Chemotherapy; Antimicrobials

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Lecture 19

done by :

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Drugs are used to prevent, control and treat diagnosed disease .(actually most of diseases are controllable rather than treatable then they are given drugs for life while in treatment the drug is given for just a period of time)

Most Antimicrobial drugs are given to the patient for 10-30 days.

Principles of antimicrobial drugs

Objectives Know:

- ✓ Principles of antimicrobial therapy
- ✓ Classes of different antimicrobials

their spectrum of activity their pharmacokinetic properties their mechanism of action their major side effects…

it includes Anti-cultural agents , Antimicrobial , Antiprotozoal , etc.

Chemotherapy :

Drugs used in treating infectious diseases and cancer

- ✓ Infectious diseases are a major cause of death worldwide (Kozier, et al. 2008)
- ✓ The control of the spread of microbes & the protection of people from communicable diseases & infections are carried out on the international, national, community, and individual levels

✓ **History:**

2500 years ago: anti-infective substances were found:

- Chinese used moldy soya beans for carbuncles & boils+
- Greeks (Hippocrates) used wine to treat wounds
- 1900's: Syphilis treated with arsenic
- 1936: Sulfonamides discovered
- 1940's: Penicillin & Streptomycin discovered
- 1950's: Golden age of antimicrobials

✓ Infection related concepts:

-Infection: is an invasion of body tissue by microorganisms (MO's) & their growth there

- Such a MO is called: infectious agent

- If the MO produces no clinical evidence of disease, the infection is called **subclinical or asymptomatic** : there is an infection , but no clinical evidence. -> the bacteria is there but doesn't produce obvious manifestations because of individual defense system. If defense system is compromised then the infection is so obvious even if it's within what's called subclinical infections))

- If a MO leads to a detectable alteration in normal tissue function, it is called an infectious disease

-Pathogenicity: is the ability to produce disease; thus a pathogen is a MO that causes disease

-True pathogen causes disease or infection in a healthy individual

-Opportunistic pathogen causes disease only in a susceptible individuals

Susceptible : the state of being predisposed to , or of lacking the ability to resist the pathogen

Communicable disease: is the ability of the infectious agent to be transmitted to an individual by direct or indirect contact or as an airborne infection

E.g.; common cold virus is more readily transmitted than the bacillus that causes leprosy (Hansen's disease)

((different species of viruses are transmitted easily and that's why antiviral agents have limited use in viral infections))

✓ Types of MOs causing infections

Four major categories of MOs cause infections in humans:

1. Bacteria: the most common, hundred species can attack humans, transferred by air, water, food, soil, body tissues & fluids, and inanimate objects
2. Viruses: consist primarily of nucleic acid, therefore must enter living cells in order to reproduce (e.g.; rhinovirus, hepatitis, HIV)

Viruses usually use the host cell component to replicate , so you can't get rid of viruses without affecting the host cell

3. Fungi: include yeasts & molds. Candida albicansis a normal flora in human mouth, GIT and vagina (they may cause problems when the immune system is compromised)
4. Parasites: live on other living organisms examples: protozoa that causes malaria, helminthes (worms), arthropods (mites, fleas, ticks)

Community-acquired:e.g. nosocomi

✓ General manifestations of infection:

Infection caused by bacteria take many forms, ranging from mild local infection to lifethreatening systemic infection

- Fever, chills, rigors (coldness, body temperature is high)
- Pain or aches (A common symptom with most diseases)
- Nausea
- Vomiting -weakness

(when we have a specific infection in a site of the body , the highest amount of the bacteria would be there so we need to have a specific antibiotic to reach this site without affecting other sites.) LIKE THOSE ANTIBIOTICS THAT WORKS ONLY IN LOW PH.

Infection vs inflammation

INFECTION : there is a pathogen MO

Inflammation : specific mediators responding to a stimulator leading to redness , swelling .

Antimicrobials

Classified into 1. antibiotics and

2. chemotherapeutic agents

Antibiotics

Agents or antimicrobials that interfere with the growth or multiplication or kill microorganisms like bacteria, fungi and they are of natural source e.g. Penicillin's

Chemotherapeutics

Agents or antimicrobials that interfere with the growth or multiplication or kill microorganisms and they are of synthetic source e.g. Sulfonamides

Antiseptics

Agents that kill or inhibit growth of microorganisms when applied to living tissues example: Iodine ((an excellent antiseptic))

Disinfectants

Agents killing or inhibiting growth of microorganisms when applied to nonliving objects- chlorine.

- **Cidal** (Irreversible inhibition of growth) An agent that kills microorganisms Bactericidal, fungicidal, viricidal…etc e.g. Penicillin's, Cephalospo-;rin's, Aminoglycosides…etc

- **Static** (Reversible inhibition of growth)
  An agent that inhibits growth of microorganism
  Bacteriostatic, fungistatic, viristatic…etc
  e.g. Sulfonamides, Tetracyclines, Macrolide antibiotics…etc (static facilitate the immune system to get rid of the inhibited bacteria)

A static agent in large doses becomes cidal and cidal agents in low doses become static
One drug (chloramphenicol) could be bacteriostatic for one organism (gram negative rods), & cidal for another (S. pneumoniae) some agents can be CIDAL for specific bacteria & STATIC for another BACTERIA

is IT IMPORTANT FOR U AS A DOCTOR TO KNOW WHICH ONE IS CIDAL OR STATIC??

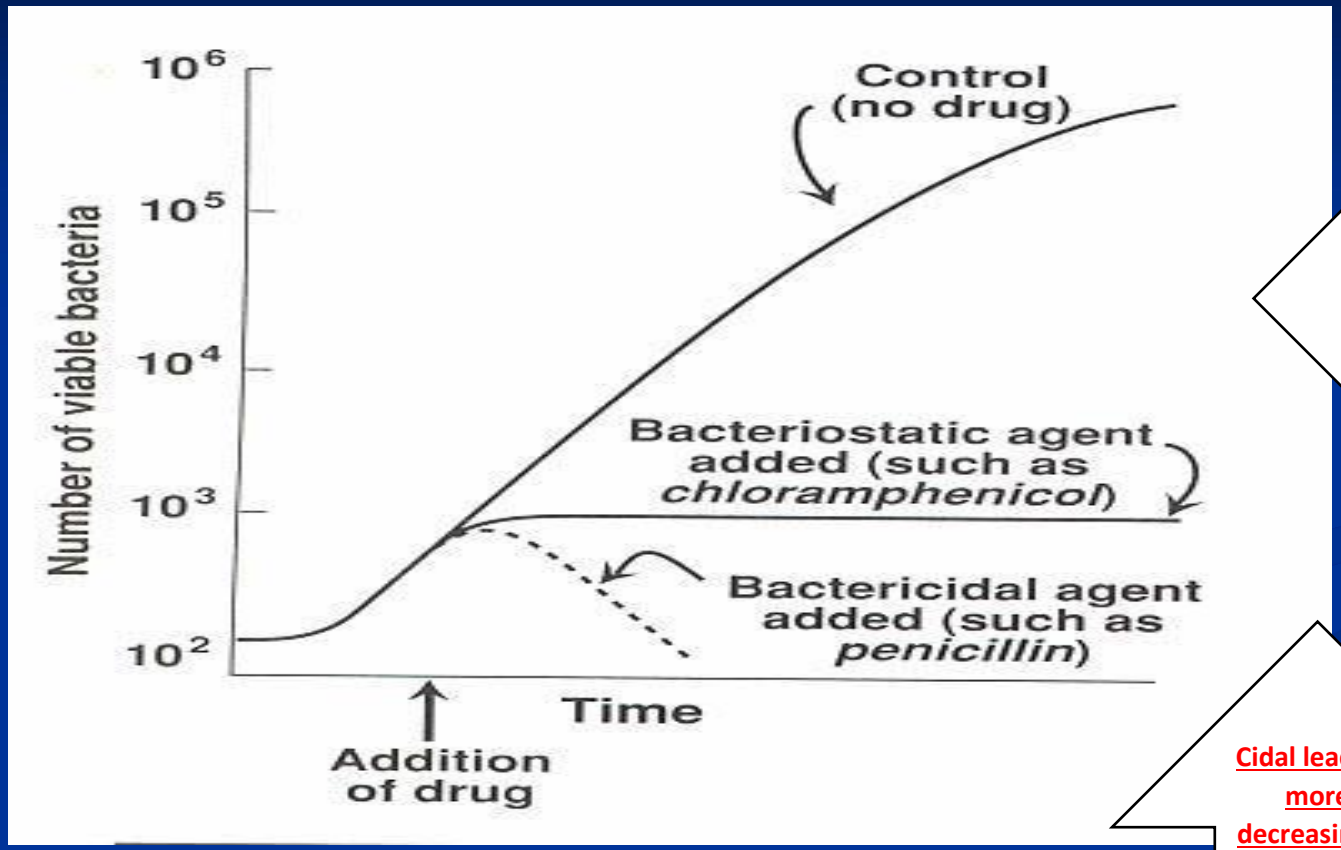
YES, because in case of using Static you are inhibiting the Growth of bacteria so it just mediates getting rid of the inhibited Bacteria by the immune system , while in case of CIDAL it kill the Bacteria and it is usually used in case of compromised immune System.
CIDAL is much stronger than STATIC

MIC: (Minimal Inhibitory Concentration) Lowest concentration of antibiotic that prevents visible microbial growth

MBC: (Minimal Bactericidal Concentration) Lowest concentration of antibiotic that reduces the number of viable cells by at least 1000-fold

The MBC of a truly bactericidal agent is equal to or just slightly above its MIC the lowest dose that expected to kill bacteria

AAL: The Attainable Anti-biotic Level is the concentration of the drug that can be reached in the target tissues without causing toxic or side effects



Remember that static inhibits bacterial growth and allow immune system to get rid of inhibited bacteria

Cidal leads to more decreasing in number of bacteria by killing it directly

- ✓ **Trough Levels:** lowest conc reached by a drug before the next dose is administered

Levels of antibiotics reach minimal levels (troughs) at roughly predictable times after administration

The troughs may be at, or below the MIC (not to much below MIC)

This may or may not be a problem because of two factors:

- Post Antibiotic Effect, a prolonged period before bacteria resume growth

- Synergism between host defenses and subMIC levels of antibiotics (even if it below MIC it will not be ineffective because host defense help in inhibiting & killing bacteria)

Post-antibiotic effect (PAE):

- 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

(several hours) require only one dose per day (e.g. Aminoglycosides & Fluroquinolones)
Trough levels may increase the frequency of drug-resistant bacteria

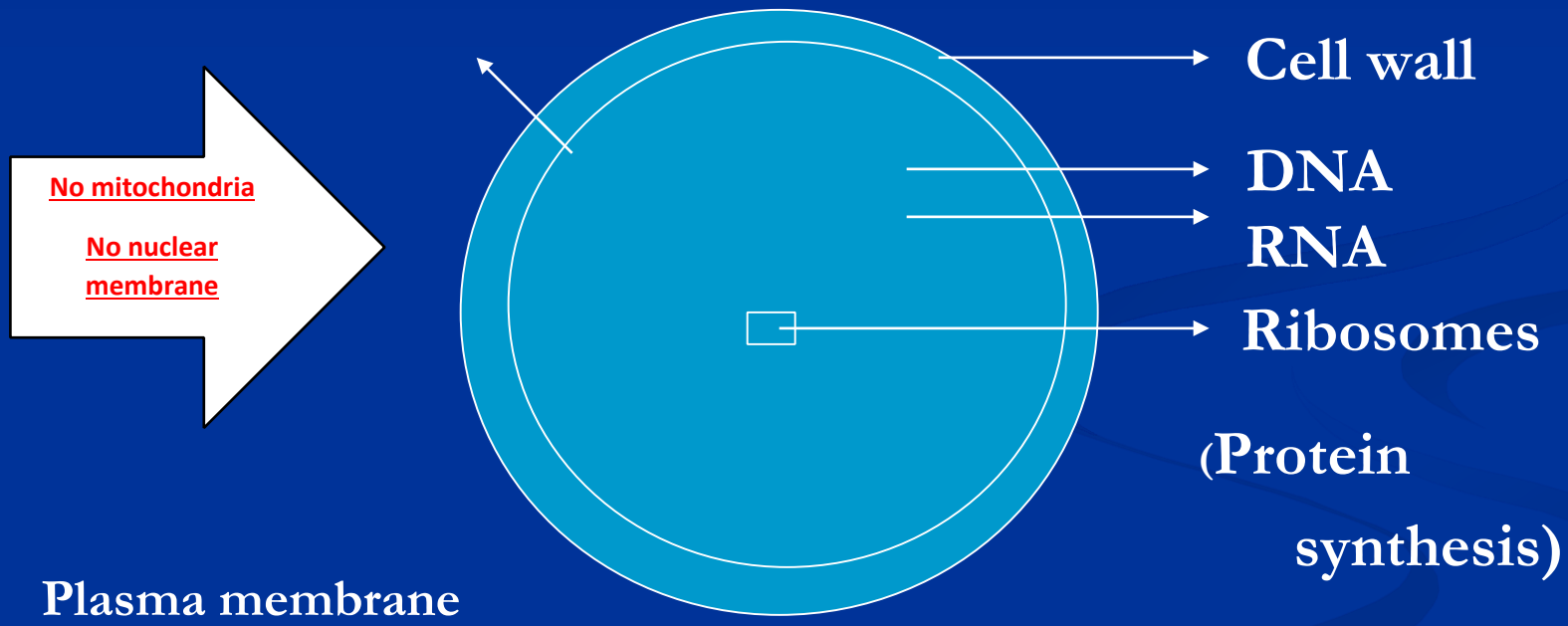
- Frequency of developing resistance is greatly increased at levels just above the MIC

Drug -Resistance bacteria : bacteria adapts the antibiotic

If trough level was greatly below MIC , the incidence of resistance is going to be higher

- Development of resistance to ciprofloxacin is 10,000 times more frequent at 2 times the MIC compared to 8 times the MIC

✓ Mechanism of action:



In general antibiotics hit structures are found in MO and not found in human cells

- Inhibitors of cell wall synthesis

Penicillins, Cephalosporins, Bacitracin, Vancomycin, Cycloserine…etc

Most bacteria have rigid cell walls that are not found in host cells (selective toxicity)

Cell wall inhibitors work by inhibiting the formation of peptidoglycans that are essential in cell wall formation

Disruption of the cell wall causes death of the bacterial cell (Bactericidal)

- Interference with permeability or function of plasma membrane

Antifungal agents (Colistin, Nystatin, Amphotericin B, Polymyxin B)

- Inhibitors of DNA synthesis or replication (DNA disturbers)

Quinolones (Nalidixic acid), Fluoroquinolones, Griseofulvin, Novobiocin…etc

- Inhibitors of RNA

  Rifampicin
- Inhibitors of protein synthesis

Aminoglycosides (Streptomycin, Gentamicin…), Chloramphenicol, Tetracyclines, Lincomycin, Clindamycin…etc

- Interference with metabolism of microorganisms

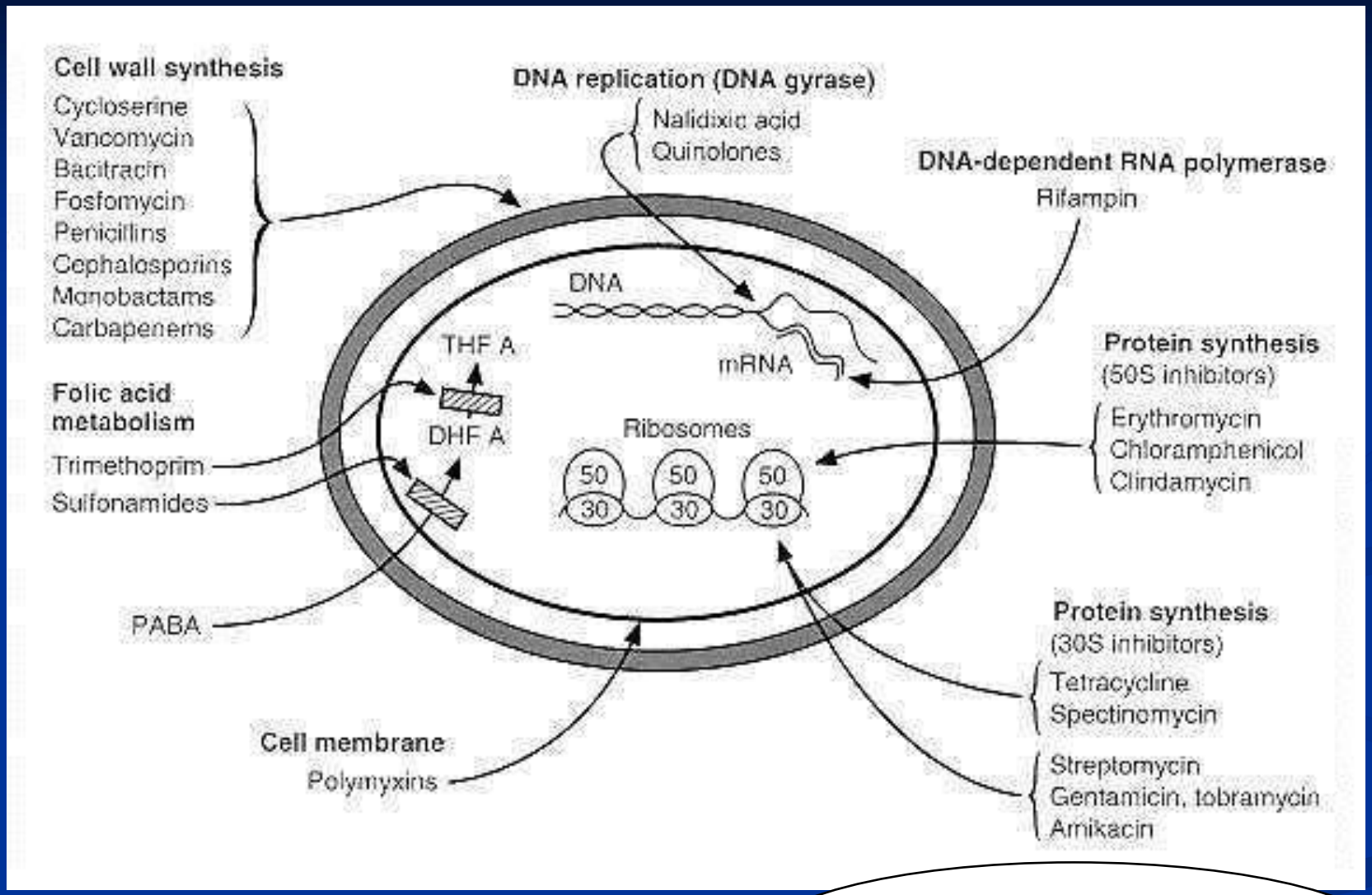
2 antibiotics : 1Sulfonamides 2 Trimethoprim

PABA DHFA THFA

Folic acid is important for producing nucleic acid

For synthesis of folic acid Bacteria requires paraaminobenzoic acid (PABA) , its converted to folic acid , so sulfonamide compete with PABA and inhibits producing folic acid.

In human cells we don't need PABA to produce folic acid.



Protein synthesis inhibitors works on 30s