Pharmacology of Quinolones & sulphonamides

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Objectives

- What are quinolones?
- Nalidixic acid
- Floroquinolones: generations, spectrum, advantages, mechanism of action, resistance, uses, adverse effects and contraindications
- Inhibitors of synthesis of essential metabolites: sulphonamides
- Sulphadiazine: PKs and PDs
- Co-trimixazole
- Other sulphonamides combinations
- Adverse effects of sulphonamides

Quinolones

But the antibiotic natural source

- ✓Synthetic antimicrobials
- ✓Bactericidal (DNA - Synthesis مجموعة هذه الأدوية تعمل على)
- ✓Primarily gram-negative bacteria

Nalidixic acid (& pipemidic acid)

- First member: prototype (First generation)
- **Advantages**:
- 1- Cover G-ve bacteria
- 2- Rapidly excreted by Kidney in urine in concentrations enough (high) for treatment of UTIs

Urinary Track infection

* $t_{\frac{1}{2}}$ is short

Disadvantages of nalidixic acid

- Concentration of free drug in plasma & most tissues is **non-therapeutic** for **systemic infections**
- Narrow spectrum عدد معين من gram-negative
- Rapid development of bacterial resistance.
- So:
- Limited therapeutic use ?? why

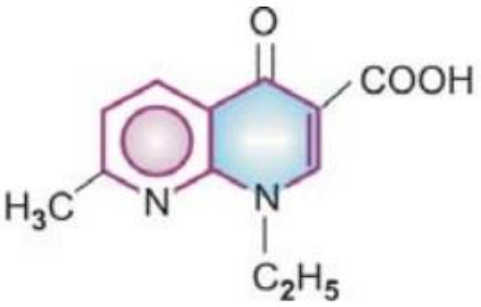
Fluoroquinolones

- Quinolones are molecules **structurally derived from the heterobicyclic aromatic compound quinoline.**

Two rings

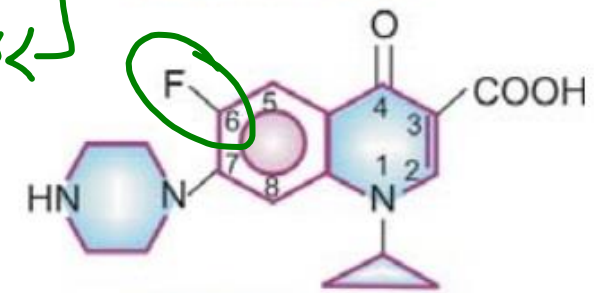
ذرة فلور

- **Fluorination** of quinolone structure at position 6 resulted in derivatives called **fluoroquinolones**



NALIDIXIC ACID

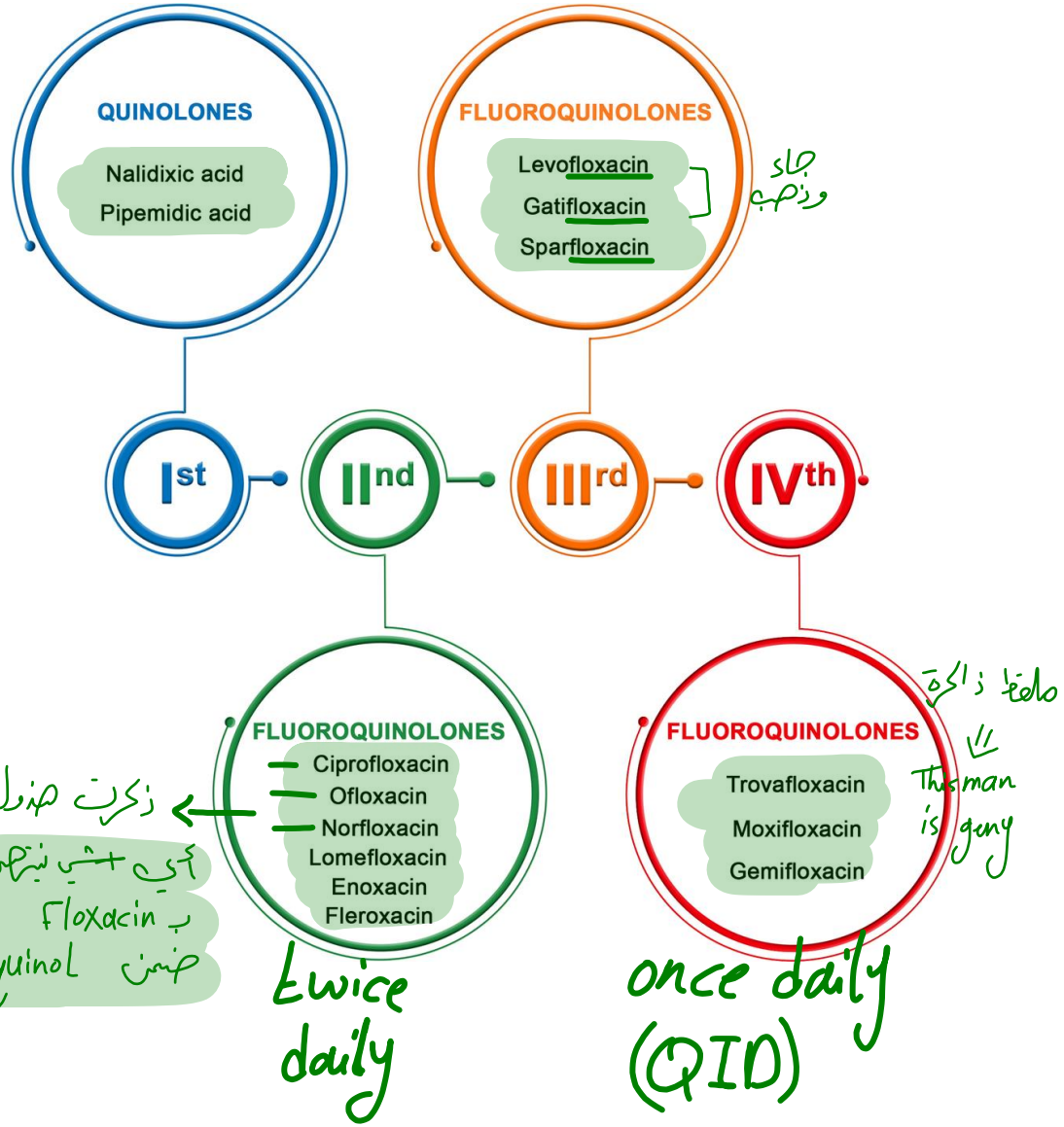
Quinolones



CIPROFLOXACIN

Generations & Spectrum

From 1st → 4th generation
1) spectrum (to broad)
2) potency
3) Duration
increased



	2nd generation	3rd generation	4th generation
mutalikpharmacology	Gram negative aerobes		
Anerobes +	++ →	+++	++++
Gram +ve +	++ →	+++	++++
Atypical +	++ →	+++	++++
Long (bd)	Longer + (qd)	Longer ++ (qd)	Longer ++ (qd)
UTI, Gonorrhea, Typhoid fever, Respiratory, CAP, Mycoplasma, Chlamydia, Tuberculosis, Post-op/Hospital infections, Gynecological infections			

Staph. Strep.

Community acquired pneumonia

Advantages of floroquinolones

1- High potency
2- Broad antimicrobial spectrum
3- Slow development of resistance
4- Better tissue penetration
5- Prolonged duration of action

❖**Used for wide variety of infectious diseases**

Pharmacokinetics of quinolones

- Key: MW less than 500, chemical structure has no –OH groups
- **Absorption**:
- Rapid and complete **oral** absorption, avoid with food (or drugs) containing Al, Ca, Iron
- **Distribution:**
- High tissue penetration: Concentration in lung, sputum, muscle, bone, cartilage (minerals), prostate, and phagocytes & neutrophils (IC) exceeds that in plasma
- Can pass BBB: reaching concentrations to treat CNS infections
- Pass placentral barrier: teratogenic
- **Excreted** in breast milk
- **Metabolism**: liver
- **Excretion**: in urine unchanged : Urinary are 10-50-fold higher than in plasma: UTIs
- **Moxifloxacin** excreted by non-renal routes: not used in UTIs

Mechanism of action

gram-positive and negative بختلف الاسم من

Quinolones target bacterial **DNA gyrase & Topoisomerase IV**

- Gram negative bacteria - **DNA Gyrase**

- Gram positive bacteria - **Topoisomerase IV**

- **In mammalian cells(human cells) Topoisomerase II**

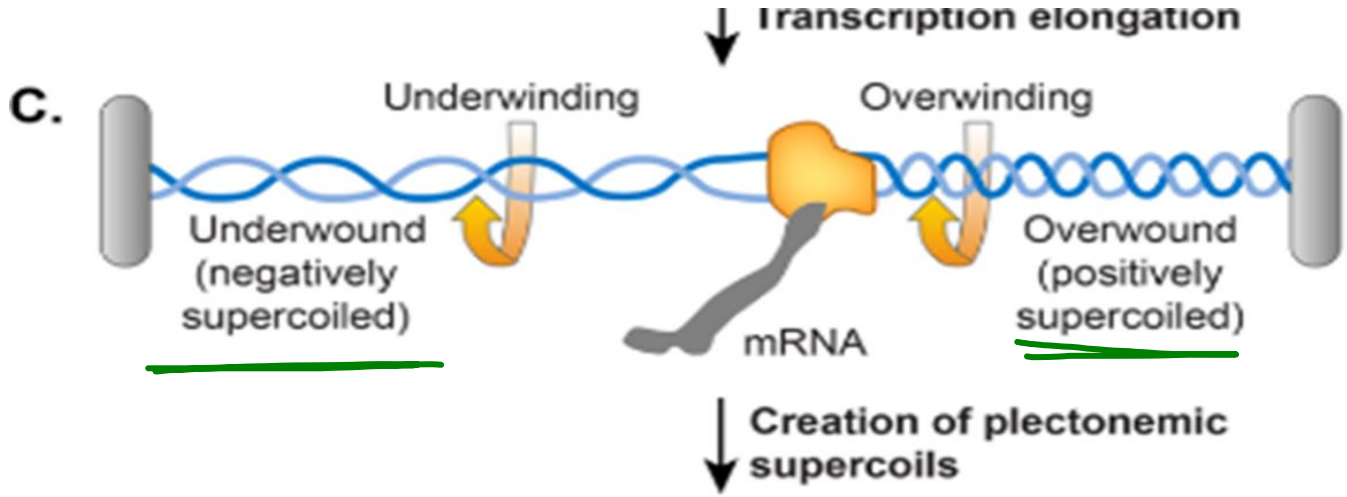
1- Low affinity for flouroquinolones

2- Inhibited by quinolones only at much higher concentrations.

Low toxicity to host cells

Mechanism of action

- Two strands of double helical DNA must separate to permit DNA replication / transcription
- “over winding” / excessive positive supercoiling of DNA leads to faulty protein synthesis and bacterial death.



Mechanism of resistance

- **1- Chromosomal mutation:**

  bacteria produce DNA Gyrase/ Topoisomerase IV with **reduced affinity** for quinolones.

- **2- Drug efflux:** across bacterial membranes

- Resistance is **slow** to develop because the mechanism of action

Therapeutic indications

1- Urinary tract infections:

- **Most commonly used antimicrobials for UTI**
- **Very effective against Gram negative bacilli like**

E.coli

Proteus

Enterobacter

Psuedomonas

Ciprofloxacin 500 mg bd

2- Salmonella typhi infection (typhoid fever):

- **Ciprofloxacin** 500 mg bd x 10 days مرتين في اليوم لمدة عشر أيام
- Prevents carrier state also عشان ما ينقل العدوى

3- Respiratory infections:

- Pneumonia
- Acute sinusitis
- Chr. Bronchitis
- **Respiratory quinolones**: **levofloxacin, moxifloxacin, Gemifloxacin**. why?
- They are distributed IC in macropgages and polymorphs
- Cover G+ve and atypical bacteria

ملحوظة ذاكرة

[my great Lung]

4-Bone and joint infections: Osteomyelitis & joint infections

5- Meningitis

6- - Atypical infections

Adverse effects

1- Musculoskeletal:

•**Tendonitis** & tendon rupture: ciprofloxacin: tendinopathy of Tendo Achillis

•**Arthropathy (Joint disease)** in immature animals

Contraindication: children less than 6-12 years, pregnancy and during breast feeding contraindicated

•**2- CNS:** excitation due to blocking of GABA receptors: seizures have occurred predominantly in patients receiving theophylline or a NSAIDs and epilepsy patients (contraindications)

Adverse effects

=> arrhythmia

- **3- QT interval prolongation**: trovafloxacin withdrawn in 2016.
- Cautious use in patients who are taking drugs that are known to prolong the QT interval: tricyclic antidepressants, Phenothiazine and class I anti-arrhythmics
- **4- Drug interactions:**

➢ NSAIDs & theophylline may enhance CNS toxicity of floroquinolones

– Seizures reported

➢ Antacids, Sucralfate, Iron salts

reduce absorption of quinolones

➢ Quinolones are cytochrome p450 inhibitors

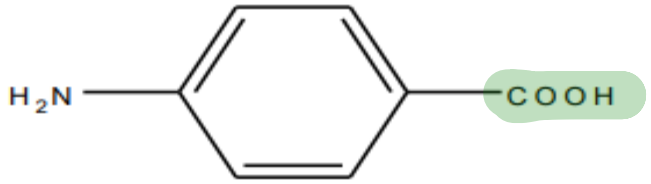
(Liver enzymes)

↳ Decrease the doses

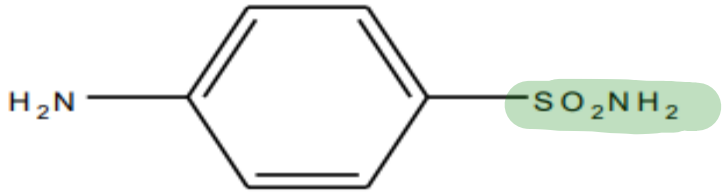
Inhibitors of synthesis of essential metabolites

Sulphonamides (sulpha drugs) & trimethoprim

- **<u>Antimicrobials in this class:</u>**
- Sulfonamides
- Trimethoprim
- **Bacteriostatic**



P-amino-benzoic acid (PABA)



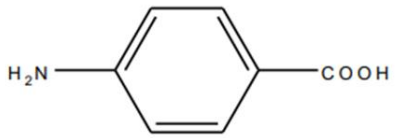
Sulfanilamide

PKs

- **Example: sulphadiazine**
- **Absorption**: good oral absorption, **not affected by food**
- **Distribution**:
- BBB: pass: used with penicillin for treatment of bacterial meningitis in 1930s-1940s
- Good tissue penetration: prostate
- Placenta: pass and excreted in breast milk
- **Metabolism**: liver
- **Excretion**: renal: acylated but active metabolite (UTIs, alkalinization of urine)
- **Uses**: treatment of CNS toxoplasmosis and plasmodium falciparum

PDs

- Competitive inhibitors of **dihydrofolate synthase** bacterial enzyme responsible for the incorporation of **PABA** into **dihydrofolic acid** (immediate precursor of folic acid).
- Folic acid required for synthesis of purines and nucleic acid
- Sulfonamides are structural analogue of P-aminobenzoic acid (PABA)



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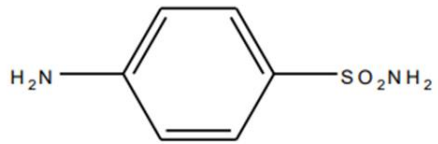
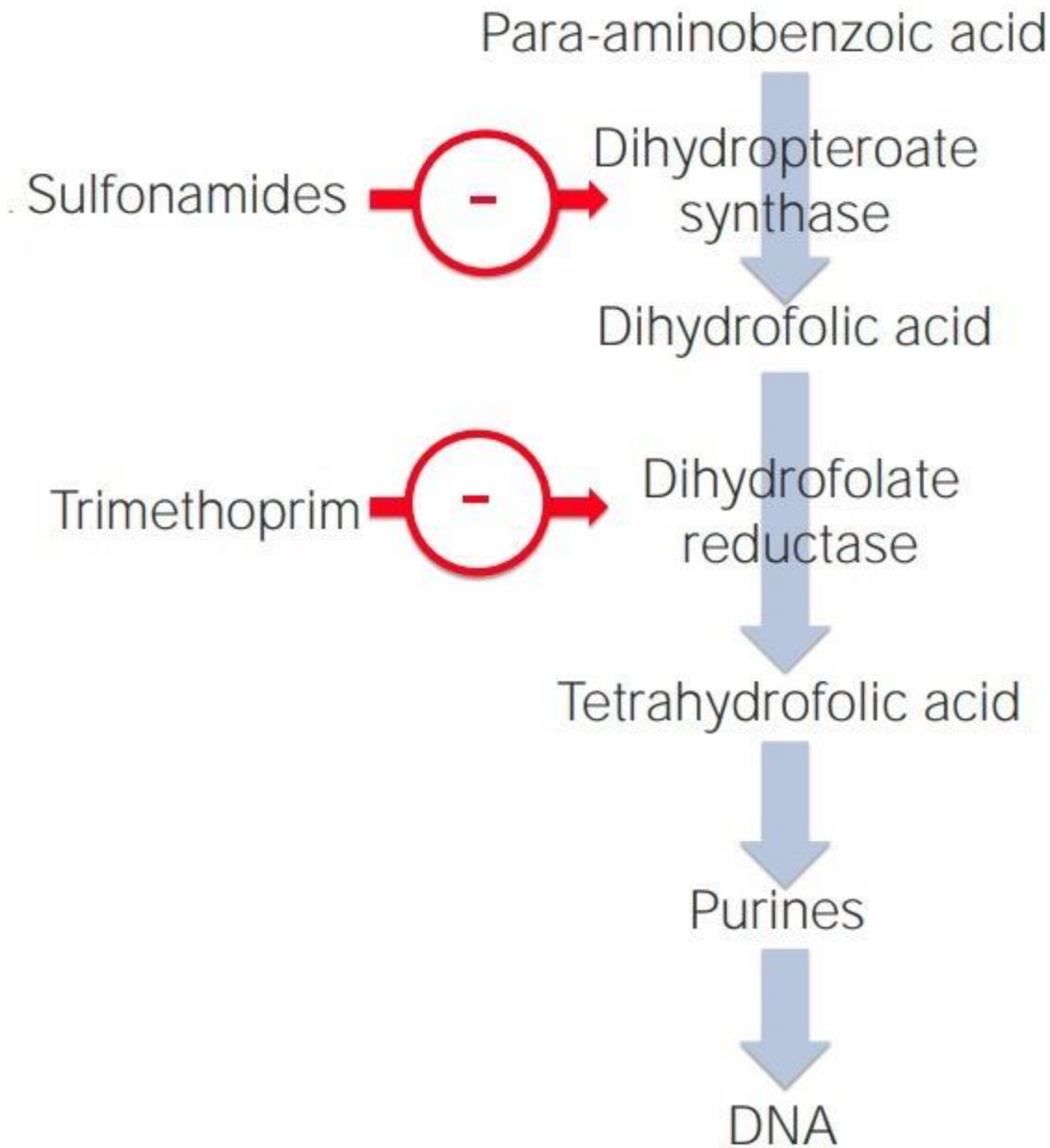


Sulfanilamide


Para-aminobenzoic acid
Sulfonamides
Dihydropteroate synthase
Dihydrofolic acid
Trimethoprim
Dihydrofolate reductase
Tetrahydrofolic acid
Purines
DNA

CO-TRİMOXAZOLE

•Sulfamethoxazole with **trimethoprim** in 5: 1

•**Tablets contain** 400 mg of sulfamethoxazole plus 80 mg of trimethoprim.

• **Mechanism of action**: Trimetoprim inhibits the enzyme dihydrofolic acid reductase (sequential block)

• **Bacteriostatic activity**.

•**Spectrum:**

•**Some G+ve**: streptococcal tonsillitis, pharyngitis

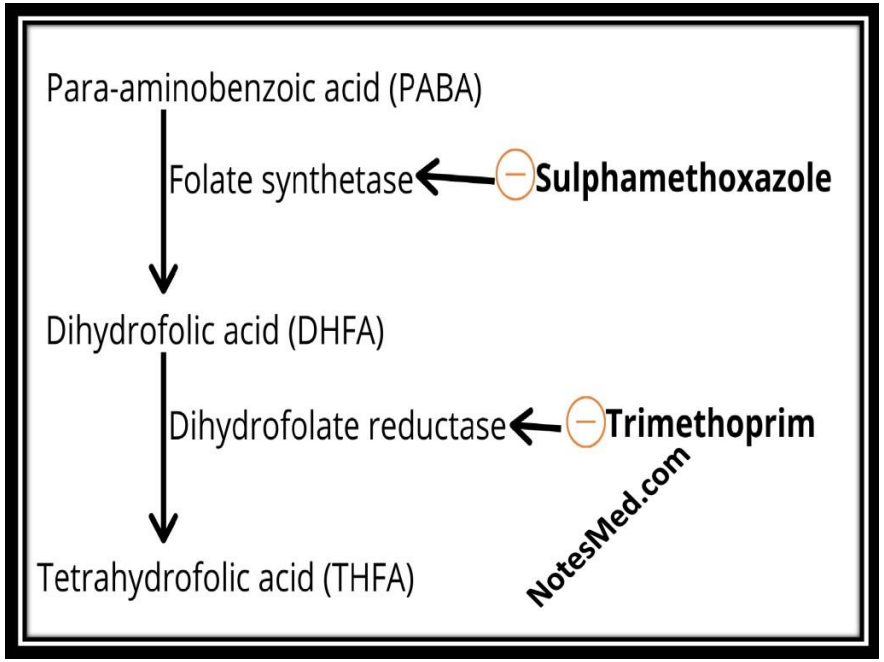
•**Some G-ve**: E.coli: UTIs

•**Atypical bacteria**: chlamydia: eye, genital

•**Toxoplasma**

•**Plasmodium falciparum**

•**Pneumocystis carinii**



Indications of co-trimoxazole

- **1- UTIs**: excreted in high concentration in urine (alkalinization of urine)
- **2- Streptococcal infections:** pharyngitis, tonsillitis
- **3- AIDS**: PCP: **Pneumocystis carinii (drug of choice): oral or IV for 3 weeks**
- **4- Toxoplasmosis of CNS**

Other sulphonamides combinations

- **Silver Sulfadiazine (cream)**

•Inhibits growth of nearly all pathogenic **bacteria (psudomonus)** & **fungi**

•Used topically to reduce incidence of infections of wounds from burns

–Slowly releases silver ions -antimicrobial action

–**Sulphadoxine & pyrimethamine**: malignant malaria (plasmodium falciparum): sequential block

–**Sulphasalazine**: sulphapyridine & **5-aminosalicylic acid: ulcerative colitis: will not cure the disease but reduce number of attacks**

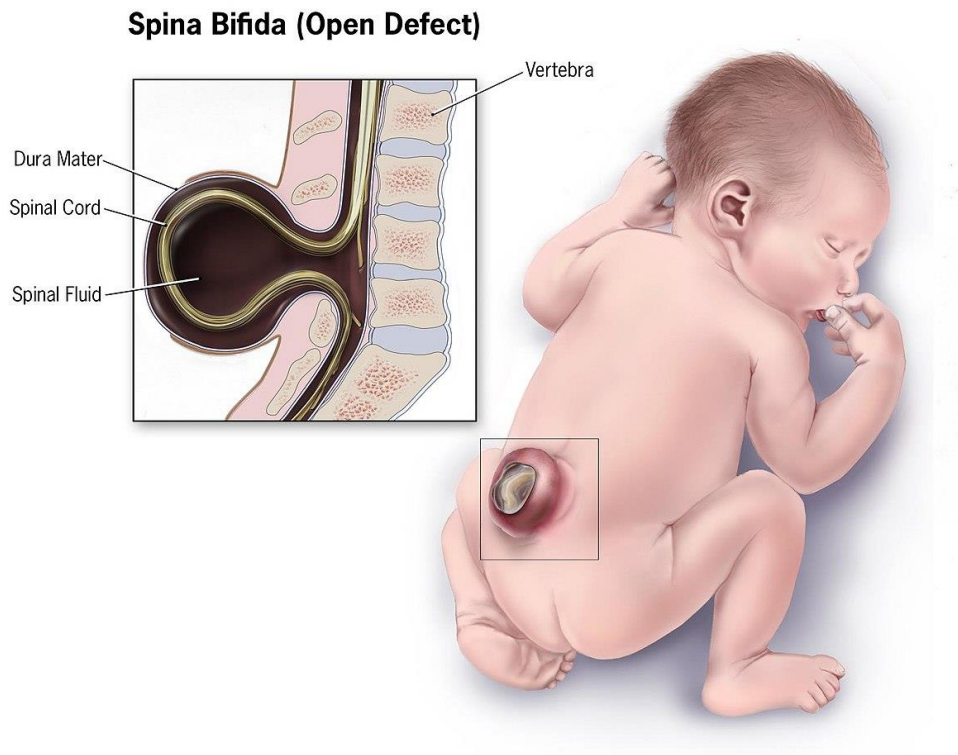
Adverse effects

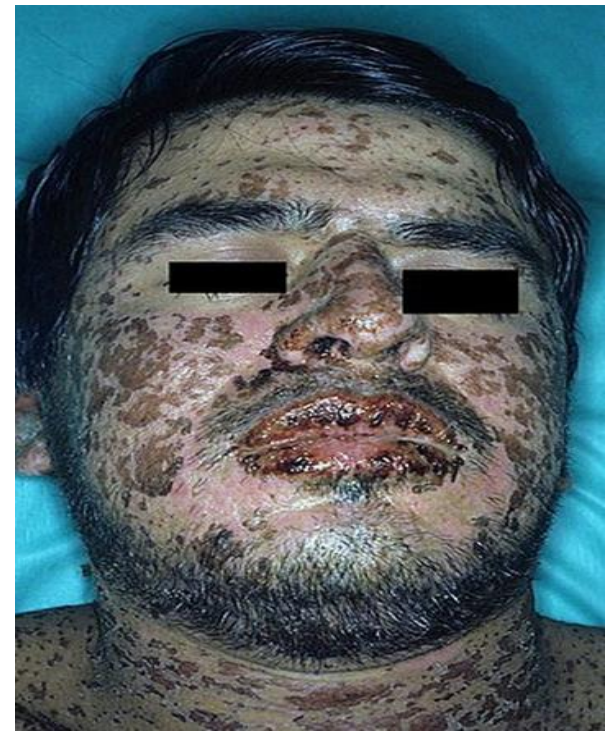
- 1- **Allergy**: skin rash: common
- Stevens-Johnson syndrome (SJS) (TEN: toxic epidermal necrolysis): rare
- **2- Crystalluria**
- Insoluble in acidic urine
- Precipitate, forming crystalline deposits that can cause urinary obstruction
- Fluid intake sufficient to ensure a daily urine volume of at least 1200ml
- Alkalinization of the urine

3- kernicterus

- Administration to **newborn infants esp. premature**
  - Sulfonamides displace **bilirubin (jaundice)** from plasma albumin.
  - Free bilirubin is deposited in **basal ganglia & sub-thalamic nuclei** of the brain causing an encephalopathy & permanent brain damage called **kernicterus**.

- **4- anemia**:
- Hemolytic anemia: G6PD deficiency
- Megaloblastic anemia: treated by folic acid tab. 5 mg once daily
- **5- during pregnancy**:
- 1st trimester: neural tube defect (spina bifida): teratogenic
- 3rd trimester: kernicterus
- **Contraindications**: pregnancy, children less than 2 y, allergy to sulpha, fauvism, renal stones


Spina Bifida (Open Defect)
Vertebra
Dura Mater
Spinal Cord
Spinal Fluid



References

Lippincott's Illustrated Review

Pharmacology, 8th edition

Lippincott Williams & Wilkins

Katzung *by Anthony Trevor, Bertram Katzung, and Susan Masters . 16th edition McGraw Hill,*

Rang & Dale's Pharmacology: *by Humphrey P. Rang ; James M. Ritter ; Rod Flower Churchill Livingstone; 10th edition*

THANK YOU