PHARMACOLOGY

Modified slides no.1
Writer: Hala Mousa
Corrector: Hamza Alabade
Doctor: Suheil Zmeili

Chemotherapy; Antimicrobials

Suheil Zmeili, MD; PhD
School of Medicine
Department of Pharmacology
University of Jordan

■ **NOTE: Everysingle wordin the slides is required!**

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 possible mechanisms of bacterial resistance
  their major side effects…

- ■ The complement in this slide:
- Spectrum of activity is related to how many bacteria could be covered using a specific drug. The more bacteria, the broader is the spectrum of activity of a given chemotherapeutic agent or antibiotic.
- Pharmacokinetic properties: we want to reach a point of cure or treatment using a specific drug and most antibiotics are useful at a certain period of time and at a specific dose so afterwards you stop the administration of the drug as the target is reached. Although, we have to adjust the dose according to several factors, like the acetylation Rate, there are rapid and slow acetylators.
- The major problem with the use of antibiotics is the development of resistance as the bacteria start to attack the antibiotics and that's mainly due to the misuse. For example, viral infections are treated using antiviral drugs only, so it's not wise to treat viral infections using anti bacterial drugs!
- There are unique side effects to each class of antibiotics.

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

■ NOTE: There's a misconception of the term 'Chemotherapy' even in medical areas. It's not confined to anti cancerous agents only, it includes antibacterial, anti fungal , antiviral and anti parasitic drugs. For example TB is treated by chemotherapeutic drugs (anti bacterial).

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

So easy!

- 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

- 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)

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 (non-living objects)
2. *Viruses:* consist primarily of nucleic acid, therefore must enter living cells in order to reproduce (e.g.; rhinovirus, hepatitis, HIV)

■ NOTE: Antiviral drugs are not highly successful in treating viral infections and many viruses are self-limiting but they take time.

3. *Fungi:* include yeasts & molds. *Candida albicans* is a normal flora in human mouth, GIT and vagina

4. *Parasites:* live on other living organisms examples: protozoa that causes malaria, helminthes (worms), arthropods (mites, fleas, ticks)

Community-acquired: e.g. nosocomial=also referred to as healthcare-associated infections (HAI)

■ NOTE: Opportunistic infections or overgrowth of a certain fungi or bacteria can occur due to the constant use or misuse of a certain antiviral or antibiotic as they don't only affect the pathogenic organisms but also the useful ones (microbiota) which normally exist and have useful functions .

■ NOTE: HAI (also known as hospital induced infections) occurs when an individual acquires an infection from a hospital or other healthcare facilities when seeking medical treatment or advice.

General manifestations of infection:

Infection caused by bacteria take many forms, ranging from mild local infection to life-threatening systemic infection

- Fever, chills, rigors
- Pain or aches
- Nausea
- Vomiting
- Weakness

Infection vs inflammation

■ NOTE: Rigors are more severe shivering of the body as compared to Chills.

■ NOTE: Manifestations usually depend on the site of infection, ex: respiratory infections are associated with cough.
In general, all infections are associated with fever as bacteria produce toxic substances that lead to fever.

■ NOTE: Many bacterial infections are associated with inflammation, but many inflammatory conditions are NOT associated with bacterial infections unless there is a bacterial infection.

- An infection occurs when germs enter the body, increase in number, and cause a reaction of the body
- Inflammation occurs when mediators and inflammatory cells travel to the place of an injury or foreign body like bacteria. It is an essential part of your body's healing process
- Anti-inflammatory drugs have no antibacterial activity e.g. steroids and NSAIDs whereas, certain antibiotics have both antibacterial and anti-inflammatory effects e.g. azithromycin (one of the main antibiotics), tetracyclines and co-trimoxazole (one of sulfur drugs)

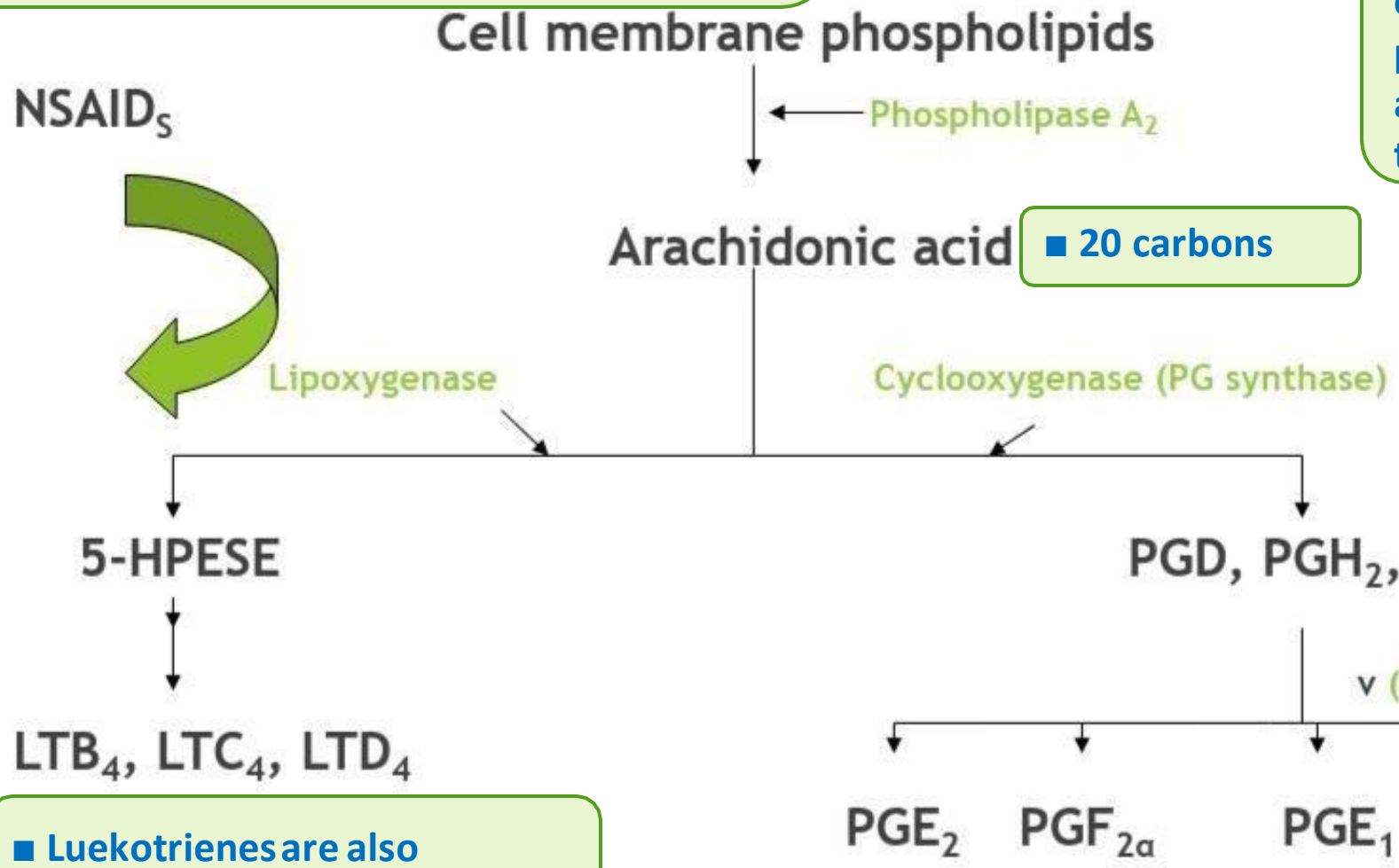
■ NOTE: Azithromycin modulates the function of Phospholipase A2, but we can't say that it acts like steroids because its mechanism differs. It delays its function and interferes with the function of PLA2 thus inhibiting both ways.

■ NOTE: Tetracyclins and co-trimoxazole supress the production of TNFs and ILs and cytokines.

- The complement in this slide: If a patient has an inflammatory disease, there's no need to use antibacterial drugs unless the patient has an infection.
- Likewise, there's no need to use anti inflammatory drugs in patients with bacterial infections except if they're useful in lowering fever or pain that originates from the inflammatory response to the bacterial infection.
- Paracetamol, which is the most commonly used analgesic in the CNS to relieve or decrease high body temperature so, it's an analgesic not antibiotic , although it's devoid of anti inflammatory effects and it has no effects on peripheral nervous system , but it inhibits prostaglandins synthesis in the CNS.

■ **NOTE**: so, the mechanism of action for paracetamol is inhibition prostaglandins synthesis in the CNS only

■ Non steroidal anti inflammatory drugsact on cyclooxygenase pathwayand inhibit the production of prostaglandins only. These are lesspotent compared to steroidalanti inflammatorydrugs. . In cases of inflammation we start with NSAIDs.



■ 20 carbons

■ Steroids; cortisone and cortisone derivatives are very potent anti-inflammatorydrugs as they inhibit phosphlipaseA2 thus inhibiting both pathways.

■ Prostaglandins are Very important and they're the major chemical mediators of inflammation.

■ Luekotrienes are also involved in inflammation.

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

■ **NOTE: If the antimicrobial agent was from a natural source then it's an antibiotic, but if it's synthetic then it's a chemotherapeutic agents.**
A hint from the doctor: he once administered a drug that has been expired since 3 years but didn't cause harm. Studies revealed that if the drug is chemotherapeutic then you shouldn't stick to the expiry date written, these drugs can remain viable for years, but if it's an antibiotic then you have to stick to the expiry date because it's accurate .

■ **NOTE: Semisynthetic drugs, the original substance is taken from a living organism and then it's modified chemically.**

Chemotherapeutics

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

Antiseptics

Agents that kill or inhibit growth of microorganisms when applied to tissues (for example: alcohols to sterilize skin and during surgeries as well as Iodine which has anti fungal, antiviral and anti bacterial effects)

Disinfectants

Agents killing or inhibiting growth of microorganisms when applied to nonliving objects (like Chlorine that is used to sterilize swimming pools or detergents that are used to sterilize floors in hospitals)

■ NOTE: Alcohol can be used as an antiseptic or disinfectant.

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

■ NOTE: when given in the therapeutic dose!

■ NOTE:: So, in the therapeutic dose, the drug could be cidal or static.
-Static drugs inhibit the growthand thus allow your immune system to get rid of the inhibited bacteria. So, the static agent will eventuallyend the infectionthereforeit's not onlythe function of cidal agents. So what determines if we're going to take a cidal or a static agent? Well, there's a criteria for the selection.

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

The MBC of a truly bactericidalagent is equal to or just slightlyabove its MIC

AAL: The AttainableAnti-biotic Level is the concentrationof the drug that can be reachedin the target tissues without causing toxic or side-effects

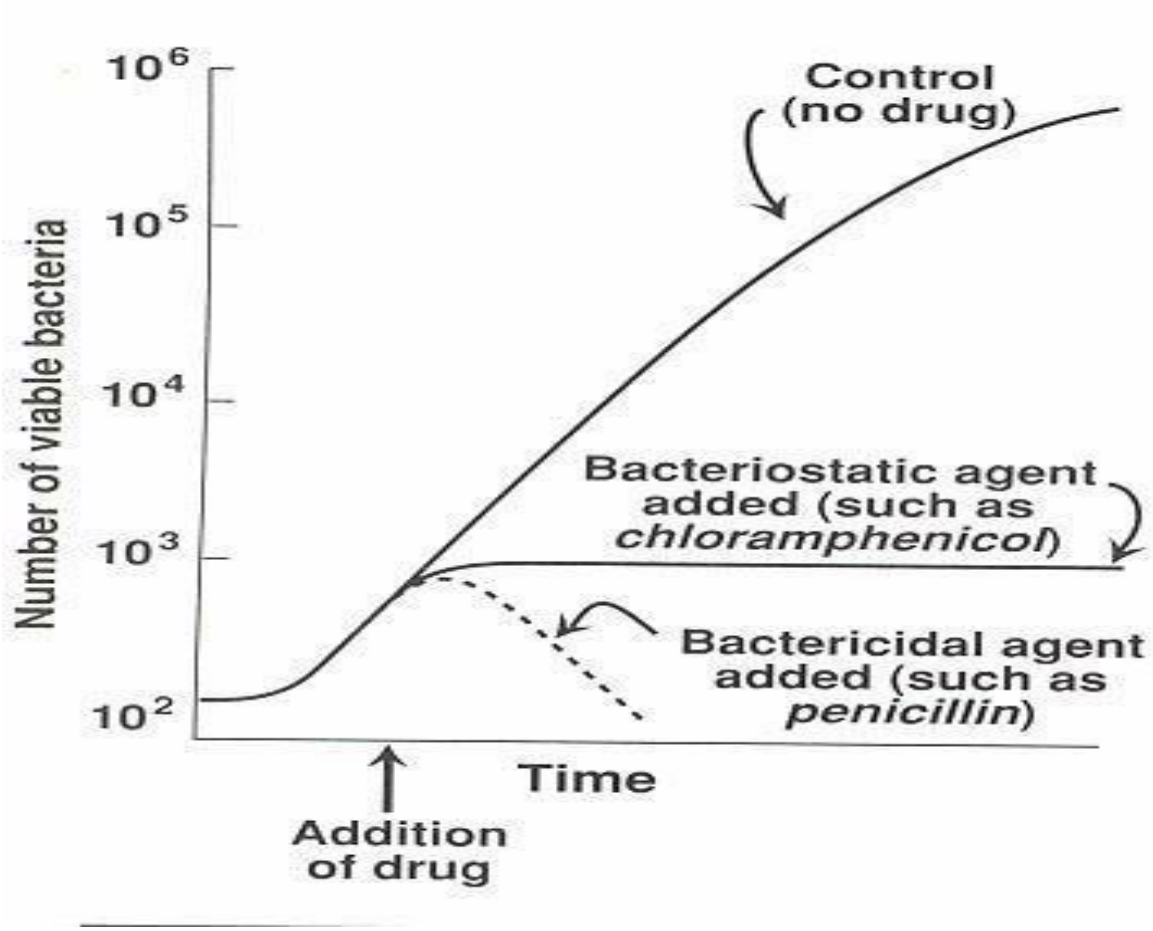
■ NOTE: Cidal or Staticchave nothing to do with spectrum of activity nor the mechanism of action. It's believed that cidal drugs are more potent in killing larger number of bacteria as compared to staticones, but it's not always the case as many bacteriocidal drugs have narrow spectrum of activity and many Bacteriostatic ones have wide spectrum of activity, it depends on the type of bacteria and what's known as the first drug choice to a specific infection.Now bacteria have cell walls that can provide some sort of selectivity to some drugs over other ones, although there's no single drug that's free of side effects. But you can't say that cidal agents will affect the cell walls and staticones will affect the protein synthesis as it has nothing to do with the mechanism of action.

A static agent in large doses provided that not reaching the toxic dose 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)

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

■ NOTE: For example, let's assume that we have Penicillin that is cidal and Sulfonamides that are static and both are in therapeutic doses. If the dose of Penicillin is lowered then it becomes static but you must be aware of not reaching subtherapeutic levels that bacterial resistance may develop. Either cidal or static, they will lead to an end of the infection and the selection differs according to the state of the patient. For instance, if a patient is immunocompromised and has a bacterial infection then we have to give him/her bactericidal because his/her immune system cannot get rid of the infection



■ **NOTE: If you grow bacteria in a medium and observe the number of viable bacteria without using a drug, their number is going to increase as they multplicate and reproduce continuously. Bacteriostatic is going to decrease the number and bacteriocidal is going to reduce it further. Bacteriostatic can lead to the same effect of bacteriocidal if the drug is used and along with a good immune system, so it will lead to a complete end of the infection.**

V1: Paracetamol is antibiotic

V2:
paracetamol is analgesic

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