and they can provoke seizures if injected intrathecally or if very high blood levels are reached. Epileptic patients are particularly at risk

5-Hematologic toxicities:

- Decreased coagulation may be observed with the antipseudomonal penicillins (carbenicillin and ticarcillin) and, to some extent, with penicillin G.
- Additional toxicities include eosinophilia.


THANK YOU!