Pharmacology

Chemotherapy

I. History and Introduction

***Chemotherapy* :** is the use of chemical agents (either **synthetic or natural**) to destroy infective agents (microorganisms' i.e. bacteria, fungus , viruses, protozoa, and helminthes) and to inhibit the growth of malignant or cancerous cells **.**

Chemotherapeutic agents: are chemical which are intended to be toxic for parasitic cell but nontoxic to the host, such selective toxicity depends on the existence of exploitable biochemical difference between the parasite and the host cell.

Antimicrobials: are chemical agents (**synthetic/natural**) used to treat bacterial, fungal and viral infections.

Antibiotics: are substances produced by various species of microorganisms (bacteria, fungi actinomycetes) that suppress the growth of other microorganisms. Antimicrobial drug exhibits *selective toxicity*. i.e. the drug is harmful to the parasite without being harmful to the host.

***Bactericidal versus bacteriostatic action*:** When antimicrobial agents lead to the death of the susceptible microbe (e.g. bacteria) it is said have bactericidal action but when it merely inhibits the growth and therefore spread of the microbial population it is said to have bacteriostatic action.

Anticancer agents: Drugs or chemicals used to manage neoplastic diseases.

Antiprotozoals: are drugs used to treat malaria, amoebiasis, gardiasis, trichomoniasis, toxoplasmosis, pneumocystis carinii pneumonia, trypanosomiasis and leshmaniasis.

Anthelminthics : are drugs used in the treatment of intestinal and tissue worms.

- **1877:** Antibiosis was first described in bacteria when Louis Pasteur and Robert Koch observed that an airborne bacillus could inhibit the growth of *Bacillus anthracis*.
- **1875:** The antibiotic properties of *Penicillium sp.* were first described in England by John Tyndall in 1875. However, his work went by without much notice from the scientific community.
- **1909:** Modern research on antibiotic therapy began in Germany with the development of the narrow-spectrum antibiotic Salvarsan by Paul Ehrlich.
- **1928:** Alexander Fleming. Discover penicillin.
- **1939:** Ernst Chain and Howard Florey became interested in Alexander Fleming work, and came up with the purified form of penicillin.

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- **1939:** Rene Dubos isolated gramicidin, one of the first commercially manufactured antibiotics in use during World War II to prove highly effective in treating wounds and ulcers.
- **1939:** Gerhard Domagk developed the Prontosil, from red tissue dye (the first commercially available antibacterial antibiotic) at the Bayer Laboratories of the IG Farben conglomerate in Germany.
- Antibiotic:-is a substance or compound (made from a living source) that kills or inhibits the growth of bacteria.
- Antibacterial:- is a substance or compound that kills or inhibits the growth of bacteria.

According to the two definitions above we can say that the antibacterial agents have a wide understood more than the antibiotics. (Can you see why?).

Classification of Antibacterial :

There are three ways to classify the antibacterials, they are:

1- According to the effectiveness:

I- Bactericidal (agent that destroys or kills bacteria).

II- Bacteriostatic (agent that slows or retards the multiplication of bacteria).

2- According to the spectrum:

I- Narrow spectrum (agent acting only on a single or a limited group of microorganisms.).

II- Extended spectrum (agent that effective against gram-positive bacteria also against significant number of gram-negative and vise versa.

III- Broad spectrum (agent that effects on a wide range variety of microorganisms).

3- According to the mechanism of action:

a. Inhibitors of cell wall synthesis.
b. Inhibitors of protein synthesis.
c. Inhibitors of cell membrane functions.
d. Metabolism inhibitors.
e. Inhibitors of nucleic acid synthesis or function.

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Mechanisms of resistance to antibiotics :

1. Production of enzymes that inactivate the drug (eg. ß -lactamase, which inactivates beta lactam antibiotics; acetyl transferases, which inactivate chloramphenicol; kinases and other enzymes, which inactivate aminoglycosides.
2. Alteration of the drug-binding site: this occurs with penicillins, aminoglycosides and erythromycin.
3. Reduction of drug uptake by the bacterium: eg. Tetracyclines
4. Alteration of enzymes: eg. Dihydrofolate reductase becomes insensitive to trimethoprim.

Antibacterial agents

Inhibitors of Cell Wall Synthesis

Penicillins

- Discovered by Felming in 1928.
- Produced by *Penicilinum spp.*(mainly *natatum*)
- Contain β-lactum ring (6-amino penicillinic acid) and and a carboxyl group.
- The mechanism of action includes:

- Inhibition the formation of peptidoglycan cross-links in the bacterial cell wall. The β-lactam moiety (functional group) of penicillin binds to the enzyme transpeptidase that links the peptidoglycan molecules in bacteria, which weakens the cell wall of the bacterium (in other words, the antibiotic causes cytolysis or death due to osmotic pressure).
- In addition, the build-up of peptidoglycan precursors triggers the activation of bacterial cell wall hydrolases and autolysins, which further digest the bacteria's existing peptidoglycan.

Penicillins can be divided to four groups they are:-

I- Natural (Basic) Penicillins:

- They are narrow spectrum, bactericidal, and penicillinase sensitive (Penicillinase is a specific type of β-lactamase, affect the penicillins by hydrolysing the β-lactam ring).

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- There are two types of natural penicillins they are:

1- Penicillin G: (Benzyl penicillin, Procain penicillin, Benzathine penicillin):

- It was the first of the penicillins, and remains an important and useful antibiotic.
- It is particularly active against Gram-positive bacteria; Sensitive micro-organisms include Gram-positive streptococci, Gram-positive Bacilli, Gram-negative cocci (*Neisseria),* most anaerobic bacteria including *Clostridium* and Spirochetes. (*Treponema*).
- *Staphylococcus aureus* resist natural penicillins because of its ability to produce penicilinase (β-lactamase).

- Penicillin G is inactivated by gastric juice (Acid labile) so that it not administrated orally but used via other routes like Intravenous and Intramuscular.

2- Penicillin V: (Phenoxymethyl penicillin)

- Semi synthetic penicillin, it has similar bacterial effect to Penicillin G.
- Penicillin V is acid stable in contrast to Penicillin G therefore it can be administrated orally.

II- Antistaphylococcal (penicillinase resistant) Penicillins:

- They are semi-synthetic, narrow spectrum, acid stable (can be administrated orally) and penicillinase resistant penicillins.
- These antibiotics are effective against streptococci and most community-acquired penicillinase-producing staphylococci (drug of choice).
- Examples; Nafcillin, oxacillin, cloxacillin, and dicloxacillin .

III- Aminopenicillins (Extended spectrum penicillins):

- Semi-synthetic, Extended spectrum, acid stable and penicillinase sensitive penicillins.
- This group has slightly less activity than natural penicillins against Gram-positive bacteria and obligates anaerobes but considerably greater activity against Gram-negative bacteria, although their action is poor against *Klebsiella*, some *Proteus* spp., and *Pseudomonas* spp.
- Examples; Ampicillin, Amoxicillin and Pivampicillin.

IV- Antipseudomonal Penicillins:

- Semi-synthetic, broad spectrum, acid labile and penicillinase sensitive penicillins.
- The antipseudomonal penicillins have comparable spectra of activity against many gram-positive and gram-negative pathogens, including most anaerobes. and (as appear from their nomination) they are the drug of choice against *Pseudomonas aeruginosa* infections .
- Examples; Carbencillin, Mezlocillin, piperacillin, and ticarcillin .

Clinical problems with penicillins :

- **Narrow spectrum:** it corrected by administration of extended or broad spectrum penicillins instead of narrow spectrum penicillins .
- **Acid lability:** it corrected by administration of acid stable penicillins .
- **Short Half- life:** it corrected by increase the half-life of penicillins by using of ***Probenecid*** which *blocks the tubular secretion of penicillin*, thereby prolonging its half-life.
- **Penicillinase sensitivity:** it solved by using of ***Clavulanic-suitable penicillin mixture*** whereas clavulanic acid has a potent penicillinase inhibitory effect.

Pharmacokinetical profile of Penicillins:

- **Absorption**: all acid stable penicillins can be absorbed well (about 70%) in contrast to acid labile penicillins (about 30%).
- **Distribution**: penicillins are well distributed throughout the body, the plasma-protein binding ratio arrange between (30-90%).
- **Metabolism**: usually the metabolism in penicillins is not significant.
- **Excretion**: all penicillins are excreted through kidney (*except Naficillin which excreted through the bile*), penicillins have been excreted via active tubular secretion (80%), and glomerular infiltration (20%).

General side effects of Penicillins

1- **Hyper sensitivity.** Skin Rashes (Type I, III), Anaphylactic Shock (Type I)
2- **GIT disturbances.** They are cause imbalance in microflora of the GIT.
3- **Nephrotoxicity.** They are cause interstitial nephritis.
4- **Neurotoxicity.** Penicillins irritant to the neural tissues so that they induce seizures.

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Cephalosporins

- The cephalosporins are semi-synthetic antibiotics derived from products of various microorganisms, including *Cephalosporium* and *Streptomyces.*
- All cephalosporins have a 7-aminocephalosporanic acid composed of a dihydrothiazine ring fused to a β-lactam ring.
- The cephalosporin β-lactam ring is the chemical group associated with antibacterial activity.
- Like the penicillins, Cephalosporins are bactericidal and relatively non-toxic (although less so than the penicillins), and less likely to cause allergic reactions.
- Cephalosporins disrupt the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity .
- The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by transpeptidases known as penicillin-binding proteins (PBPs). PBPs bind to the D-Ala-D-Ala at the end of muropeptides (peptidoglycan precursors) to crosslink the peptidoglycan. Beta-lactam antibiotics mimic the D-Ala-D-Ala site, thereby irreversibly inhibiting PBP crosslinking of peptidoglycan.

❖ Cephalosporins can be divided in to four generations, they are:-

I- ***1st generation of Cephalosporins:***

- The first generation drugs are active against a range of both Gram-positive and Gram-negative organisms comprising staphylococci (including beta-lactamase- producing strains), *Pasteurella*, *E. coli*, *Actinobacillus*, *Actinomyces*, *Haemophilus*, *Erysipelothrix*, *Clostridium*, and *Salmonella* spp. However *Pseudomonas* and many *Proteus* spp. are resistant.
- Examples; *Cefadroxil* Oral, *Cefazolin* IM, IV, *Cephalexin* Oral, *Cephapirin* IM, IV and *Cephradine* Oral .

II- ***2nd generation of Cephalosporins:***

- Second generation cephalosporins have good activity against Gram-positive organisms and the Enterobacteriaceae but are not effective against the most intract Gram-negative organisms such as *Klebsiella* spp. or *Pseudomonas aeruginosa*.
- Examples; *Cefaclor* Oral, *Cefamandole* IM, IV, *Cefmetazole* IV, *Cefonicid* IM, IV, *Cefotetan* IM, IV, *Cefoxitin* IM, IV, *Cefprozil* Oral, *Cefuroxime* IM, IV, *Cefuroxime axetil* Oral and *Loracarbefa* Oral.

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III- *3rd generation of cephalosporins:*

- Third-generation cephalosporins generally are less active than first-generation agents against gram-positive cocci but are much more active against the Enterobacteriaceae, including β-lactamase producing strains. A subset of third generation agents (*e.g., ceftazidime* and *cefoperazone*) also is active against *P. aeruginosa* but less active than other third-generation agents against gram-positive cocci.
- Examples; *Cefdinir* Oral, *Cefepime* IM, IV, *Cefixime* Oral, *Cefoperazone* IM, IV, *Cefotaxime* IM, IV, *Cefpodoxime proxetil* Oral, *Ceftazidime* IM, IV, *Ceftibuten* Oral, *Ceftizoxime* IM, IV, *Ceftriaxone* IM, IV, *Carbapenems* Imipenem-*cilastatin* IM, IV, *Meropenem* IV, *Monobactam, Aztreonam* IM, IV.

IV- *4th generation of Cephalosporins:*

- They are extremely broad-spectrum being highly active against Enterobacteriaceae, staphylococci, and enterococci. In addition, they are not destroyed by the most common β-lactamase of Klebsiella spp. And Pseudomonas aeruginosa. Example; *Cefepime* IV.

Pharmacokinetical profile of Cefalosporins :

The pharmacokinetical pr

ofile of Cefalosporins is similar to that in Penicillins.

Side effects of Cefalosporins

1- **Hypersensitivity**: Those who are allergic to penicillin may also be allergic to Cephalosporins (10-15%).
2- **Renal Toxicity:** Interstitial nephritis, tubular necrosis. Effect can be synergistic with the aminoglycosides.
3- **Thrombophlebitis**, after IV administration.
4- **Superinfection**: 3rd generation agents may show superinfection of gram-positive organisms (Staphylococcal Enterocolitis).
5- **Disulfiram:** they increase toxicity of alcohol by blocking the mechanism of metabolism.

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Other cell wall synthesis inhibitors: and include:-

Bacitracin:

- Bacitracin is a mixture of polypeptide antibiotics produced by *Bacillus subtilis.*

- The mechanism of action includes inhibition of the carrier "*lipid pyrophosphate"* that transports cell wall precursors to the growing cell wall.

- Bacitracin inhibits gram-positive cocci, including *Staphylococcus aureus,* streptococci, a few gram negative organisms, and one anaerobe, *Clostridium difficile.*

- Side effects include: ototoxicity, nausea, vomiting and nephrotoxicity.

Vancomycin and Teicoplanin.

- Vancomycin (*Vancocin*) is a glycopeptide antibiotic produced by *Streptomyces orientalis,* while Teicoplanin (*Targocid*) is derived from *Actinomyces teichomyceticus.*
- They inhibit cell wall synthesis by preventing the polymerization of the linear peptidoglycan by peptidoglycan synthase.
- They are Bacteriostatic and narrow-spectrum agents that are active against gram- positive organisms. Teicoplanin is active against staphylococci, streptococci, and enterococci. Gram-positive rods, such as *Bacillus anthracis, Corynebacterium diphtheriae, Clostridium tetani,* and *Clostridium perfringens,* are also sensitive to the glycopeptides. The glycopeptides are not effective against gram-negative rods , mycobacteria , or fungi.
- **Major side effects include**: Nephrotoxicity and ototoxicity may be seen with the administration of these drugs. Additional adverse reactions include nausea, chills, fever, urticaria, sudden fall in blood pressure with parenteral administration, and skin rashes.

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Carbapenems

Carbapenems are synthetic ß-lactam antibiotics that differ in structure from the penicillins in that the sulfur atom of the thiazolidine ring has been externalized and replaced by a carbon atom .Imipenem, meropenem, doripenem , and ertapenem are the drugs of this group currently available. Imipenem is compounded with cilastatin to protect it from metabolism by renal dehydropeptidase.

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Antibacterial spectrum:

Imipenem resists hydrolysis *by most* ß-lactamases. This drug plays a role in empiric therapy because it is active against ß-lactamase–producing gram-positive and gram-negative organisms, anaerobes, and P. *aeruginosa* .

Pharmacokinetics:

- *Imipenem/cilastatin and meropenem are* administered IV and penetrate well into body tissues and fluids, including the CSF when the meninges are inflamed.
- They are excreted by glomerular filtration. *Imipenem undergoes cleavage by a dehydropeptidase found* in the brush border of the proximal renal tubule. This enzyme forms an inactive metabolite that is potentially nephrotoxic. Compounding the *imipenem with cilastatin protects the parent* drug and, thus, prevents the formation of the toxic metabolite.

Adverse effects:

Imipenem/cilastatin can cause nausea, vomiting, and diarrhea. Eosinophilia and neutropenia are less common than with other ß-lactams. High levels of *imipenem* may provoke seizures; however, the other carbapenems are less likely to do so.

ß-lactamase inhibitors

Hydrolysis of the ß-lactam ring, either by enzymatic cleavage with a ß-lactamase or by acid, destroys the antimicrobial activity of a ß-lactam antibiotic. ß-Lactamase inhibitors, such as *clavulanic acid, sulbactam, and tazobactam* , contain a ß-lactam ring but, by themselves, do not have significant antibacterial activity or cause any significant adverse effects. Instead, they bind to and inactivate ß-lactamases, thereby protecting the antibiotics that are normally substrates for these enzymes.

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Inhibitors of Cell Membrane Functions:

Cytoplasm of each living cell is bounded by cytoplasmic membrane, which serves as a selective permeability barrier and performs active transport functions. By performing such vital functions, cell membrane controls the internal composition of the cell. If the functional integrity of cell membrane is interrupted, macromolecules and ions escape from the interiors of the cells resulting in damage or death of the cell.

This group of antibiotics will alter with cell membrane permeability (cationic detergents) and this action will lead to loss the integrity of bacterial cell membrane, consequently causing death of bacteria.

Selectivity of chemotherapeutic agents is due to effect that cytoplasmic membrane of certain bacteria and fungi can be more readily disrupted by some agents than cell membrane of humans and animal cells.

Example of this mechanism

Polymyxines

- The polymyxins are a group of antibiotics produced by *Bacillus polymyxa*. Polymyxin B (*Aerosporin*) and polymyxin E (*Colistin*) are used in the treatment of bacterial diseases.

- The polymyxins are active against gram-negative bacteria, *Pseudomonas aeruginosa* in particular.

- Polymyxins are not well absorbed from the gastrointestinal tract. Parentral administration of polymyxins results in high drug concentrations in the liver and kidneys, the polymyxins are slowly excreted by glomerular filtration; the slow elimination rate is due to binding in tissues. Elimination is decreased in patients with renal disease, and drug accumulation can lead to toxicity. There for polymyxins are used topically only with few exceptions.

- Side effects: Polymyxins can cause extreme nephrotoxicity when used parenterally, and any

preexisting renal insufficiency will potentiate the nephrotoxicity caused by these antibiotics.

Protein Synthesis Inhibitors :

- A **protein synthesis inhibitor** is a substance that stops or slows the growth or proliferation of cells by disrupting the processes that lead directly to the generation of new proteins.
- This group of antibiotics has been exerting their effect by inhibition of synthesis of bacterial protein by interfering with ribosomal subunits (30S or 50S) of bacteria.
- This inhibition may be either reversible (Bacteriostatic) or irreversible (Bactericidal).
- **This group includes:-**

Aminoglycosides:

- They are hydrophilic, polycationic, amine containing carbohydrates.
- The major clinically important aminoglycosides are:-
- Gentamicin \ derived from *Micromonosporium Spp.*
- Streptomycin.
- Kanamycin
- Neomycin
- Tobramycin

Derived from *Streptomycis Spp.*

- Amikacin \ Semi-synthetic from Kanamycin.
- Netilmicin \ Semi-synthetic from Gentamicin.

- The mechanism of action of aminoglycosides includes irreversible binding to various sites on bacterial 30S ribosomal subunit, thereby disrupting the initiation of protein synthesis, consequently misreading of genetic code and production of false protein.
- All aminoglycosides are bactericidal and active against Gram-negative organisms and some Gram-positive organisms, but not streptococci. Amikacin, gentamicin, and tobramycin are active against *Pseudomonas aeruginosa*.

- Pharmacokinetics of aminoglycosides include:

- Absorption: Poor oral absorption. There for they administrated usually IM. And occasionally IV.

- Low distribution in most tissues.

- Half-life 2-3 hrs. Excreted by passive glomerular filtration.
- The important side-effects of aminoglycosides are vestibular or auditory ototoxicity, and nephrotoxicity.
- Risk of toxicity following systemic administration varies with different members of the group. Neomycin is particularly toxic to the auditory and renal systems. Streptomycin is ototoxic and gentamicin is ototoxic and nephrotoxic.

Tetracyclines

- They are broad-spectrum and Bacteriostatic polyketide (Secondory metabolite of the microorganism) antibiotic. Produced *Streptomycis Spp.*
- The mechanism of action of Tetracyclines includes reversible binding to bacterial 30S ribosomal subunit.
- Tetracyclines are active against *Mycoplasma*, *Chlamydia*, and *Rickettsia* in addition to bacteria. They are active against a range of Gram-positive and Gram-negative bacteria but have little useful activity against *E. coli*, *Salmonella*, *Proteus*, or *Pseudomonas* spp.

Tertacyclines are classifies according to the duration of action to:-

- **Short acting ($t_{1/2}$ = 6 – 12 hrs.) Tetracyclines. Examples :**

- Tetracycline.
- Chlorotertacycline.
- Oxytetracycline.

- **Intermediate acting ($t_{1/2}$ = 10 – 17 hrs.) Tetracyclines. Examples :**

- Demclocycline.
- Methacycline.

- **Long acting ($t_{1/2}$ = 20 – 24 hrs.) Tetracyclines. Examples :**

- Doxycycline.
- Minocycline.

Pharmacokinetics of Tetracyclines:

- Absorption: Tetracyclines are partially absorbed from the stomach and upper gastrointestinal tract. But the absorption will decrease in case of presence of calcium, Iron magnesium and Aluminum. Due to chelating nature of Tetracyclines.
- Distribution: tetracyclins are well distributed throughout the body (depending on degree of

lipid solubility of each individual agent) even in CNS and placenta.

- Metabolism: they are metabolized in the liver and concentrated in the bile due to enterohepatic circulation.
- Excretion: They are excreted unchanged, in both the kidneys (passive filtration) and feces.

- **Side effects of Tetracyclins:**
- Metal Chelation: Tetracyclines chelate calcium, as well as Mg^{+2}, Fe^{+2}, Al^{+3}. So that they may cause discoloration of teeth and dysplasia of bones.

- GIT: Direct irritation to GI tract (nausea, vomiting, and anorexia)

- Photosensitivity: Tetracyclines are broken down by sunlight. Outdated, deteriorated samples can cause a Fanconi-like syndrome (renal tubular acidosis).

Chloramphenicol

- It is a broad-spectrum and Bacteriostatic Nitrobenzene Derivative antibiotic. Produced *Streptomycis Venezuela.*
- The mechanism of action of Chloramphenicol includes reversible binding to bacterial 50S ribosomal subunit and inhibition of protein synthesis.
- It is active against rickettsial and chlamydial infections, the majority of obligate anaerobes, most Gram-positive aerobes, and non-enteric aerobes including *Actinobacillus*, *Bordetella*,*Haemophilus*, *Pasteurella multocida*, and *Mannheimia haemolytica*. Enterobacteriaceae including *Escherichia* and *Salmonella* spp. are Chloramphenicol has activity against *Mycoplasma* and *Proteus* spp. but is unreliable. It is inactive against *Pseudomonas* spp.

- **Pharmacokinetics of Chloramphenicol:**

- Absorption: Chloramphenicol is rapidly and completely absorbed from the gastrointestinal tract and is not affected by food ingestion or metal ions.
- Distribution: Although up to 60% of Chloramphenicol is bound to serum albumin, it penetrates the brain and CSF and crosses the placental barrier.
- Metabolism: Chloramphenicol is extensively metabolized (glucuronidated) by the liver.

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- Excretion: through the kidney by tubular secretion and glomerular filtration.

- **Side effects of Chloramphenicol:**

- Anemias:

1- Anemia (Dose-related): Chloramphenicol inhibits mitochondrial protein synthesis in RBC's in the bone marrow, causing a dose-dependent anemia.

2- Aplastic Anemia (Idiosyncratic): Dose-independent, rare (1/40000), aplastic anemia. Usually fatal.

- Gray-Baby Syndrome (in Human): Happens in babies because they are deficient in *glucuronyl-transferase*. Gray color, flaccidity, hypothermia, vomiting, shock.
- Inhibits P450 synthesis, potentiating the effects of warfarin, phenytoin, and other drugs metabolized by P450 enzymes.
- Diarrhea: due to Fungal Super-infections in GIT.

Macrolides

- They are broad-spectrum and Bacteriostatic antibiotics consist from a large macrocyclic lactone ring to which one or more deoxy sugars may be attached.
- The mechanism of action of Macrolides includes reversible binding to bacterial 50S ribosomal subunit and inhibition of protein synthesis.
- The macrolides include Erythromycin, Josamycin, Spiramycin, Tilmicosin, Tylosin, Clarithromycin, Azithromycin and Oleandomycin
- The macrolides are effective against a number of organisms, including *Mycoplasma* spp., *Haemophillus influenzae, Streptococcus* spp. (including *S. pyogenes* and *S. pneumoniae*), staphylococci, gonococci, *Legionella pneumophila,* and other *Legionella* spp., Clarithromycin is very active against *H. influenzae, Legionella,* and *Mycobacterium avium-intracellulare,* whereas azithromycin is superior against *Branhamella, Neisseria,* and *H. influenzae* but less active against mycobacterial species.

- **Pharmacokinetics of Macrolides:**

- Absorption: Macrolides are well absorbed orally, but the problem represented by their acid lability. To solve this problem they administrated within acid resistant capsule or as an acid-resistant

ester. Or given via IV or IM routes.

- Distribution: Macrolides are well distributed through the body except the CNS.
- Metabolism: occur in the liver.
- Excretion: Bilary excretion.

- **Side effects of Macrolides:**

- GIT: Distress, nausea, vomiting, diarrhea.
- Hepatotoxicity: found particularly with erythromycin. May be a hypersensitivity reaction.
- Inhibiting of P450, altering the metabolism of Digoxin and Warfarin.

Lincosamides

- They are broad-spectrum and Bacteriostatic antibiotics derived from *Streptomyces lincolnensis*.

- Like Macrolides, Lincosamides inhibit protein synthesis in bacteria through binding to 50S ribosomal subunit of bacteria reversely.
- Lincosamides group include Clindamycin, Pirlimycin and Lincomycin.
- They are normally used to treat staphylococci and streptococci, and have proved useful in treating *Bacteroides fragilis* and some other anaerobes.
- Pharmacokinetics of Lincosamides is extremely similar to that of Macrolids.

- **Side effects of Lincosamides:**

- Hypersensitivity (rashes).
- Gastrointestinal intolerance with abdominal pain, nausea, and vomiting occurs infrequently.
- Hepatotoxicity and Bone marrow suppression has been noted.

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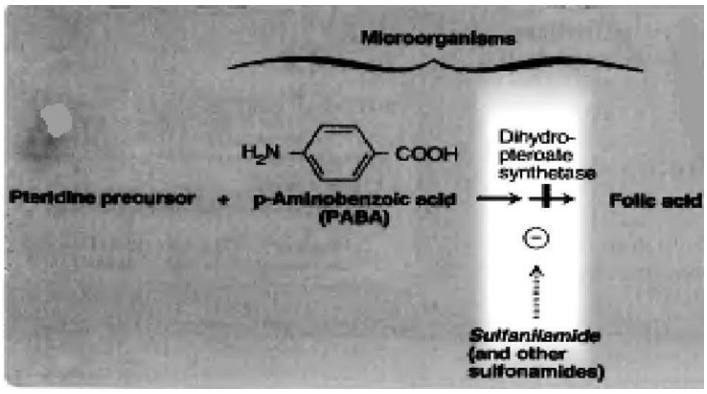
Bacterial Metabolism Inhibitors

- This group of antibacterials are exert their effect by inhibition of folic acid which endogenously synthesized in the bacteria, while this particularity is absent in the animals, there for they get their demands of folic acid exogenously.
- Folic acid is involved in the synthesis of precursors of nucleic acids and other necessary compounds for bacterial growth and replication.

Sulfanamides:

- Sulfanamides are a bactriostatic and synthetic antibacterials which act reversely by blocking the synthesis of folic acid.
- The sulfonamides, as structural analogues, competitively block Para Amino Benzoic Acid (PABA) incorporation; sulfonamides inhibit the enzyme dihydropteroate synthase, which is necessary for PABA to be incorporated into dihydropteroic acid, an intermediate compound in the formation of folinic acid.



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- **Antibacterial spectrum**: The sulfanamides are broad-spectrum antimicrobials that are effective against gram-positive and some gram-negative organisms of the Enterobacteriaceae. There are good activity against *Escherichia coli*, moderate activity against *Proteus mirabilis* and *Enterobacter* spp.; poor activity against indole-positive *Proteus* and *Klebsiella* spp., and no inhibitory activity against *Pseudomonas aeruginosa* and *Serratia* spp. They are also effective against *Chlamydia spp*. and *Toxoplasma gondii* and *Eimeria Spp.*

The Sulfanamides are located in two groups they are:

1- Absorbable Sulfanamide: which divided according to the dose interval to:

A- Short acting Sulfanamides (6 hours dose interval):

- Sulfanamide
- Sulfasoxazol
- *Sulfadiazine*
- *Sulfamerazine*
- *Sulfamethazine*

Triple Sulfa. (Used to solve the crystal Urea problem of sulfanamides)

B- Intermediate Sulfanamides (12 hours dose interval):

- Sulfamethoxazol

C- Long acting Sulfanamides (1-2days dose interval):

- Sulfamethoxypyridazine

D- Extra-long acting Sulfanamides (2-3 days dose interval):

- Sulfamethylphenazole

2- Non-absorbable sulfanamides (Intestinal Sulfanamides): they are non-absorbable and they used in treatment of bacterial or protozoal enteritis:

- Sulfaguanidine
- Succinyle sulfathiazole.

- **Pharmacokinetics of Sulfanamides:**

- Absorption: well oral absorbed orally (in case of absorbable sulfafanamides).
- Distribution: well distribution including CNS.
- Metabolism: in the liver mainly by acetylation.
- Excretion: through the kidney.

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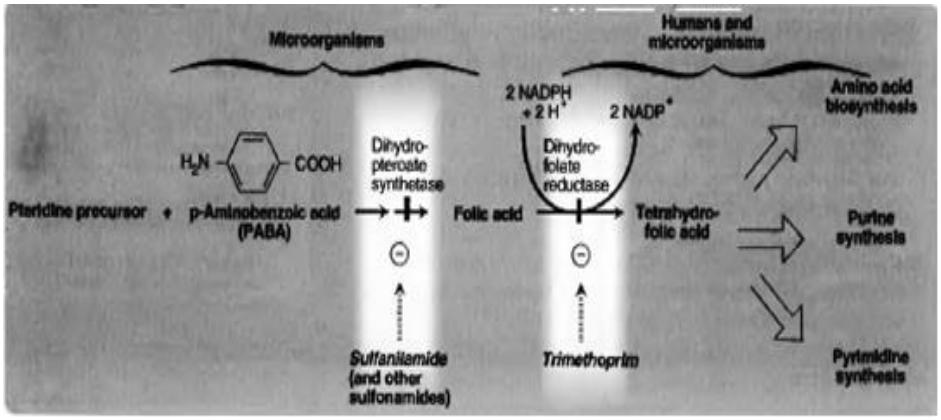
- **Side effects of Sulfanamides :**
- Hypersensitivity: is common and it graduates from mild rashes to sever hypersensitivity (Steven-Johnson syndrome).
- Crystal urea: Sulfanamides can precipitate in the urinary tract at acidic pH. So that we must maintain adequate hydration to prevent this side effect.
- Hemolytic anemia.
- Hepatotoxicity.

Trimethoprim

- Trimethoprim is a structural analogue of the pteridine portion of dihydrofolic acid. It differs from the sulfonamides in that it acts at a second step in the folic acid synthetic pathway competitively inhibits dihydrofolate reductase. This is the enzyme that catalyzes the reduction of dihydrofolic acid to tetrahydrofolic acid, the active form of folate. Dihydrofolate reductase is present in both mammalian tissues and bacteria, but 20,000 to 60,000 times more drug is required to inhibit the mammalian enzyme; this accounts for its *selective toxicity* against bacteria.



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- Trimethoprim is bacteriostatic broad spectrum antibacterial and it is predominantly used in a combination with intermediate sulfanamides especially Sulfamethaxazol due to approximation in their t1/2, for Trimethoprim is 11 hrs. While for Sulfamethaxazol is 10 hrs. (In veterinary medicine the combination is between Trimethoprim and short-acting Sulfanamides like Sulfadiazine because of the half life of Trimethoprim in animals is arranged 2-6 hrs.); this combination is active against most gram-positive and gram-negative organisms, especially the Enterobacteriaceae. There is little activity against anaerobic bacteria; Pseudomonas aeruginosa, enterococci.

Pharmacokinetics of Trimethoprim:

- Absorption: Trimethoprim is well absorbed orally.
- Distribution: well and it can enter to the CSF in cases of inflammations.
- Metabolism: in the Liver mainly.
- Excretion: it excreted within kidney.

- **Side effects of Trimethoprim:**

- Anti-folate effects: Megaloblastic anemia, leukopenia, granulocytopenia. These effects can result from the drug's inhibition of the mammalian dihydrofolate reductase enzyme. These side effects can be treated with folinic Acid which given as adjacent in order to prevent these side effects.

Pharmacology

Inhibitors of nucleic acid synthesis or function

- This group of antibacterials acts by inhibition of nucleic acids synthesis or by interaction with their functions.

Nitrofurans

- They are a number of 5-nitro-2-furaldehyde derivatives, which are relatively broad-spectrum, bactericidal and synthetic antibacterials.
- The mechanism of action of Nitrofurans illustrated in that the sensitive bacteria to this group will reduce the pro-drug (nitrofuran) to active form of Nitrofuran by *Nitrofuran reductase*, consequently this active form will modify various bacterial macromolecules that affect a variety of biochemical processes (e.g., DNA and RNA synthesis, protein synthesis).

Nitrofurans are two types:

A- Non absorbable Nitrofurans: including; Furazalidone and Nitrofurazon

B- Absorbable Nitrofurans: including; Furaltidone and Nitrofurantoin.

- Antibacterial spectrum of Nitrofurans includes; gram-positive (including *Staphylococcus* Spp.) And gram-negative like *Salmonella* spp., coliforms, also *Mycoplasma* spp., *Eimeria* spp., and some other protozoa.

- **Pharmacokinetics of Nitrofurans:**

- Absorption: well and rapidly absorbed orally (For absorbable Nitrofurans).

- Distribution: Nitrofurans have low distribution because they are metabolized rapidly.

- Metabolism and Excretion: Nitrofurans have a rapid metabolism followed by rapid excretion too via kidney.

- **Side effects of Nitrofurans:**

- GIT disturbances.

- Hepatotoxicity.

- Hemolytic anemia.

Pharmacology

Rifampicin:

- Rifampicin is a broad spectrum and bactericidal antibiotic derived from *Streptomycis* Spp.
- It acts by inhibition of RNA synthesis .
- The ability of Rifampicin to penetrate into cells makes it an ideal drug for treating intracellular infections. It is used in the treatment of tuberculosis in humans and has been suggested for use in treating atypical mycobacterial infections in cats.
- Rifampicin is frequently used in combination with erythromycin for the treatment of some pneumonic conditions in foals, particularly those caused by *Rhodococcus equi* infection.

Pharmacokinetics of Rifampicin:

- Absorption: Adequate absorption from the GIT.
- Distribution: adequate levels are attained in the CSF.
- Metabolism: by liver and the drug undergoes the enterohepatic circulation.
- Excretion: through bile also through kidney too.

Side effects of Rifampicin:

- Enzyme induction: Rifampicin induces P450 in the liver and increases the metabolism of many drugs like Anticonvulsants and anticoagulants.
- GIT disturbances.

Fluroquinolones

- They are broad spectrum, bactericidal and synthetic (4- quinolone) antibacterials.
- Fluroquinolones inhibit DNA replication by inhibiting of DNA gyrase (is an enzyme that unwinds DNA).
- Fluroquinolones are classified in to four generations according to their antibacterial spectrum:

1- **1st generation: including Nalidixic acid and Cinoxacin:** this generation is active against gram-negatives rods.

2- **2ndgeneration: including Norfloxacin, Ciprofloxacin, Ofloxacin, Enrofloxacin, and Lomefloxacin:** this generation is active against garm-positive cocci, garm-negative rods, *Chlamydia* and *Mycoplasma*.

3- 3rd generation: including Levofloxacin, Sparfloxacin, Gatifloxacin:

this generation has a similar antibacterial activity of the 2nd generation

4- 4th generation: including Trovafloxacin and Moxifloxacin:

this generation possess an antibacterial effect against gram-positive cocci, gram positive bacilli, gram-negative rods and anaerobic microorganisms.

- **Pharmacokinetics of Floroquinolones:**

- Absorption: the Fluroquinilones are rapidly and completely absorbed after oral administration in all species.
- Distribution: they are widely distributed among all the body.
- Metabolism: in the liver by oxidation.
- Excretion: via kidney by glomerular filtration and tubular secretion.

- **Side effects of Floroquinolones:**

- GIT disturbances.
- Inhibition of articular cartilages growth: Fluoroquinolones may inhibit the growth of articular cartilage and therefore should not be administered to growing dogs or cats.
- Xanthines toxicity: Fluroquinolones inhibit the execration of Xanthines thereby increasing their toxicity.

Metronidazole

- It is a Bactericidal, antibacterial and antiprotozoal agent; works by disrupting DNA and nucleic acid synthesis
- Metronidazole has activity against most obligate anaerobes including *Bacteroides* sp. (including *B. fragilis*), *Fusobacterium, Veillonella, Clostridium sp., peptococcus*, and *peptostreptococcus.* Metronidazole is also Trichomonacidal and Amebicidal in action .
- It has therapeutic activity against *Entamoeba histolytica*, *Trichomonas, Giardia*, and *Balantidium coli.*

Pharmacology

Pharmacokinetics of Metronidazole:

Metronidazole is relatively well absorbed after oral administration, with good distribution even in the CNS, metabolized in the liver and excreted within urine and feces.

- **Side effects of Mitromedazole:**

- Neurologic disorders.
- GIT disturbances.
- Hematuria.

Basis of Antibacterial combinations:

Although in principle the use of antibacterial mixtures is not recommended, in some cases antibacterials may be used in combination for the following causes:

- To treat mixed infections.
- Prevention of resistance.
- Reducing toxicity.
- For empiric purposes.

Types of Antibacterial combinations are:

1- Synergistic combination: this type of combination happens when the antibacterials in combination exert a greater antibacterial effect than either one alone. **{1 + 1 > 2}**

Examples:-

- Penicillins + Aminoglycosides.
- Amoxicillin + Clavulanic acid.
- Sulfa + Trimethoprim.

2- Additive combination: this type of combination occurs when the antibacterials in combination exert an equal antibacterial effect for each one of them alone. **{1 +1 = 2}**.

Examples:-

- Sulfa + Tetracyclines
- Amoxicillin + Metronidazole.

3- Antagonistic combination: this type of combination occurs when the antibacterials in combination exert a lesser effect than each antibacterial acting alone. **{1 + 1< 2 = 0}**

Examples:

- Penicillin + Tetracyclines
- Penicillin + Sulfa
- Macrolides + Chloramphenicol.
- Aminoglycosides + Tetracyclines.

Bacterial resistance to chemotherapy:

- *Antibiotic resistance* is the ability of a microorganism to withstand the effects of antibiotics. It is a specific type of drug resistance.
- Antibiotic resistance develops via mutations, adaptation or gene transfer.
- This resistance may be natural or acquired (Permanent or temporary).

Mechanisms of bacterial resistance to antibacterial :

The four main mechanisms by which microorganisms exhibit resistance to antimicrobials are:

1- Drug inactivation or modification: e.g. enzymatic deactivation of Penicillin G in some penicillin-resistant bacteria through the production of β-lactamases.

2- Alteration of target site: e.g. alteration of Protein (the binding target site of penicillins) in some resistant Staphylococcus aureus and other penicillin-resistant bacteria.

3- Alteration of metabolic pathway: e.g. some sulfonamide-resistant bacteria do not require para-aminobenzoic acid (PABA), an important precursor for the synthesis of folic acid and nucleic acids in bacteria inhibited by sulfonamides. Instead, like mammalian cells, they turn to utilizing preformed folic acid.

4- Reduced drug accumulation: by decreasing drug permeability and/or increasing active efflux (pumping out) of the drugs across the cell surface.

Pharmacology

Reasons of treatment failure with antibacterials:

1- Incorrect diagnosis.
2- Improper dose.
3- Inadequate course of treatment.
4- Bacterial resistance.
5- Presence of super-infections.

Genetic Alterations Leading to Drug Resistance

The bacteria with a mutation that allows them to survive live to reproduce. They then pass this trait to their offspring, which leads to the evolution of a fully resistant colony .

Staphylococcus aureus is one of the major resistant pathogens. Found on the mucous membranes and the human skin of around a third of the population, it is extremely adaptable to antibiotic pressure. It was one of the earlier bacteria in which penicillin resistance was found—in 1947, just four years after the drug started being mass-produced. Methicillin was then the antibiotic of choice, but has since been replaced by oxacillin due to significant kidney toxicity.

1. Mutations

- Specific genetic mutations are the molecular basis for resistance to :
  e.g. streptomycin (ribosomal mutation) to quinolones (DNA gyrase gene mutation) and rifampin (RNA polymerase gene mutation).

2. Transduction

- The resistance occurs when a bacteriophage which includes bacterial DNA in its protein coat infects the bacteria .
- This bacterial DNA may contain a gene confirming resistance to antibacterial drugs.
- For example , *Staphylococcus aureus* strain resistance development to penicillin may occur by transduction .
- Some bacteriophages carry plasmids that code for penicillinase , other phages can transfer genes which confer resistance to tetracycline , erythromycin and chloramphenicol .

Pharmacology

3. Conjugation

- Conjugation is anther mechanism for single and multi -drug resistance development.
- In conjugation , direct passage of resistance – conferring DNA between bacteria proceeds by way of a bridge .
- The genetic material transfer in conjugation requires two elements ; an B-determinant plasmid which codes for the resistance and a resistance – transfer factor (RTF) plasmid which contains the genes necessary for the bacterial conjugation process .
- For example most resistance of gram – negative bacilli mediated by conjugation .