PHARMACOLOGY

Modified slides no.6 V2
Writer: Hala Mousa
Corrector: Subhi Nassar
Doctor: Suheil Zmeili

- In this modified there’re many notes that are added **(not mentioned by the doctor)** to clarify and simplify the information. So when you study, make sure to memorize the slides and understand the simple notes.

Microbial DNA Synthesis Inhibitors

Quinolones; Fluoroquinolones

Inhibitors of microbial DNA synthesis (inhibit bacterial DNA replication by inhibiting bacterial gyrase enzyme which is a type II topoisomerase)

Most widely used antibiotics in 2002 but their use has been recently reduced due to toxicity, development of resistance and the introduction of safer new macrolides

Chemotherapeutic agents

Cidal

Broad spectrum (effective against pseudomonas)

■ NOTE: DNA gyrases: Enzymes that belong to a class called topoisomerases that are involvd in the control of DNA transitions.

■ NOTE: This inhibition increases the number of permanent chromosomal breaks, triggering cell lysis.

- **Quinolones are classified into:**

1st generation

Nalidixic acid Pipemidic acid Oxolinic acid

2nd generatipon

Ciprofloxacin Ofloxacin Norfloxacin Enoxacin Lomefloxcin Nadifloxacin

3rd generation

Levofloxacin Sparfloxacin Gatifloxacin

4th generation

Moxifloxacin Prulifloxacin Gemifloxacin

- - 1st generation e.g. Nalidixie acid effective more in G-ve infections and only in UTT's (urinary tract antiseptic). Has good activity against E-coli; Proteus; Shigella, Enterobacter and klebsiella. No effect against Pseudomonas and little effect on G+ve bacteria

-2nd generation exhibit more activity against G-ve & G+ve bacteria

-3rd & 4th generations have good activity against pseudomonas and anaerobic microorganisms

- Most widely used quinolones include: Ciprofloxacin (2nd); levofloxacin (3rd); moxifloxacin (4th)

■ **NOTE**: Ciprofloxacin (2nd Generation): It is one of the most commonly prescribed quinolones. It possesses good activity against a wide range of Gram-negative and some Gram-positive bacteria. Levofloxacin (3rd Generation): It maintains activity against Gram-negative bacteria and has expanded efficacy against other microbes. Moxifloxacin (4th Generation): Has an even broader spectrum of activity, including against Pseudomonas and anaerobic organisms.

■ **NOTE**: These elements can bind to quinolones in the gastrointestinal tract, reducing their absorption.

Quinolones are orally effective and well absorbed but affected by food containing Ca^{++} and iron

Mainly (particularly Ciprofloxacin & levofloxacin) used in complicated UTI's, respiratory infections, invasive external otitis, bacterial prostatitis and cervicitis, bacterial diarrhoea caused by shigella, salmonella and E. coli

■ **NOTE**: Quinolones can be effective against certain bacterial causes of diarrhea, including infections from these specific bacteria.

■ **NOTE**: Quinolones can be effective in treating severe outer ear infections.

■ **NOTE**: They might be prescribed in cases of bacterial infections affecting the prostate in men or cervix in women.

▶ Mechanisms of bacterial resistance to quinolones:

- Some types of bacterial efflux pumps can act to decrease intracellular quinolone concentration
- Production of certain proteins especially by Gram-ve bacteria that can bind to DNA gyrase, protecting it from the action of quinolones
- Mutations in DNA gyrase or topoisomerase which could lead to a decrease in quinolones binding affinity and hence decreasing their effectiveness

■ **NOTE**: **Bacterial efflux pumps limit the drug's access to topoisomerases.**
They can acetylate flouroquinolones, rendering them inactive.
They alter their target site structure thus reducing binding efficiency of fluroquinolones

▶ Quinolones side effects:

- GIT irritation; photosensitivity
- Cardiac toxicity (many may be associated with prolongation of QT interval) (many were withdrawn because of this side effect)
- Some are not recommended in children or during pregnancy because they may interfere with cartilage development
- Some have been reported to be carcinogens

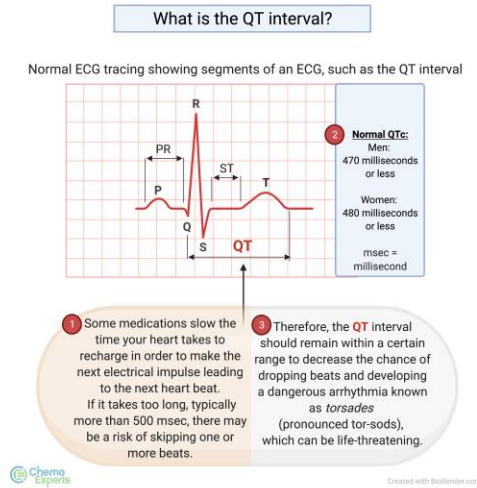
■ **NOTE: GIT irritation leads to symptoms like nausea, vomiting and diarrhea**

■ **NOTE: Characteristic**

■ **NOTE: Patients taking fluroquinolones are at risk for phototoxicity resulting in exaggerated sunburn reactions, thus they should use sunscreen and avoid excessive exposure to UV light.**

■ **NOTE: Fluroquinolones may prolong QT interval and these agents should be avoided in patients predisposed to cardiac arrhythmias or taking medications associated with QT prolongation**

The QT interval is a measurement made on an electrocardiogram used to assess some of the electrical properties of the heart



Nitrofurantoin

Synthetic, bactericidal orally effective antibiotic

It is effective against G+ve & G-ve bacteria

Has good activity against G-ve bacteria particularly E. coli

Highly effective in UTI's (cystitis) (known as UT antiseptic)

■ **NOTE**: **These work by damaging the bacterial DNA and RNA.**
Have a broad spectrum activity that they're effective against G+ve and G-ve.
Nitrofurantoin is notably effective against Escherichia coli, a common cause of urinary tract infections (UTIs). It concentrates in the urine, which makes it particularly useful for treating lower urinary tract infections like cystitis.

▶ Nitrofurantoin MOA (multiple):

It is converted by bacterial reductases into many reactive intermediates leading to direct damaging effect of bacterial DNA, disruption of RNA and protein synthesis and also interfering with many metabolic processes in bacteria

■ **NOTE**: This drug is special in its multiple MOA on DNA/RNA and also protein synthesis.

■ **NOTE**: Nitrofurantoin is converted within bacteria by specific enzymes known as reductases this leads to the formation of reactive intermediates which exert their effect by directly damaging bacterial DNA. Nitrofurantoin's action extends beyond DNA damage to interfere with RNA and protein synthesis within bacterial cells. Additionally, it disrupts various metabolic pathways critical for the survival and functioning of the bacterial cell.

- Development of resistance to nitrofurantoin is rare, due to multiple sites of action (the bacteria that is sensitive to it remain sensitive forever)
- Pulmonary fibrosis is a major side effect to nitrofurantoin
- Nitrofurantoin is contraindicated in patients with G-6-PD deficiency

■ **NOTE**: 1. Bacteria that are sensitive to nitrofurantoin tend to remain sensitive to it for a longer time.
2. May lead to cystic fibrosis, a severe lung condition characterized by scarring of lung tissue.
3. It causes hemolytic anemia if given to patients with G-6-PD deficiency.

Fosfomycin

It is a broad-spectrum bactericidal drug

primarily used to treat lower UTI (cystitis) and occasionally is used for prostate infections

It disrupts cell wall synthesis by inhibiting phosphoenolpyruvate synthetase and thus interferes with the production of peptidoglycan

■ **NOTE**: **It interferes with the production of peptidoglycan, an essential component of bacterial cell walls. This disruption weakens the bacterial cell wall, leading to the bactericidal effect.**

Fosfomycin has a broad spectrum of activity against both gram-positive and gram-negative organisms, including many antibiotic-resistant organisms

■ **NOTE**:This makes it valuable in treating infections where other antibiotics might be ineffective due to resistance.

It is available in 3g oral powder dosage form for reconstitution

Use of fosfomycin is commonly restricted to only a single dose because of rapid microbial resistance

■ **NOTE**: One notable challenge with fosfomycin is the relatively rapid development of microbial resistance after its use. Therefore, it's commonly restricted to a single-dose regimen to mitigate the risk of resistance. The single-dose approach aims to reduce the likelihood of bacteria developing resistance over prolonged exposure to the drug.

Fosfomycin is well tolerated but may lead to the following side effects:

- **Metallic taste**
- **Stomach upset**
- **Dizziness**
- **Stuffy nose**
- **Back pain**
- **Vaginal itching or discharge**

Antimetabolites (Sulfonamides)

■ **NOTE: They inhibit the growth and reproduction of bacteria rather than directly killing them.**

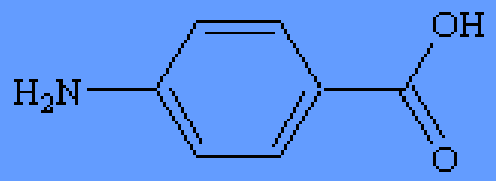
Static; broad spectrum chemotherapeutic agents

Structural analogs of PABA required for synthesis of dihydrofolic acid in bacteria

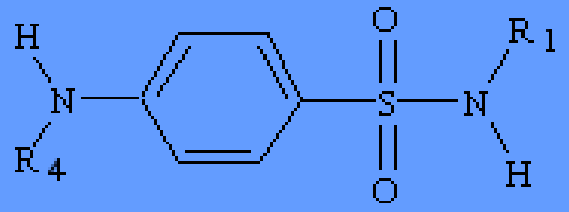
Effective against many G+ve & -ve bacteria, nocardia, lymphogranuloma, trachoma, blastomycosis, and many protozoal infections…

■ **NOTE:They work by mimicking PABA, so they interfere with the production of folic acid, which is necessary for bacterial DNA synthesis.**
Have broad spectrum activity

Sulfa Drugs



para-aminobenzoic acid
PABA



Sulfonamide base structure

Widely used in the management of:

Upper respiratory tract infections

UTI's (Sulfamethoxazole; Sulfisoxazole); Toxoplasmosis; Chlamydia infection; protozoal infections; infected burns, eye infection (Sulfacetamide; Sufadiazine)

Sterilization of bowel before surgery (Sulfadiazine=not absorbed=no systemic effects)

Sulfasalazine (sulfapyridine - salicylate combination) is used in inflammatory bowel disease (ulcerative colitis, Crohn's disease)

■ **NOTE**:Sulfadiazine, specifically when administered orally, is not absorbed systemically, making it suitable for the sterilization of the bowel before surgery without causing systemic effects.

- **Sulfa Preparations:**

Sulfamerazine
Sulfamethazine
Sulfisoxazole
Sulfadiazine-local
Sulfacetamide-local

} well absorbed } short $t_{1/2}$

Sulfamethoxazole (Most widely used sulfa); well absorbed; intermediate-acting

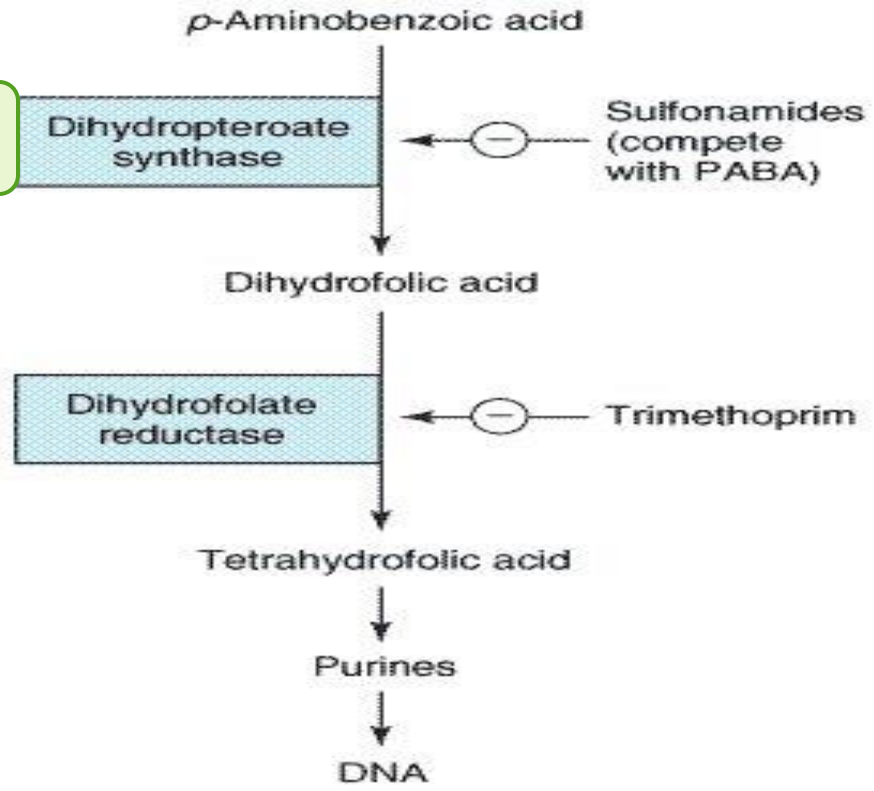
Phthalylsulfathiazole (sulfathalidine) long acting orally effective

Sulfasalazine; poorly absorbed (10-20%) from the GIT, long acting

Sulfa MOA

Interference with metabolism of MO's

- **Or Dihydrofolic acid synthase**



Mechanisms of resistance to sulfa:

- ↓ permeability of bacteria to sulfa
- ↑ production of PABA
- Altered dihydropteroate synthase enzyme
- Obtained folate by bacteria from environment

- Some bacteria can modify their cell membranes or transport systems to limit the entry of sulfa drugs into their cells, reducing the drug's effectiveness.
- Bacteria can amplify their production of para-aminobenzoic acid (PABA), which bypasses the need for the PABA precursor inhibited by sulfa drugs. This increased production counteracts the effect of sulfa drugs.
- Sulfa drugs inhibit the dihydropteroate synthase enzyme, which is crucial for folate synthesis in bacteria. Some bacteria develop mutations in this enzyme, rendering it less susceptible to inhibition by sulfa drugs, thus maintaining folate production despite the presence of the drug.
- Certain bacteria can acquire folate directly from their environment. This bypasses the inhibited pathway targeted by sulfa drugs, allowing bacterial survival even in the presence of these antibiotics.

Sulfa pharmacokinetics

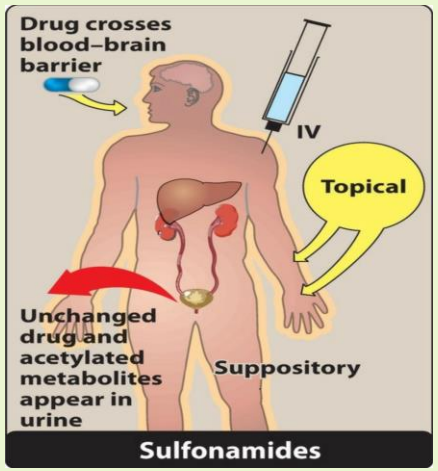
Bind plasma proteins (compete with bilirubin binding sites →↑ bilirubin levels in blood → kernicterus)

■ **NOTE**:**High levels of unbound bilirubin can potentially lead to kernicterus (صفار الجنين), a condition of bilirubin toxicity primarily affecting infants.**

Distribution good including CSF

Sulfa drugs are metabolized by acetylation (metabolites are toxic but devoid of any antibacterial effects) and metabolites are excreted renally

■ **Attachment**:



■ **NOTE**: **Able to treat CNS infections.**

Sulfa and their metabolites usually precipitate in urine → stones (more common (&most dangerous) with long acting sulfas)

■ **NOTE**:In order to reduce the risk of renal precipitation:

- Ensure good fluid intake → good renal flow
- Use sulfa with good urine solubility (Sulfisoxazole)
- Use combined sulfa drugs (synergistic effect, lower doses → less precipitation)
- Alkalization of urine (altering the pH)

▶ Trimethoprim

-Is a chemotherapeutic agent and is a structural analog to folic acid

- Inhibits dihydrofolate reductase, effective against E. coli; H. influenza; K. pneumonia ineffective against Pseudomonas & Proteus MO's

- Used in Rx and prophylaxis of UTI's

■ **NOTE**: **It's commonly used both for treating active urinary tract infections and as prophylaxis to prevent recurrent UTIs.**

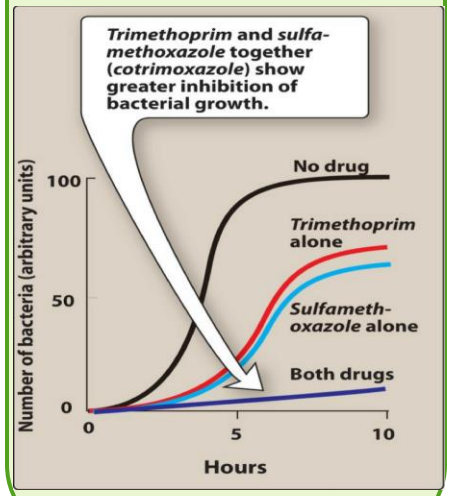
■ **NOTE**: **Trimethoprim binds to bacterial dihydrofolate redctase more readily than it does to human dihydrofolat reductase, which accounts for the selective toxicity of the drug.**

Onset of action

- Trimethoprim is static and has more rapid OOA as compared to sulfa
- Well absorbed orally like sulfa
- Has similar $t_{1/2}$ life to sulfamethoxazole
- Less crossing to BBB unlike sulfa
- Excreted unchanged (without metabolization) by the kidney
- Associated with less side effects

■ **NOTE**: Often paired with sulfamethoxazole because they have similar half lives , forming co-trimoxazile

■ **Attachment**:



▶ **Sulfamethoxazole + trimethoprim combination:**

- is known as **Co-trimoxazole**
- acts sequentially in preventing nucleic acid synthesis in bacteria (selective)
- is synergistic,
- has more spectrum (but still ineffective against Pseudomonal infections)
- more cidal and bacterial resistance is less likely

■ **NOTE**: They have a synergistic effect, enhancing their antibacterial action compared to their individual effects. Resistance is less because it requires bacterium that is resistant to both drugs.

■ **NOTE**: They inhibit different steps in the folate synthesis pathway of bacteria, hindering the production of nucleic acids crucial for bacterial growth. Used to treat UTIs.

■ NOTE: Adverse reactions related to cotrimoxazole are similar to those expected with each of the individual components, sulfamethoxazole and trimethoprim.

■ NOTE: Remember that sulfa drugs displace bilirubin from binding sites on serum albumin, the bilirubin is then free to pass into the CNS, because the BBB is not fully developed in infants.

▶ **Sulfa side effects:**

- Allergic reactions (frequent)
- Kernicterus
- Renal damage (toxic nephrosis, allergic nephritis, drug crystals)
- Liver damage (rare)
- N & V

■ NOTE: Nausea and vomiting, common GI side effects.

- Blood dyscrasia, hemolysis in G-6PD deficient pts
- Steven-Johnson Syndrome (uncommon); inflammatory condition of skin & mm's

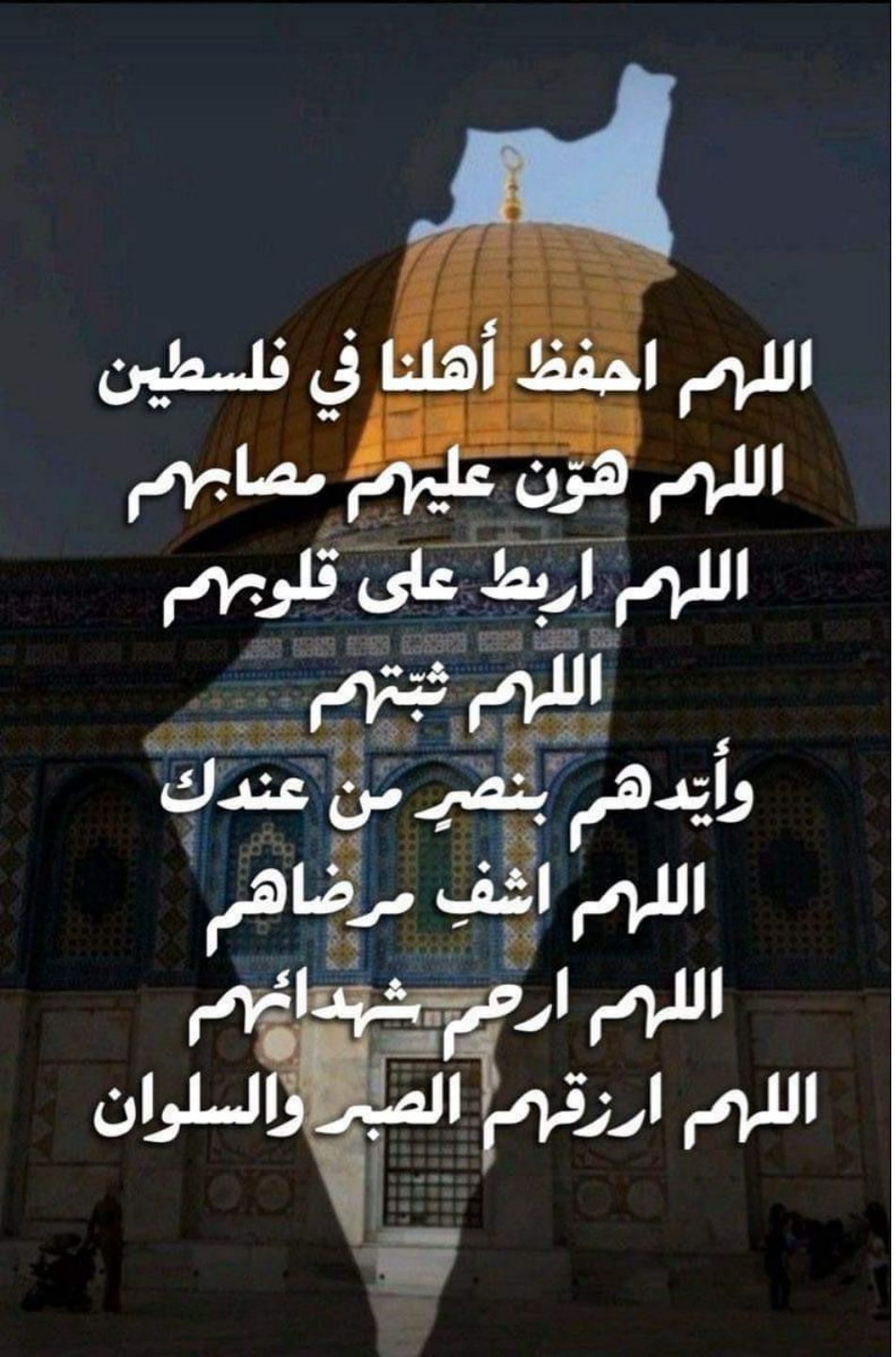
■ Characteristic

■ NOTE:This is a severe and uncommon inflammatory reaction affecting the skin and mucous membranes. It's considered an emergency and requires immediate medical attention.

Some Questions that is mentioned by the doctor (characteristic side-effects of drugs)

- With what Steven-Johnson syndrome side effect happen?
- Co-trimoxazole
- Red Man Syndrome?
- Vancomycin
- Dental staining?
- Tetracyclins
- Cardiotoxicity?
- Quinolones
- Allergy (Most frequent with) ?
- PNCs

■ لا تنسَ خلال دراستك تشيّك على الشغلات المميزة في الاعراض الجانبية لكل دوا، واضح الدكتور بركز عليهم



ادعي لغزة كأنّك الوحيد الذي تذكُرها وتتعاهدها بالدعاء..ادعُ لغزة بيقين أن دعوتك ستقلبُ الموازين وتدفعُ عنها ضرًّا لا تدركه..كثفوا دعوات لاهل غزة
اللهم إنا نستودعك أهل غزة وكل فلسطين

V2: SLIDE 5