# Quinolones and Folic Acid Antagonists

Pharmacology and Toxicology

General Pharmacology

Second Year Medical Students

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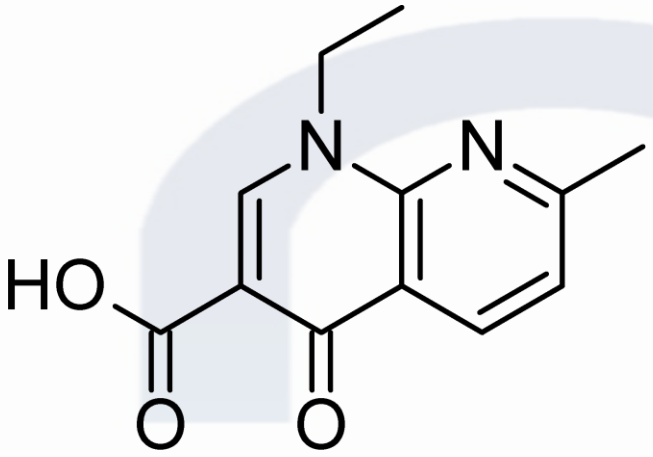
Faculty of Medicine

The Hashemite University

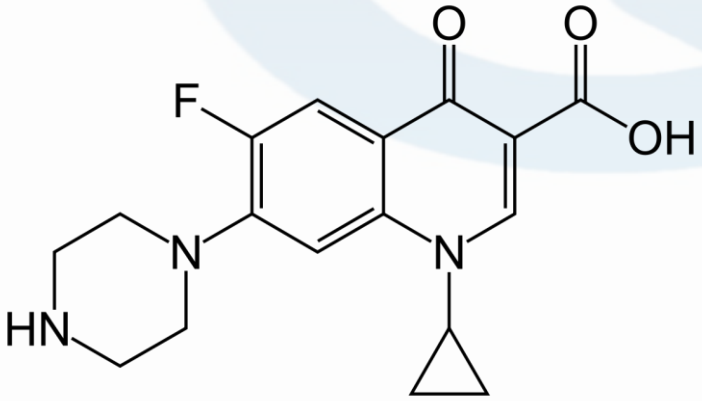
**Textbook**: Chapter 31 pp 400-412

# Fluoroquinolones

# Quinolones




Nalidixic acid




Ciprofloxacin

**FLUOROQUINOLONES**

*Ciprofloxacin* CIPRO
*Levofloxacin* LEVAQUIN
*Moxifloxacin* AVELOX
*Nalidixic acid*
*Norfloxacin* NOROXIN
*Ofloxacin*

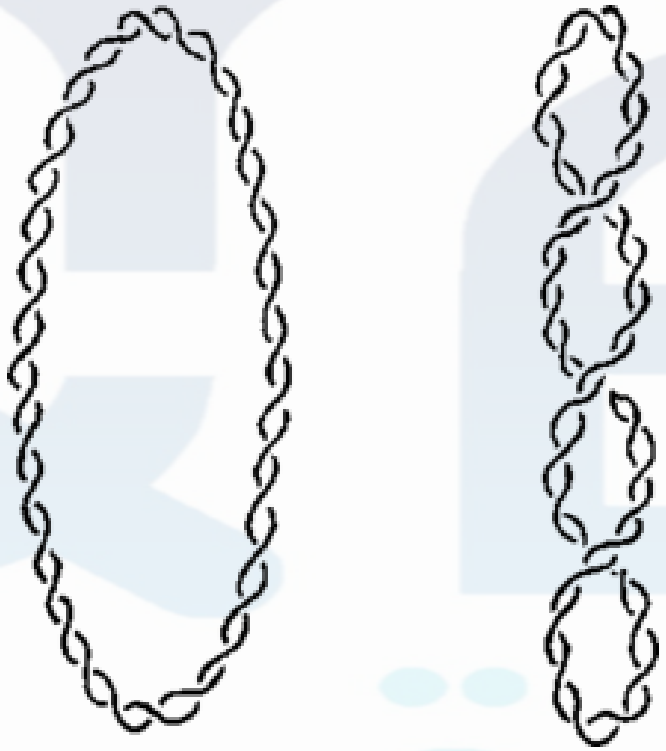
Fluoroquinolones are a big family of drugs ,not only limited to antibiotics, there is some drugs whose actions aren't related to the antibacterial effects.  Here , we are interested about quinolones which are used as antibiotics.

Nalidixic acid was the basic and the oldest quinolone to be used.
The structure is simple with 2 rings fused together.
Nalidixic acid was used as antibiotic for long period of time and still up to now used for the treatment of certain infections despite it not widely used

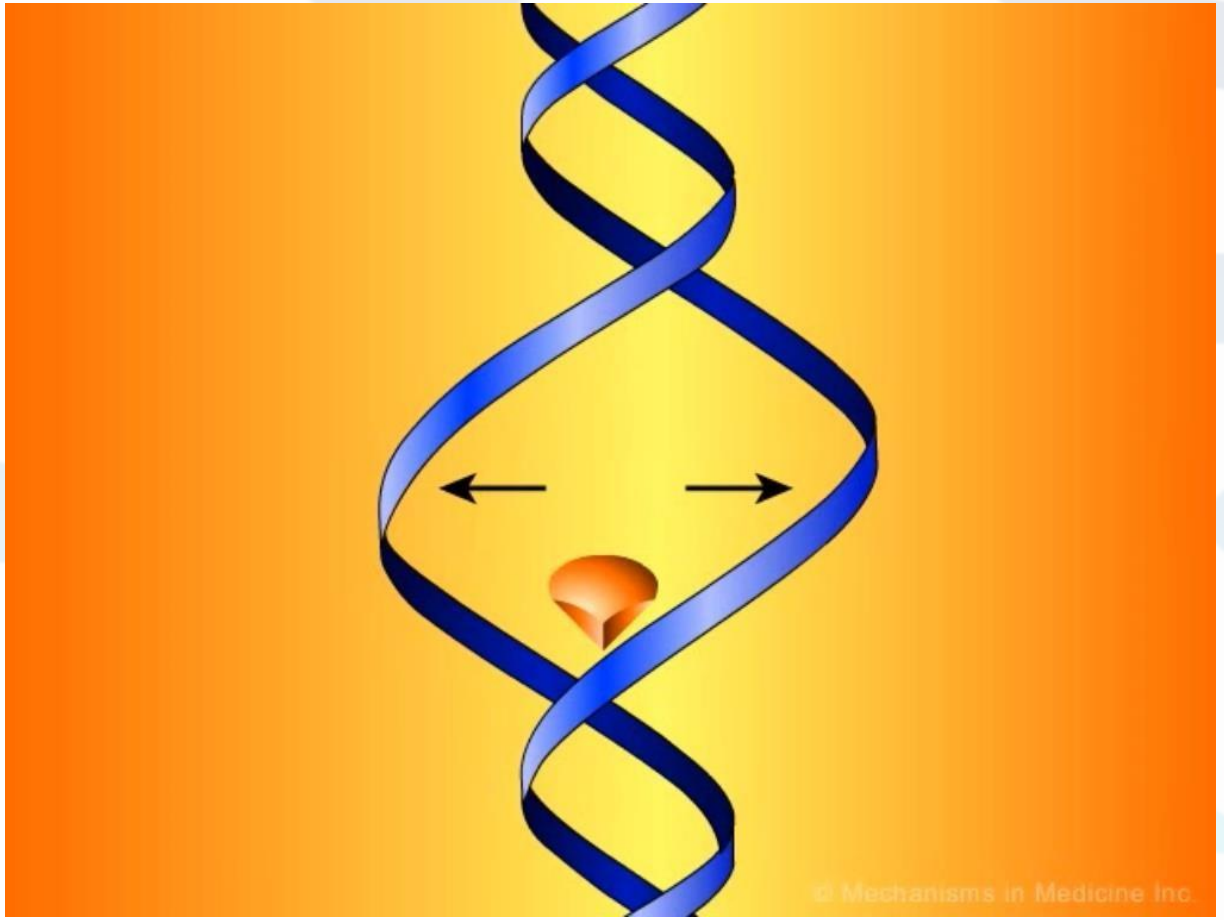
Flouroquinolones have a fluoride atom added to the basic quinolone backbone(nalidixic acid) along with some other modifications that expanded the spectrum of activity, improved pharmacokinetics, and stabilized compounds against common mechanisms of resistance

# DNA Supercoiling

The circular DNA structure of bacterial genome creates a problem for bacteria which is supercoiling of some areas of the genome. Supercoiling will prevent genetic enzymes from accessing the supercoiled area and performing transcription but the bacteria already has some solutions!



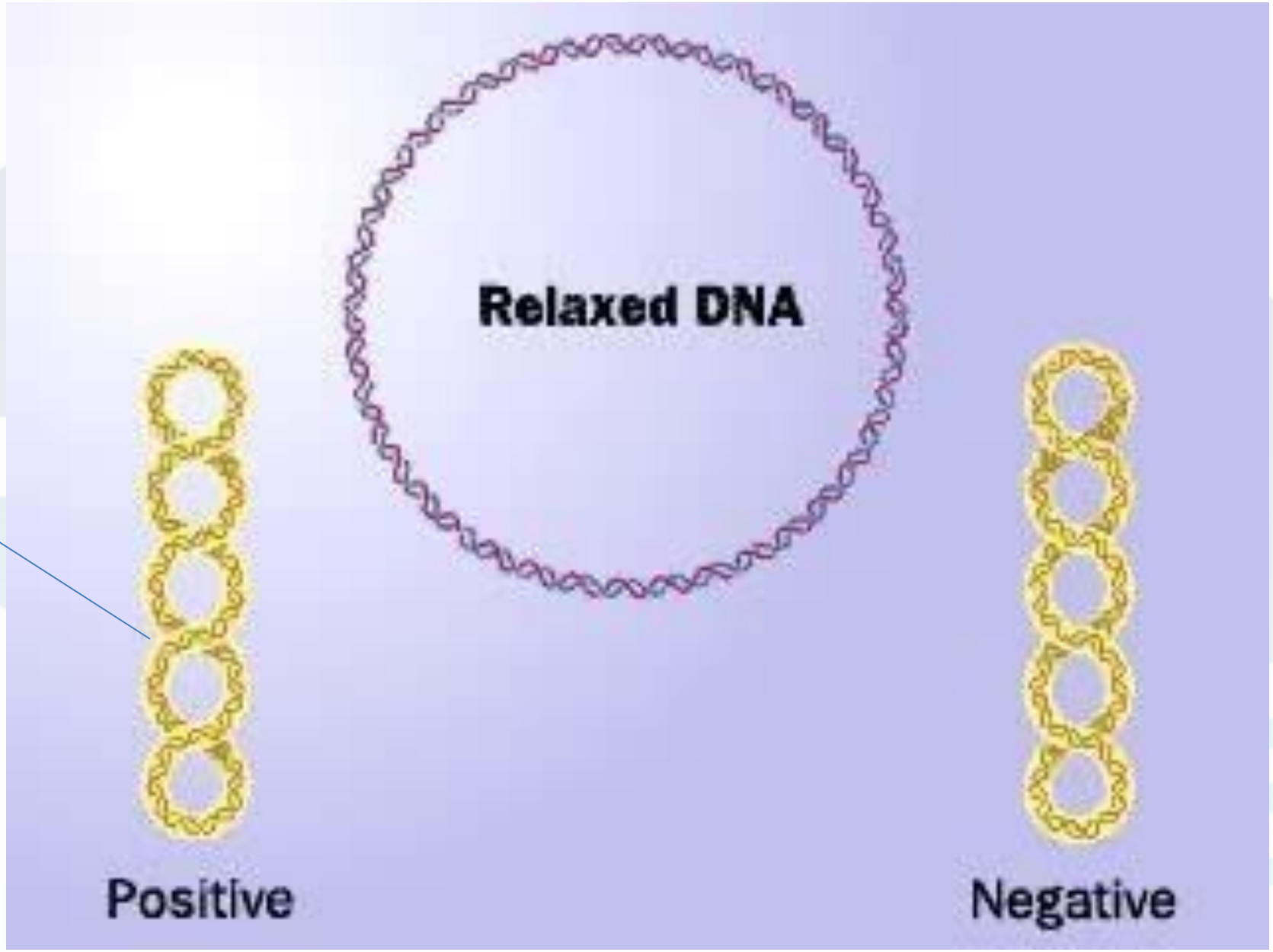
# DNA Helicase



during DNA replication , we need to separate the DNA strands from
each other, one of these strands become leading strand in which the DNA
polymerase scan it from 3’ to 5’ , while the other strand is called the lagging strand
to which a replication occurs by an Okazaki fragments .
The enzyme that is responsible for the separation of the 2 strands from each other and for the formation of the replication fork is called the bacterial DNA helicase

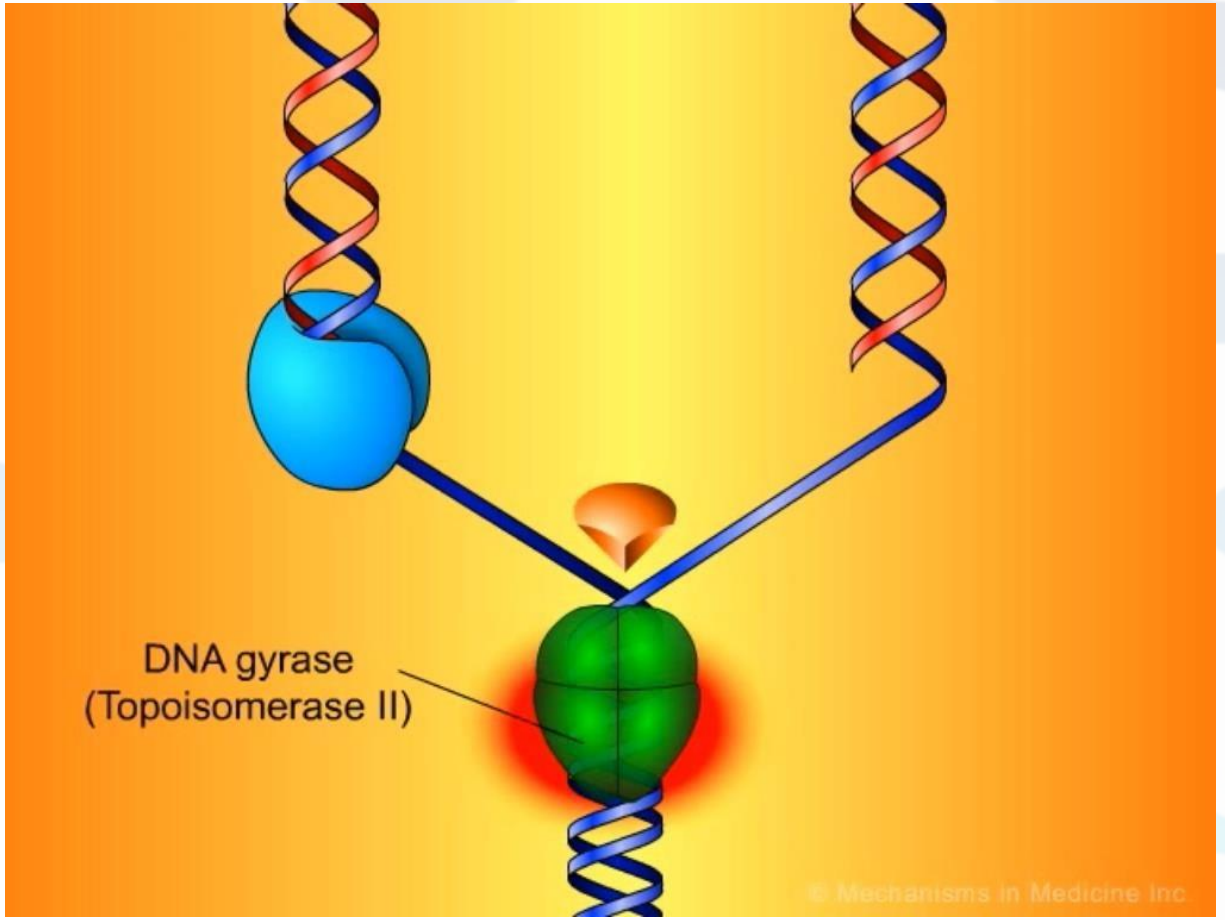
Super coiling will prevent dna helicase from completing the separation of the 2 strands , because supercoils act ass barrier.

Clockwise coiling(rotation) →positive supercoil. More common than counterclockwise coiling



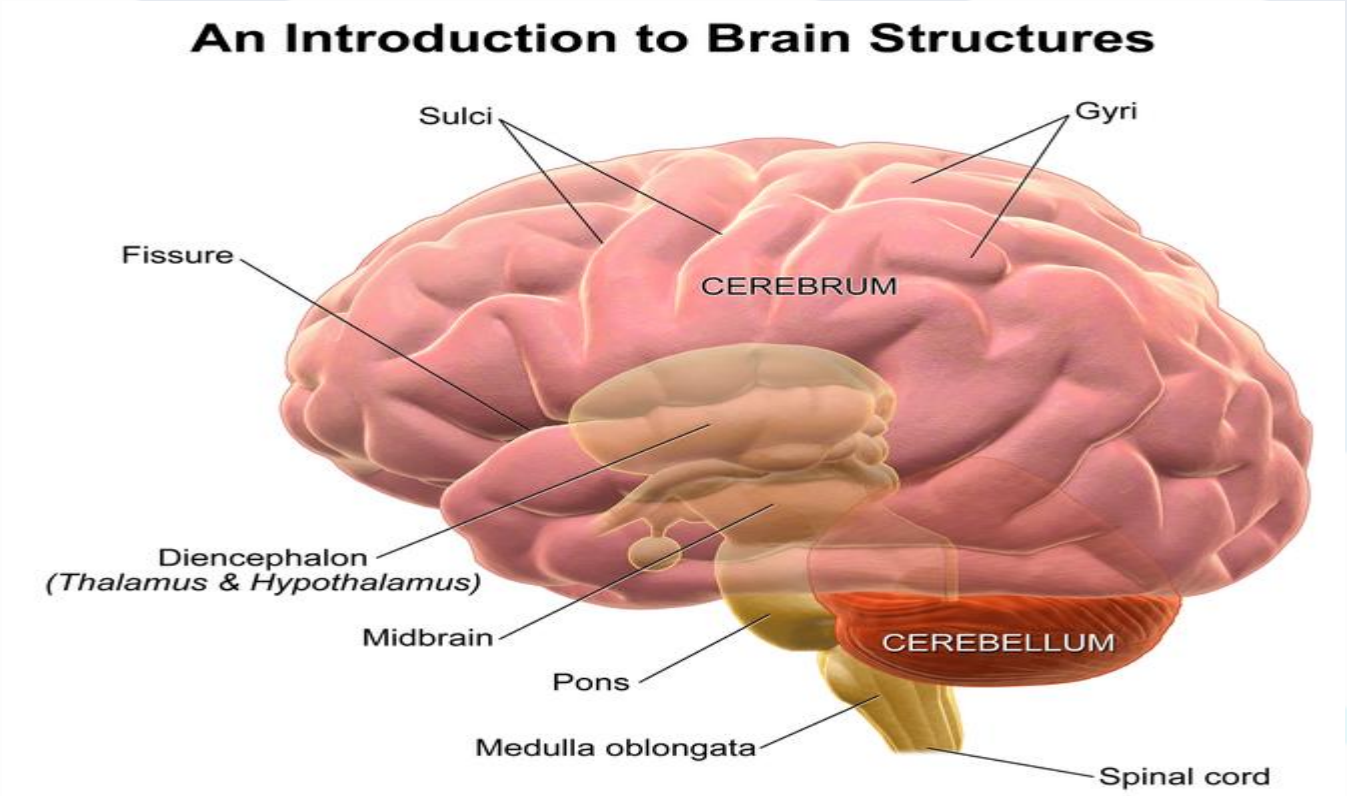

Counterclockwise rotation→negative supercoil

# DNA Gyrase



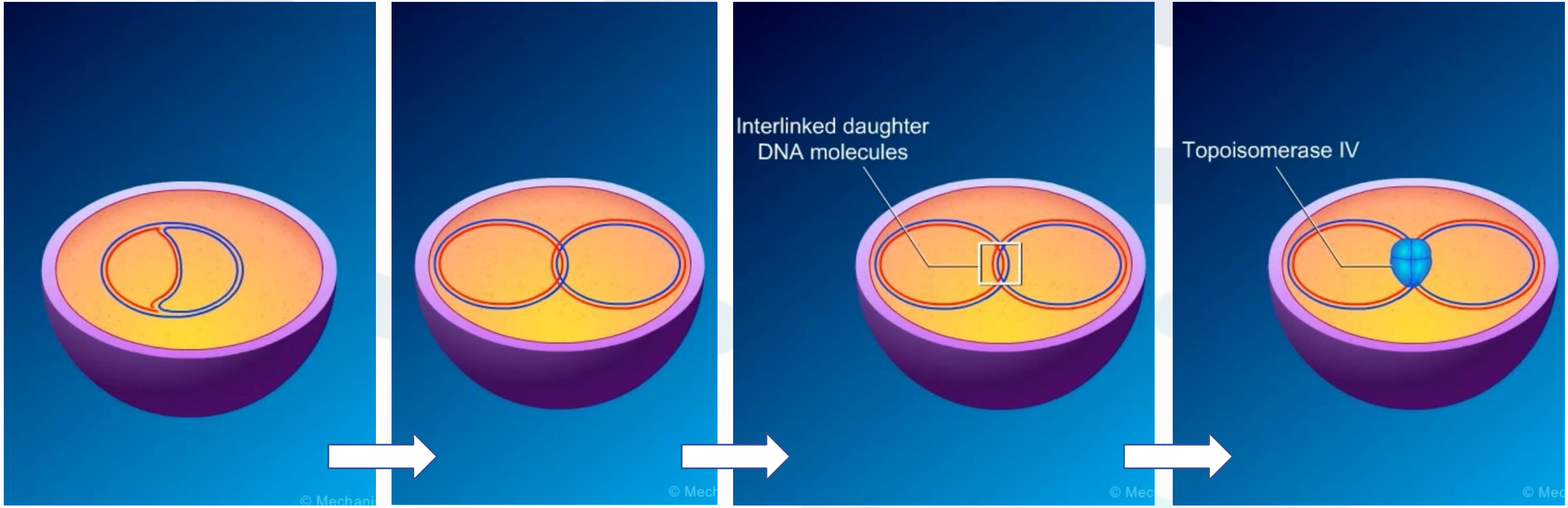

Gyrase cuts the supercoiled part from the rest of the DNA and then ligate it with the rest of DNA in a relaxed fashion.The end result is the rotation of the dna in the direction that is opposite to the original one i.e. if the supercoils are +ve ,it will be -ve and vise versa.

# Anatomy reminder




Gyrus means a fold in latin.
DNA gyrase corrects any folds"supercoils" in DNA

# Topoisomerase IV



Topoisomerase 4 solves another supercoiling problem that is present when the bacteria produces 2 daughter DNA. These daughter DNA are interlinked together by a supercoil and here topoisomerase comes to separate them.

In short gyrase(topoisomerase 2)and topoisomerase 4 relax supercoils by:-

1. Separation step: Cutting and separating the supercoiled part from the rest of DNA.
2. Ligation step: Ligating the cut part in a relaxed fashion by introducing a negative supercoil

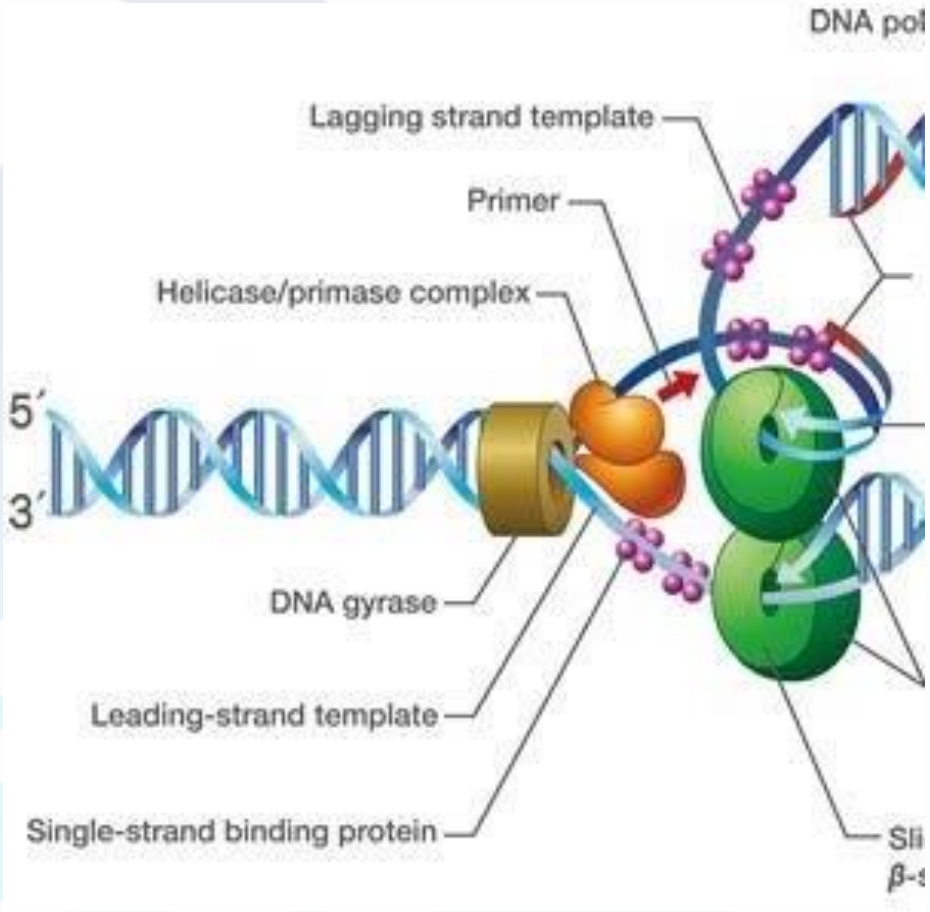
# Quinolones

**Mechanism of action**

- Inhibit ligation step of bacterial DNA gyrase and bacterial topoisomerase IV

-Inhibition of gyrase: increases the number of permenant chromosomal breaks(because gyrase inhibits the ligation but not the cutting action of DNA gyrase)

-Inhibition of topo IV: interferes with the separation of newly replicated DNA



# Quinolones

**Mechanism of action**

In gram-negative: inhibition of gyrase>topo IV

In gram-positive: inhibition of topo IV>gyrase *What does that mean?*

Answer: There is selectivity of floroquinolones to one of these 2 enzymes over the other. v In gram -ve (we choose the floroquinolones which is selective to gyrase like ciprofloxacin). v In gram +ve (we choose the floroquinolones which is selective to topo 4.

# Quinolones

**Antibacterial spectrum**

- Bactericidal
- Time-dependent killing(They require frequent dosing, but they are special in that their dosing regimen parameter is AUC24/MIC)
- Effective against gram-negative (including E.coli and Pseudomonas), atypical, gram-positive (strep), mycobacteria…. (mnemonic: The queen"flouroquinolones" has wide coverage against bacterial enemies)
- Levofloxacin: excellent activity against *S. pneumoniae*

# Quinolones

**Antibacterial spectrum**

- **First-generation (nonfluorinated): nalidixic acid**

-narrow-spectrum: aerobic gram-negative bacilli, mostly Enterobacteriaceae

- **Second-generation: ciprofloxacin and norfloxacin**

-gram-negative (pseudomonas, H.influenzae, legionella, Neisseria,etc…) and atypicals, and anthrax

- **Third-generation: levofloxacin(mnemonic: at 3 pm you leave the school)**

-gram-negative, atypical and gram-positive (including S. pneumoniae and MSSA)

- **Fourth-generation: moxifloxacin, Gemifloxacin, delafloxacin**
- **(mnemonic: a deal for max gems**

-enhanced gram-positive effects including staph and strep + coverage of gram-negative Enterobacteriaceae(wider spectrum with lower resistance profile than older generations)

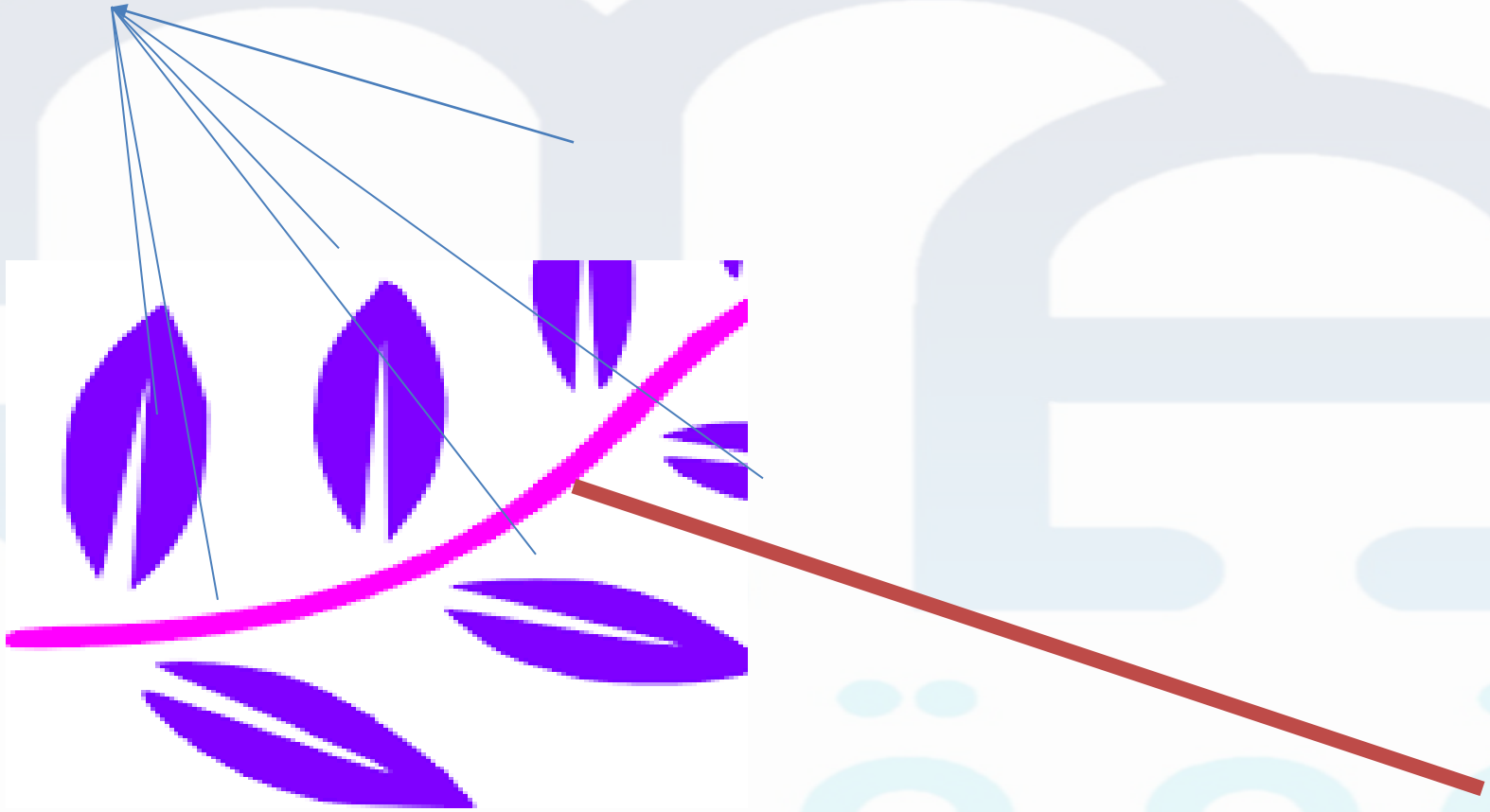
-Homework: Which fourth-generation fluoroquinolone is effective against MRSA?

Delafloxacin

Two ships→ciprofloxacin is a 2nd gen floroquinolone
Ships are pink→ cipro covers gram negative and atypicals
Colored boxes on ships→cipro is effective against pseudomonas
Ships have ants→ cipro is drug of choice against anthrax


Gram positive diplococci “leaves”
levofloxacin→**effective for pneumonia**

Levofloxacin



Gram negative bacilli→**effective for UTI and GI infections**

# Examples of Clinically Useful Fluoroquinolones

**Ciprofloxacin**

- Effective against gram-negative including P. aeruginosa(at high doses)
- Clinical indications:

1. Gastroenteritis e.g., traveler's diarrhea
2. Typhoid fever(salmonella)
3. Anthrax (drug of choice)
4. Urinary tract infections (these infections are classified into either lower: urethritis+cystitis"bladder"

Or upper: pyelonephritis"kidney"

# Urinary tract infection(UTI)

Lower UTI:-
Cystitis(bladder)
Urethritis

Signs and symptoms:
Dysuria(painful urination)+frequency and urgency بيروح يبول كثير

Lower+Upper UTI:-
Pyelonephritis
Cystitis/urethritis

Signs and symptoms:
Lower UTI+ fever,chills, flank pain ألم بالخاصرة

# Examples of Clinically Useful Fluoroquinolones

**Levofloxacin**

- Similar to cipro but also effective against gram-positive (strep not staph)
- Clinical indications:

**First-line therapy** for **community acquired-pneumonia**

Is levofloxacin effective against **Nosocomial** hospital acquired pneumonia? No!

Keep this in mind!!

Both 2nd generation(ciprofloxacin) and 3rd generation(levofloxacin) are used for UTI. But only 3rd generation levofloxacin is used for pneumonia because of its gram positive(especially pneumococcal) coverage

# Examples of Clinically Useful Fluoroquinolones

**Moxifloxacin**

- Effective against gram-negative, S. pneumonia and mycobacterium
- Clinical indications:

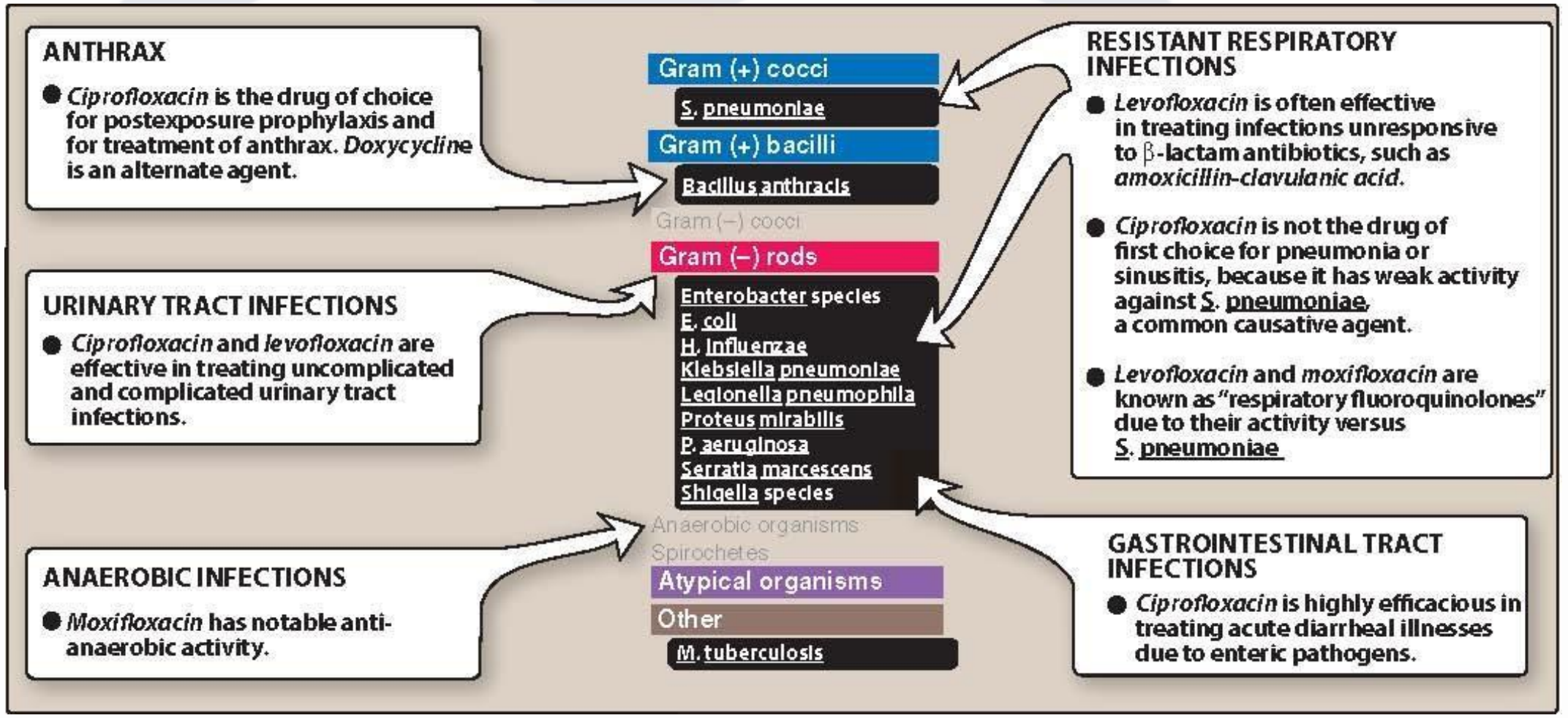
1. For community-acquired but not nosocomial pneumonia (weak against pseudomonas)
2. Second-line for TB
3. Useful against anaerobes like B.fragilis

It may be considered for mild-to-moderate intra-abdominal infections(anaerobic), but should be **avoided if patients have fluoroquinolone exposure within previous three months**, due to increasing B. fragilis resistance

Gemifloxacin is indicated for management of **community-acquired respiratory infections**. Unlike the other compounds, it is only available as an oral formulation.

Delafloxacin is active against strep pneumoniae,anaerobes(B.fragilis) mycobacteria,Enterocoocus,MRSA and pseudomonas!! (mnemonic: delafloxacin is an excellent deal(صفقة)

# Clinical Uses of Fluoroquinolones



# Fluoroquinolones and UTIs

"Fluoroquinolones (eg, ofloxacin, ciprofloxacin, levofloxacin) are **highly effective in UTIs**, but these agents have a propensity for **causing collateral damage** and should be reserved for important **uses other than acute uncomplicated cystitis**. IDSA guidelines recommend that **fluoroquinolones be used as second-line agents for acute uncomplicated cystitis and as first-line oral therapy for complicated cystitis".**

**International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases**

Complicated UTI(anything that **aids bacteria in ascending and causing infection and resisting antibiotics** or **weakens immune system**) :-

- Urinary tract anatomical obstruction/deformity, indwelling catheter, stent, nephrostomy tube
- Antibiotic-resistant organism
- History of pyelonephritis in last year
- Diabetics
- renal failure
- Pregnancy
- Immunocompromised patients (e.g., HIV patients, transplant recipients)

# Fluoroquinolones

**Mechanisms of resistance**

-mainly chromosomal(mnemonic:the queen doesn't accept plasmid resistance

- **Altered target(main mechanism):**

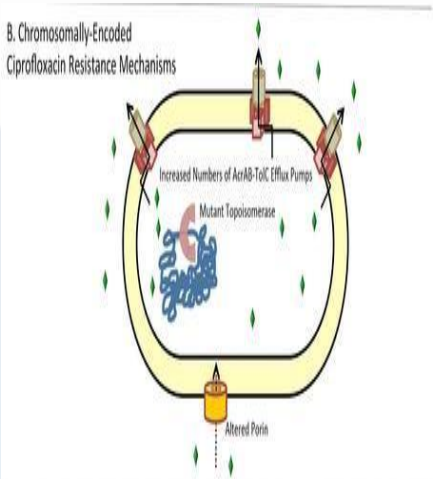
-mutations in *gyrA* or *parC* →alter target site structure and reduce binding efficiency of fluoroquinolones.

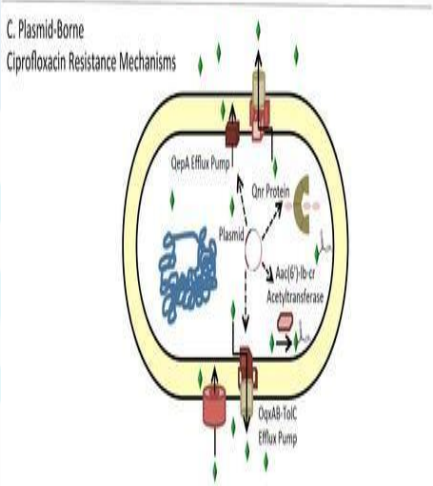
- **Decreased accumulation**

-porin channels

-efflux pumps

- **Fluoroquinolone degradation:** an aminoglycoside acetyltransferase variant can acetylate fluoroquinolones, rendering them inactive
- Cross-resistance



# Fluoroquinolones

**Pharmacokinetics**

- **Absorption**

90% bioavailability

-mainly oral – IV/ophthalmic preps of cipro and levo

-Sucralfate ,food,$Ca^{++}$, $Al^{+3}$ and $Mg^{++}$interfere with absorption

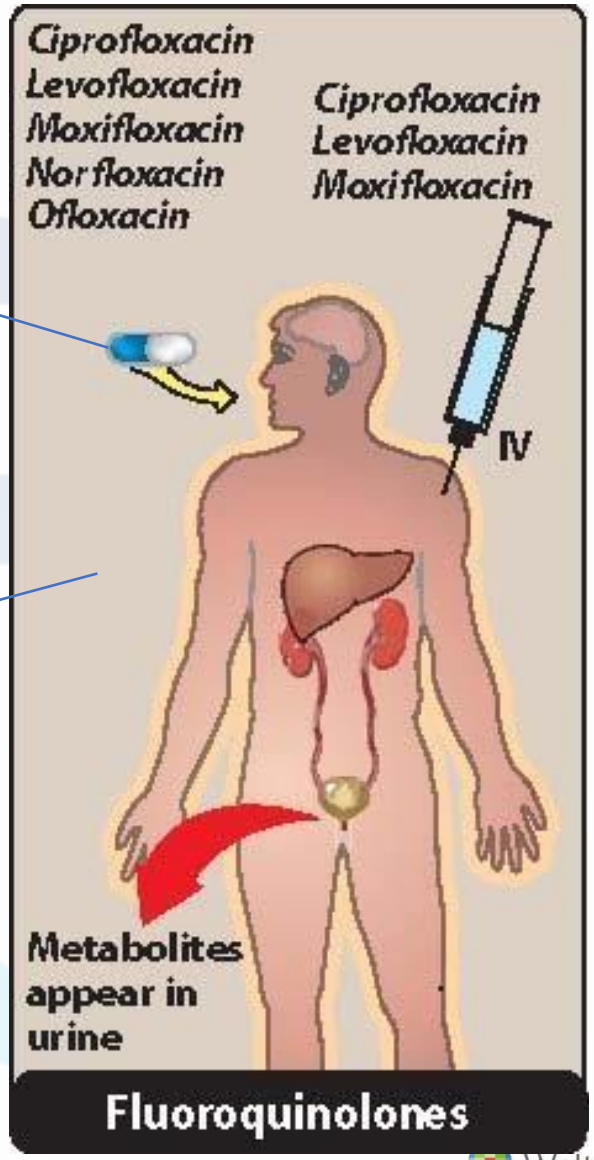
20-80% are protein-bound

- **Distribution**

-very well distributed (high conc in bone, urine"except moxi" and lung)

-good CSF distribution

-concentrate in macrophages and neutrophils→effective against intracellular pathogens like TB, listeria, and chlamydia



# Fluoroquinolones

**Pharmacokinetics**

- **Absorption**

-mainly oral – IV/ophthalmic preps of cipro and levo

-food, $Ca^{++}$, $Al^{+3}$ and $Mg^{++}$ interfere with absorption

90% of the drugs are given orally (high bioavailability).

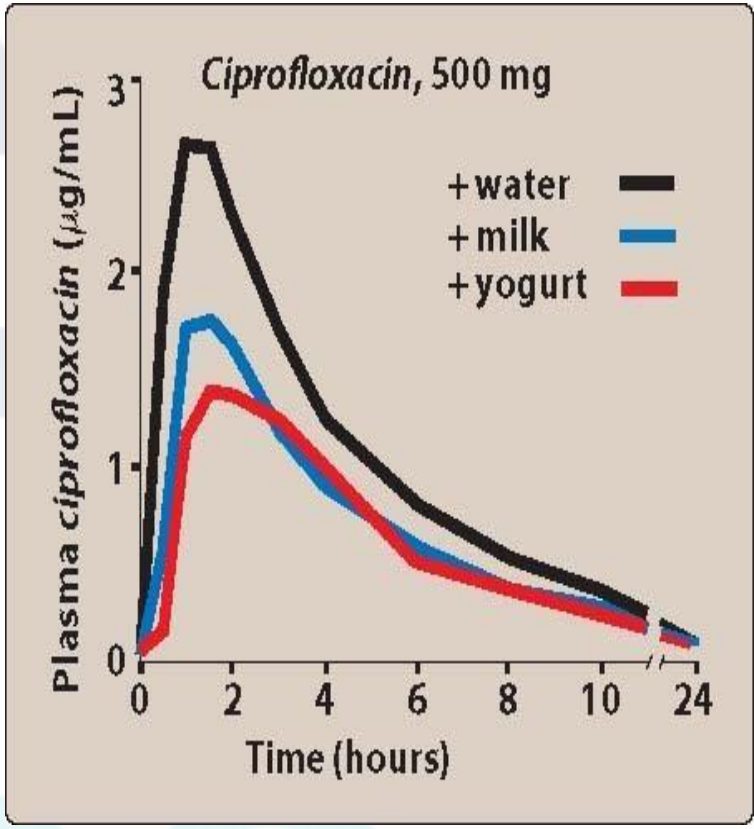
- **Distribution**

-very well distributed (high conc in bone, urine and lung)

-good CSF distribution

-concentrate in macrophages and neutrophils

They have variable degrees of proteins binding to plasma proteins in the plasma (20%-80%) depending on the drug



# Fluoroquinolones

**Pharmacokinetics**

- **Elimination**

-After hepatic metabolism, most fluoroquinolones are **excreted renally**

-**Moxifloxacin** is excreted by liver in bile (can be used in patients with renal impairment)

# Quinolones

**Adverse effects**

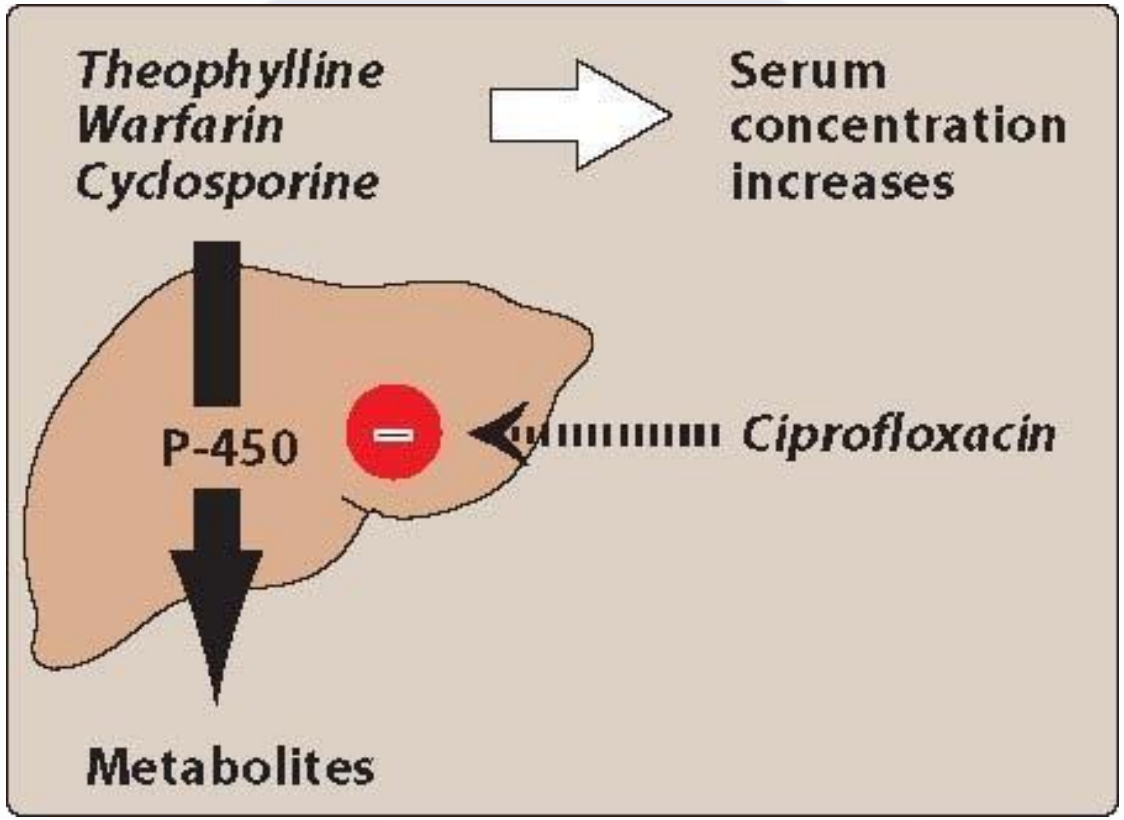
-generally well-tolerated

- **N/V/D**
- **Headache and dizziness**(الملكة راسها مصدع من إدارة المملكة)
- **Hepatoxicity**
- **Peripheral neuropathy and glucose dysregulation** (أعصابها تلفت وصابها سكري من ضغوطات إدارة المملكة
- **CNS neuropathy(hallucinations,anxiety, seizures, etc..)**
- **Phototoxicity→use sunscreen**بتتعرضش الملكة للشمس فأول ما تطلع بتنحرق
- **(boxed warning) Articular cartilage erosion, tendinitis, tendon rupture(contraindicated in children less than 18 years old)**قصيرة فبتلبس كعب بيضايق مفاصلها وأوتار رجلها
- **QT prolongation→don't use with macrolides**الملكة قلبها رهيف

# Quinolones

**Drug-drug interaction**

- Cirp inhibits Cytochrome p450 family,including CYP 3A4, CYP 1A2
- Cipro can inhibit metabolism of theophylline, others
- Quinolones can raise serum warfarin→ bleeding



**Examples of Enzyme Inducers**

**Ph**enytoin & carbamazepine- **ph**enobarbitone – **ri**fampicin - griseo**fu**lvin - ♂ androgen- nicotine- chronic alcohol ingestion.

***Clinical significance of Enzyme Inhibition:***

- ❖ Drugs inhibiting the microsomal enzyme systems → ↓ activity →
  - ↓ their <u>own</u> metabolism →↑ drug level.
  - ↓ metabolism of <u>other drugs</u> metabolized by these enzymes → drug interactions e.g.:
    - **Ciprofloxacin** →↓ **warfarin** metabolism → bleeding
    - **Cimetidine** →↓ **carbamazepine** metabolism → toxicity
- It occurs faster than enzyme induction.

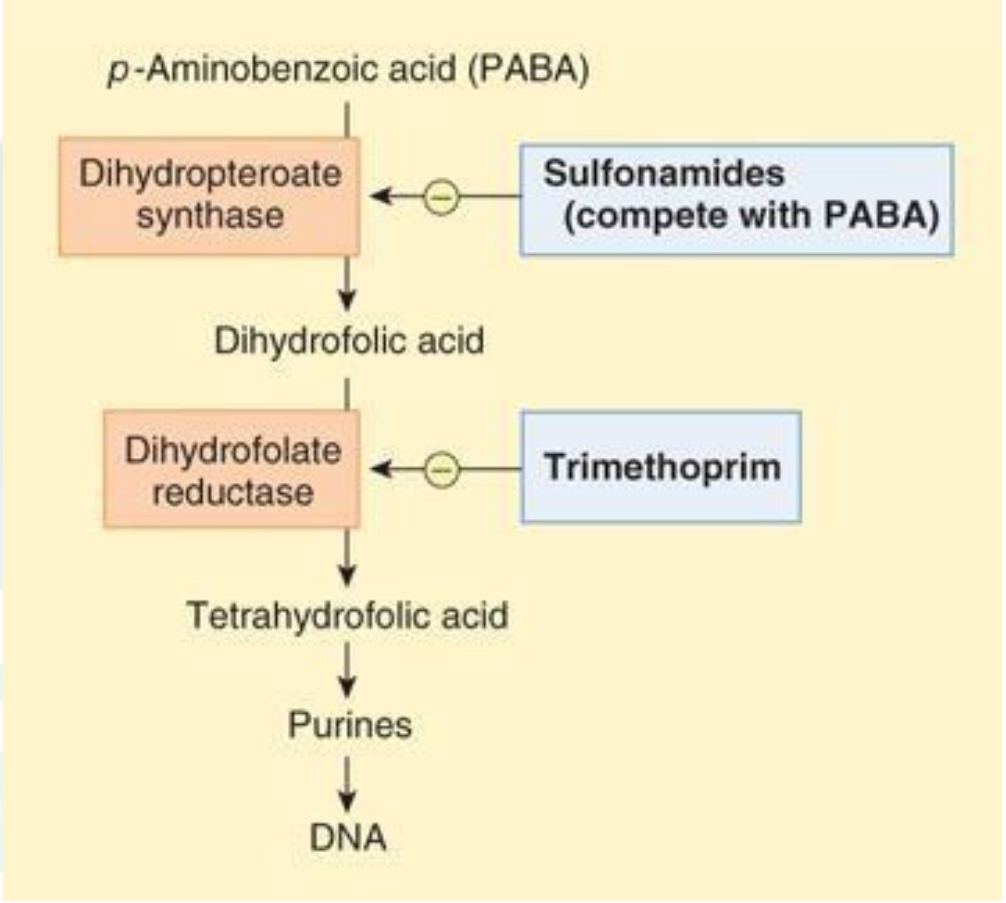
**Examples of Enzyme Inhibitors**

**C**imetidine- **ch**loramphenicol - **ci**profloxacin- erythromycin - ketocenazol - ♀ **(F)** estrogen, progesterone, contraceptive pills.

# Folate Antagonists

# Folic Acid Antagonists

- Purine and pyrimidine synthesis requires folate-derived cofactors
- Folic acid is necessary for DNA replication and cellular growth
- Many bacteria are impermeable to folate →rely on de novo synthesis
- Folic acid must be converted into tetrahydrofolate

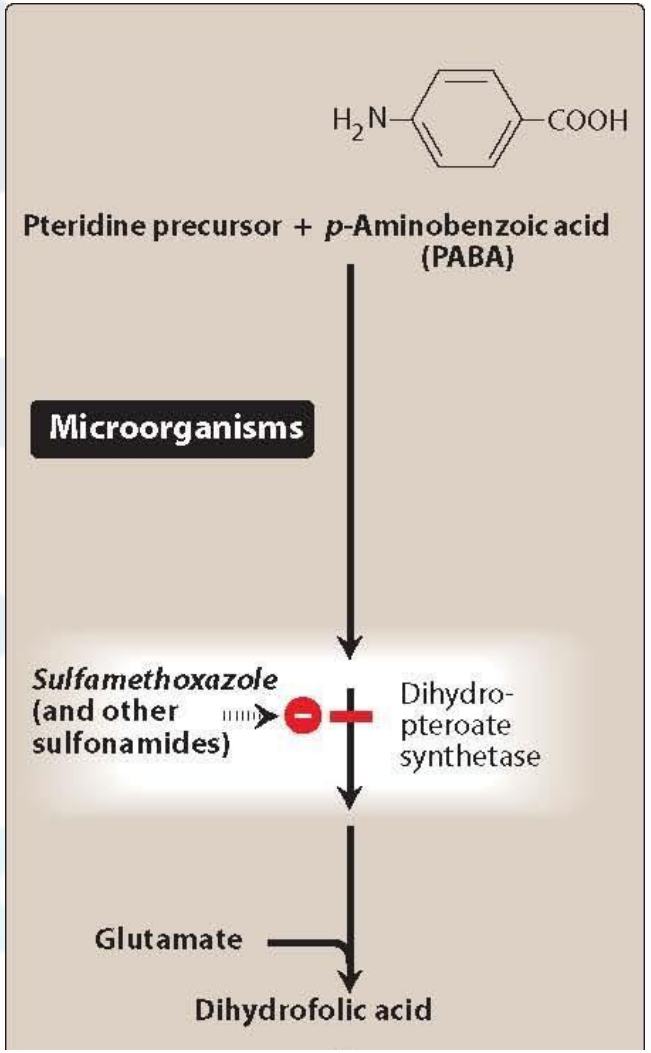


# Sulfonamides

# Sulfonamides

**Mechanism of action:**

- Sulfonamides are **synthetic analogues** of PABA
- PABA is used to synthesize dihydrofolate
- Sulfonamides inhibit *dihydropteroate synthetase*
- Bacteriostatic



# Sulfonamides

**Antibacterial spectrum**

- Effective against Enterobacteriaceae causing UTIs
- Effective against H. influenza, streptococcus,(so can be used in RTI too!) staphylococcus spp,, and Nocardia

**Mechanisms of resistance**

Bacteria that obtain folate from their environment are naturally resistant to sulfa drugs. Acquired bacterial resistance to the sulfa drugs can arise from plasmid transfers or random mutations.

- Altered dihydropteroate synthetase
- Decreased cellular permeability
- Enhanced production of PABA

**INHIBITORS OF FOLATE SYNTHESIS**

*Mafenide* SULFAMYLON
*Silver sulfadiazine* SILVADENE
*Sulfasalazine* AZULFIDINE

[Note: Organisms resistant to one member of this drug family are resistant to all. Compare this with tetracycline resistance]

# Sulfonamides

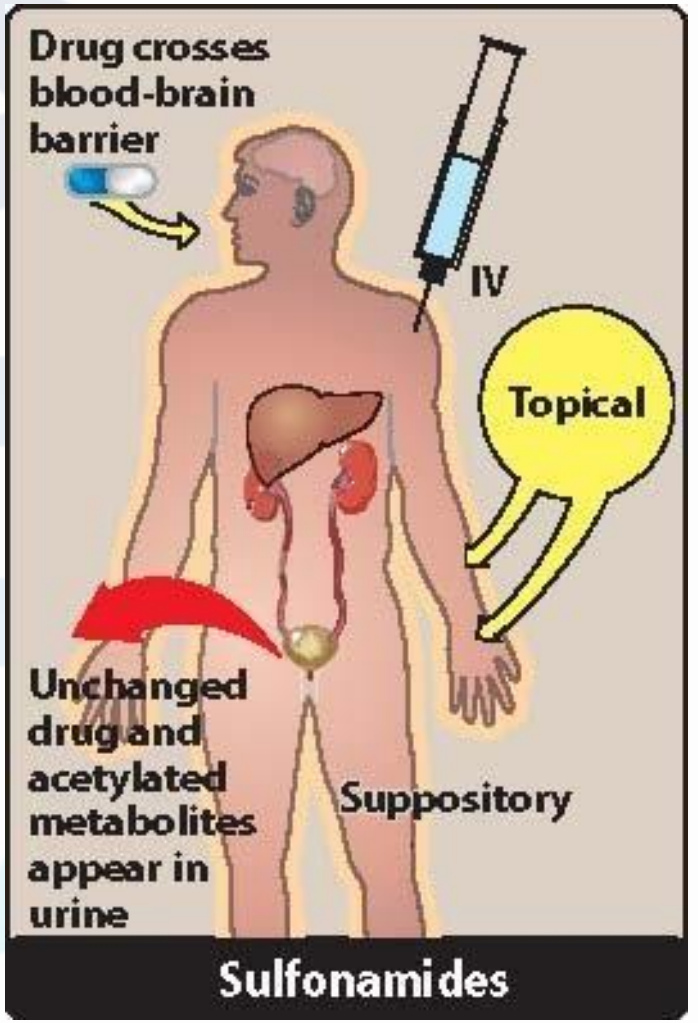
**Pharmacokinetics**

- **Absorption**

-oral: well-absorbed (except sulfasalazine)

-how can you use sulfasalazine?

for treatment of chronic **inflammatory bowel diseases**
Intestinal flora split sulfasalazine into sulfapyridine and 5-aminosalicylate(5-ASA), with the latter exerting the anti-inflammatory effect. Absorption of sulfapyridine can lead to toxicity in patients who are slow acetylators.]



Intravenous sulfonamides are generally reserved for patients who are unable to take oral preparations or have severe infections.

Because of the risk of sensitization, sulfa drugs are not usually applied topically.

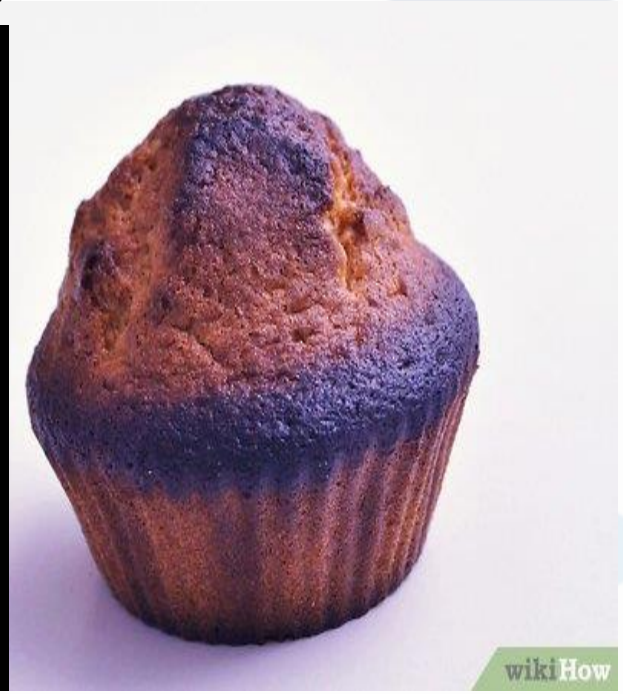
However, in burn units, silver sulfadiazine or mafenide acetate creams have been effective in reducing burn-associated sepsis because they prevent colonization of bacteria.

[Note: Silver sulfadiazine is preferred because mafenide produces pain on application and its absorption may contribute to acid-base disturbances.]

# Mnemonic

**كبريت كبريت...**

Mafenide is a **sulfon**amide




Burned muffin cake

Mafenide is used for burns

Burning diamond

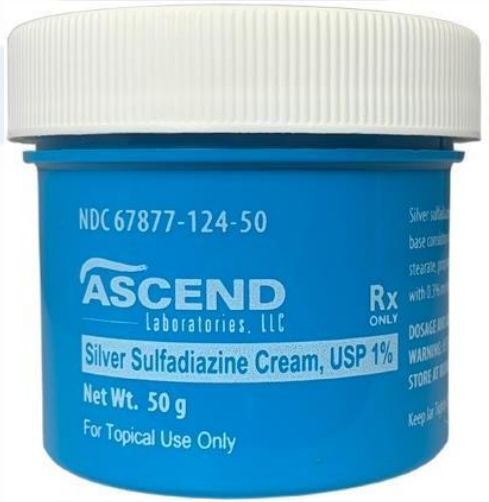
Silver Sulfadiazene is used for burns

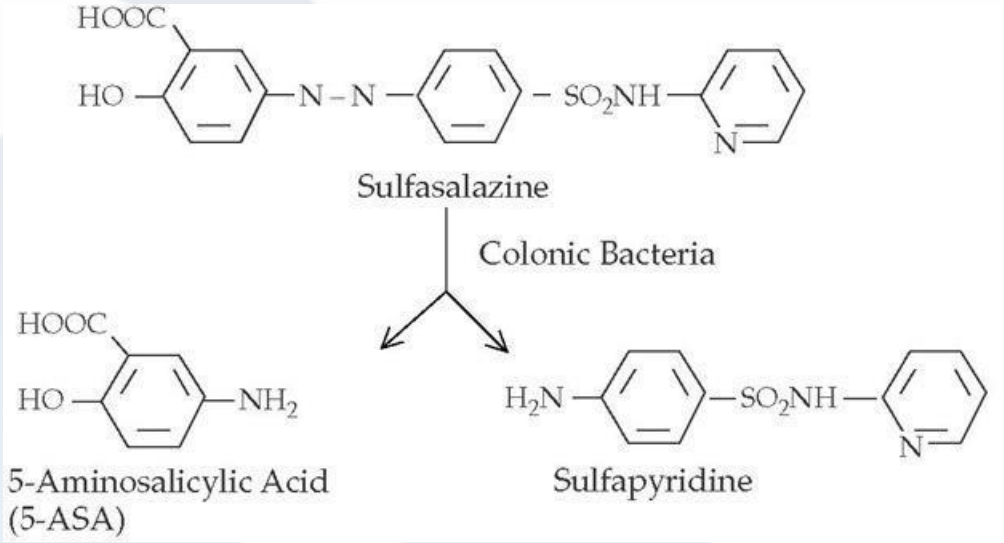
# Special Uses

## TOXOPLASMOSIS RX

**First Line**

- Pyrimethamine (200mg-L/75C) + Sulfadiazine(6-8g/d -4d/d) till improve CD4 count
- Pyrimethamine + Clindamycine



**Pyramids**
**Pyrimeth**amine

**Dia**mond
Sulfa**dia**zine

# Dr sheriff slide reminder

**2. Extracellular fluid (two compartmental models):**

- If a drug has a **low molecular weight** and is **hydrophilic**
- It can move through the endothelial slit junctions of the capillaries into the interstitial fluid BUT cannot move across the lipid membranes of cells
- e.g. Aminoglycoside antibiotics, Mannitol.

**3. Extra & intracellular fluid (multi-compartmental model)**

- If a drug has a **low molecular weight** and is **lipophilic**
- It moves into the interstitium through the slit junctions and also moves through the cell membranes into the intracellular fluid.
- Some drugs uniformly distribute throughout whole body water e.g. Ethanol, sulphonamides.

# Dr sheriff slide reminder

4. Competition for binding sites between drugs ⟶ **displacement of each other** ⟶ **clinically-significant drug interactions** e.g.

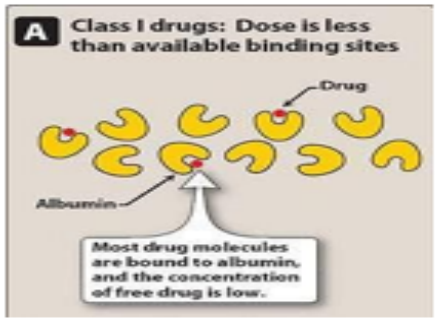
- Aspirin, sulphonamide displace warfarin ⟶ bleeding.
- Sulphonamide displaces bilirubin ⟶ kernicterus in premature neonates.

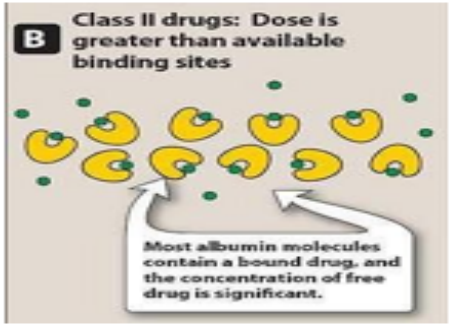
{When two drugs with high affinity for albumin are given, they compete for the available binding sites. The drugs with **high affinity** for albumin can be divided into two classes:

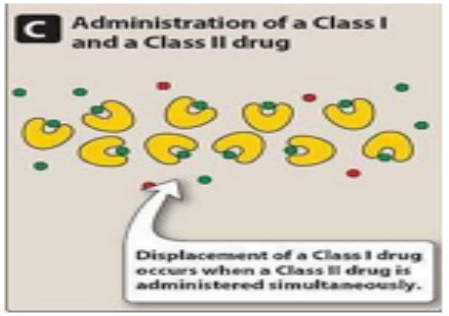
**1.Class I drugs:** If the dose of drug is less than the binding capacity of albumin i.e. **low dose/capacity ratio** ⟶ high bound fraction and **small free fraction**

**2.Class II drugs:** If the doses greatly exceed the number of albumin binding sites i.e. **high dose/capacity ratio ⟶ high free fraction**.

* When a patient taking a Class I drug, such as warfarin, is given a Class II drug, such as a sulfonamide antibiotic. Sulfonamide displaces warfarin from albumin, leading to a rapid increase in the concentration of free warfarin in plasma ⟶ ↑ therapeutic effects, as well as ↑ toxic effects ⟶ bleeding}



# Sulfonamides

**Pharmacokinetics**

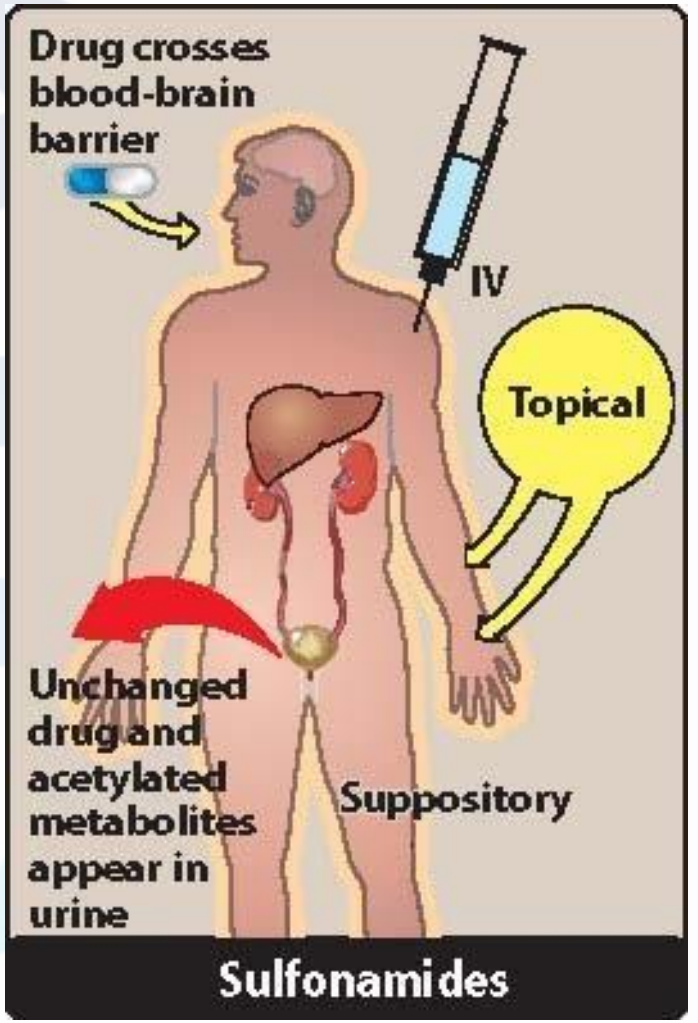
- **Distribution**

-highly-bound to serum albumin

-distribute well through body fluids **including CSF**

-cross placenta!!!

-eliminated in breast milk



# Sulfonamides

**Pharmacokinetics**

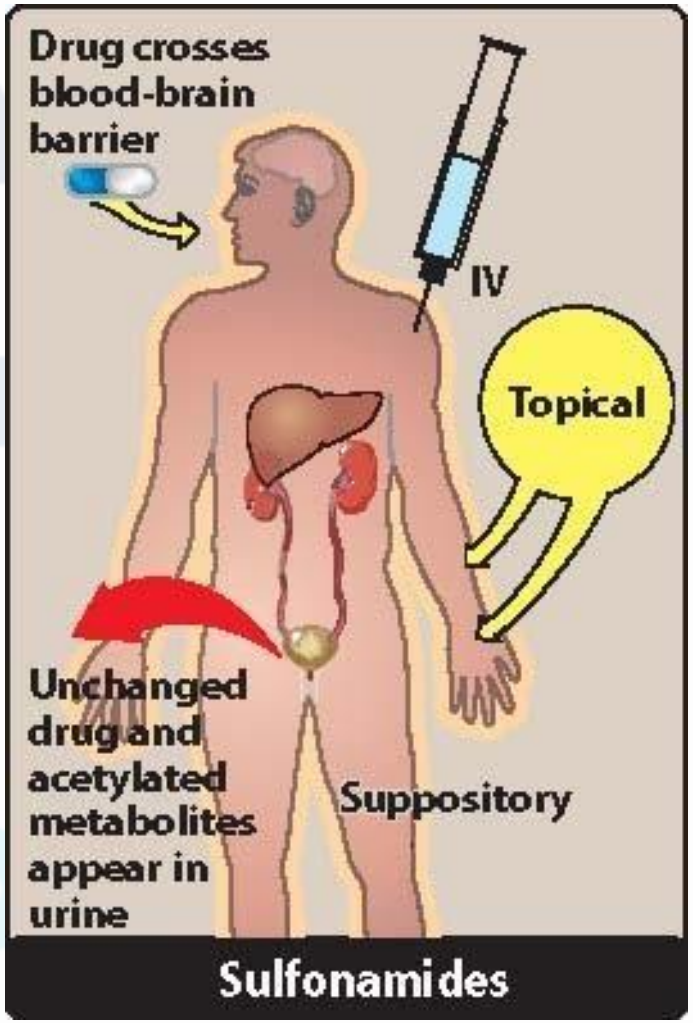
- **Metabolism**

-metabolized in the liver (Phase 2 conjugation with acetic acid→acetylation)

-**acetylated acidic metabolites** can **crystalize** and become hydrophobic in **acidic** urine causing renal stones

- **Elimination**

-eliminated by glomerular filtration and secretion(dose adjustments with renal impairment). Sulfonamides may be eliminated in breast milk.



# Sulfonamides

**Adverse effects**

- **Crystalluria and renal stones**

-nephrotoxicity

-requires adequate hydration and urine alkalinization

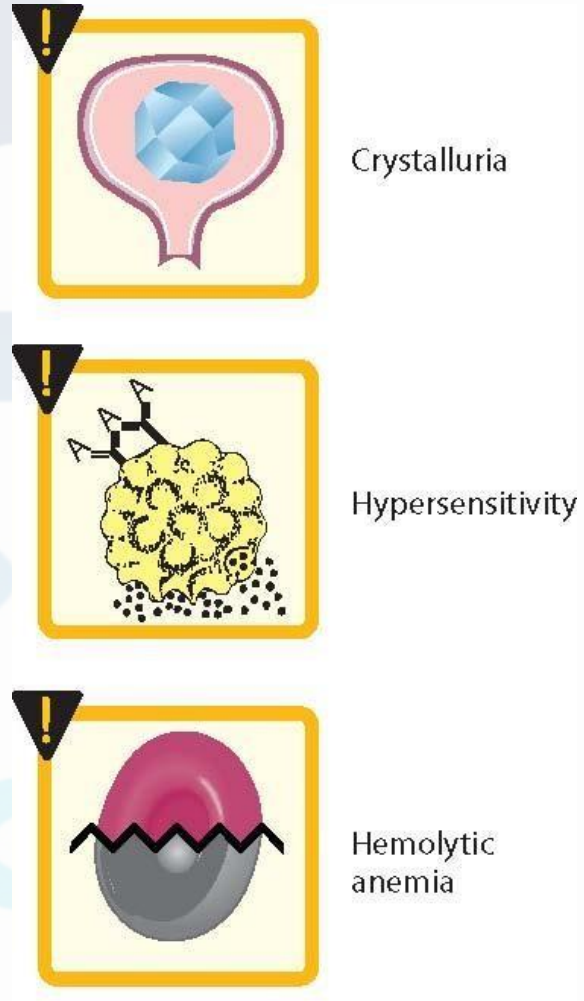
- **Hypersensitivity**

-sulfa allergies→may cause steven johnsons

- **Hematopoietic disturbances:**

-hemolytic anemia in patients with G6PD deficiency.

Granulocytopenia and thrombocytopenia can also occur.



# Sulfonamides

**Adverse effects**

- **Kernicterus**

-sulfa displace protein-bound bilirubin in plasma→more free bilirubin that will penetrate CNS and damages neurons!

Only occurs in **newborn**s(because they have immature BBB)

Kernicterus

- **Drug-drug interaction**

-increase anticoagulant effect of warfarin by **inhibiting CYP2C9+ displaces warfarin from plasma proteins**

Other drugs may have increased effects too like phenytoin and methotrexate


- **Contraindications**

-newborn, infants, breastfeeding women

-with methenamine(increases crystallization in urine)

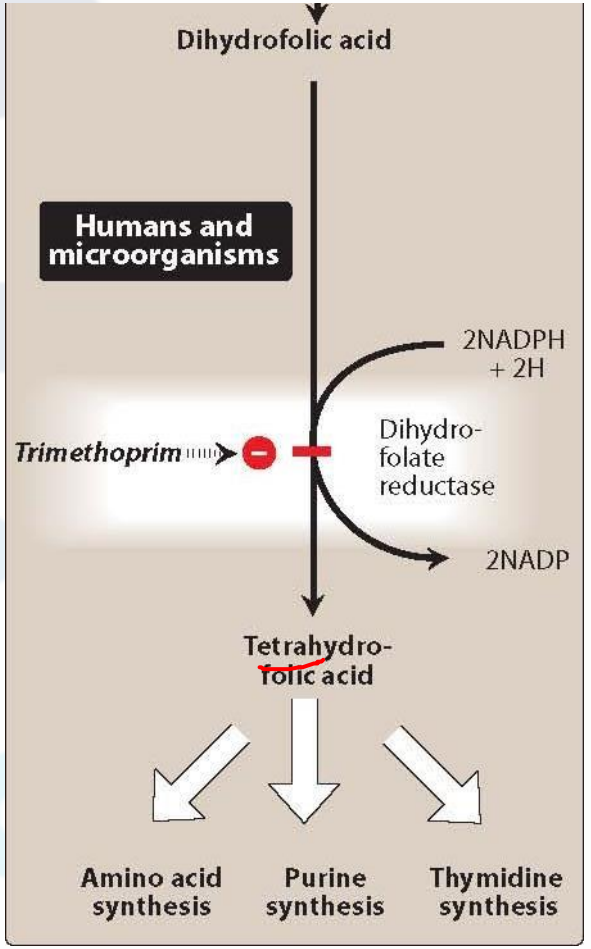
# Trimethoprim

# Trimethoprim

**Mechanism of action**

- Dihydrofolate is reduced to tetrahydrofolate (active form of folate) by dihydrofolate reductase
- Trimethoprim inhibits dihydrofolate reductase

- Decreases purine and pyrimidine synthesis
- Bacterial vs mammalian selectivity(it has more selectivity for bacterial dihydrofolate reductase)
- **Mostly combined with sulfa drugs**



# Trimethoprim

**Antibacterial spectrum**

- Similar to sulfa drugs e.g., sulfamethoxazole
- More potent as a single agent(trimethoprim is 20- to 50-fold more potent than the sulfonamides)
- Can be used alone. For what?

… but not very often…

in the treatment of urinary tract infections (UTis) and in the treatment of bacterial prostatitis (although fluoroquinolones and cotrimoxazole are preferred).

**Mechanisms of resistance**

- Altered dihydrofolate reductase
- Efflux pumps and reduced permeability may play a role

# Pharmacokinetics:- Trimethoprim

Trimethoprim is rapidly absorbed following oral administration.

Because the drug is a weak base, higher concentrations of trimethoprim are achieved in the relatively acidic prostatic and vaginal fluids.

The drug is widely distributed into body tissues and fluids, including penetration into the cerebrospinal fluid.

Trimethoprim undergoes some 0-demethylation, but 60% to 80% is renally excreted unchanged.

# Trimethoprim

**Adverse effects**

- can produce the effects of folic acid deficiency.

-megaloblastic anemia

-leukopenia

-granulocytopenia,

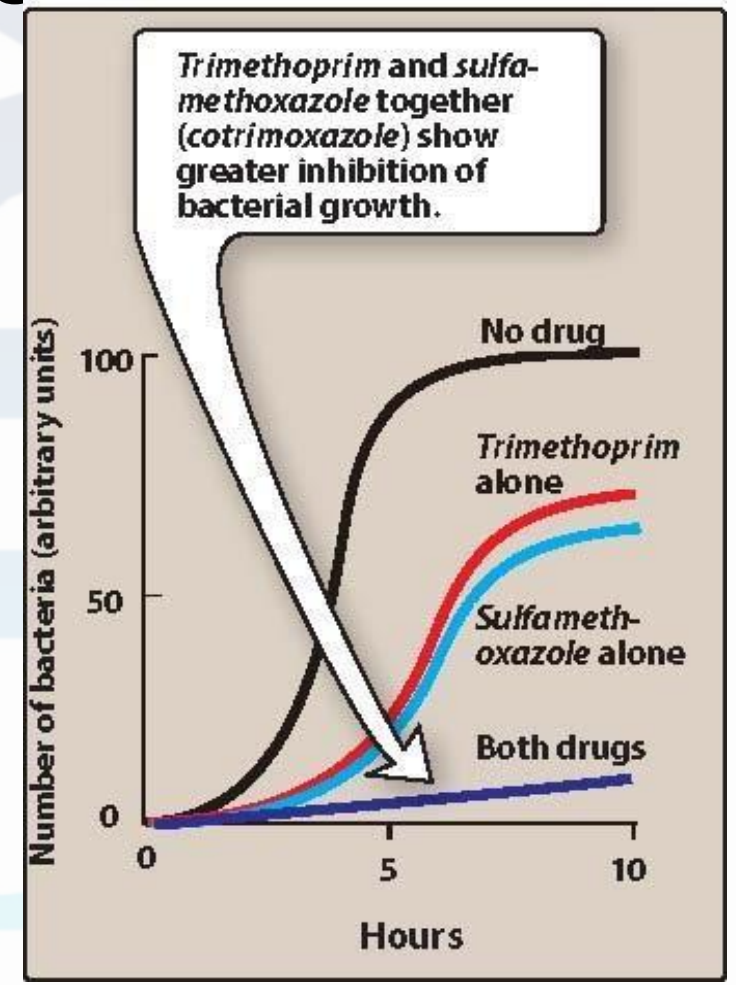
especially in pregnant patients and those with nutrient-poor diets.

***Reversed by administration of folinic acid, which does not enter bacteria.

- Hyperkalemia, especially at higher doses and when administered with agents that cause hyperkalemia like ACE inhibitors

# Trimethoprim/Sulfamethoxazole (Co-trimoxazole)

- The combination has a synergistic effect
- inhibition of two sequential steps in the synthesis of tetrahydrofolic acid.



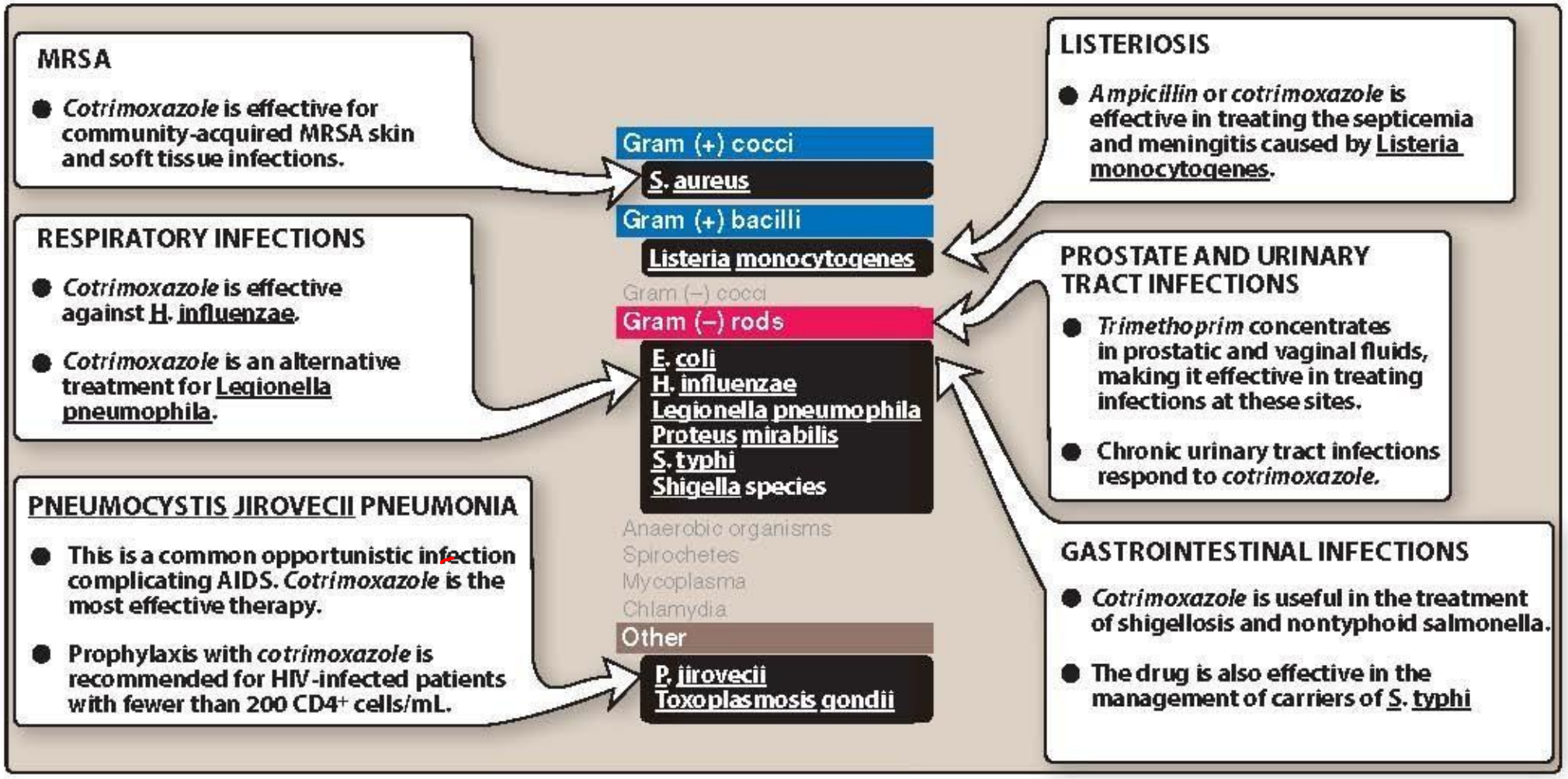
# Trimethoprim/Sulfamethoxazole (Cotrimoxazole)

**Antibacterial spectrum(Cotrimoxazole has a broader spectrum of antibacterial action than the sulfa drugs alone)**

- Effective in treating UTIs and RTIs
- Drug of choice for infections caused by Nocardia spp.
- Effective against *Pneumocystis jirovecii* pneumonia
- Skin and soft tissue MRSA infections
- Prostatic infections(prostatitis)

Coatrimoxazole(lab coat)→
pneumocystis jirovici(jerry)
lab coat card→ nocardia
With lab coat you prepare to kill MRSA

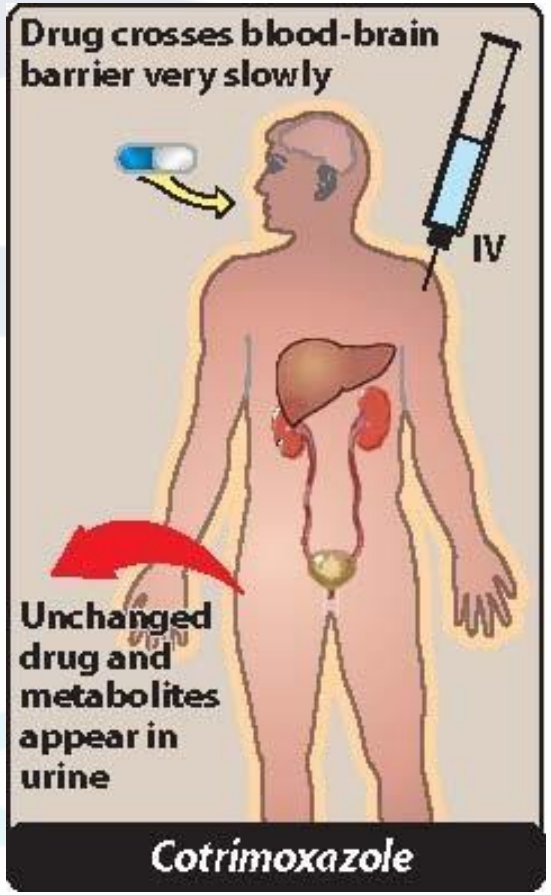
# Trimethoprim/Sulfamethoxazole (Cotrimoxazole)



# Trimethoprim/Sulfamethoxazole (Cotrimoxazole)

**Pharmacokinetics**

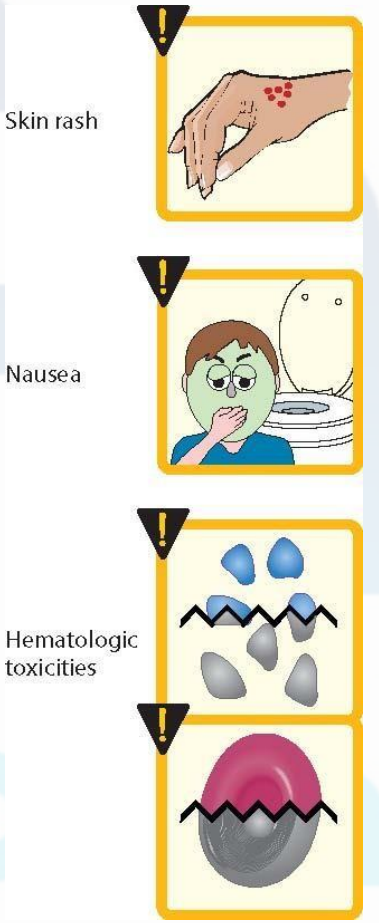
- Administered orally (IV reserved for severe cases of PCP)
- Crosses BBB
- Excreted in the urine



# Trimethoprim/Sulfamethoxazole (Cotrimoxazole)

**Adverse effects**

- N/V/D
- Skin reactions
- Glossitis/stomatitis
- Hyperkalemia
- Megaloblastic anemia
- Hemolytic anemia in patients with G6PD def
- Drug-drug interaction with warfarin



# Urinary Tract Antiseptics/Antimicrobials

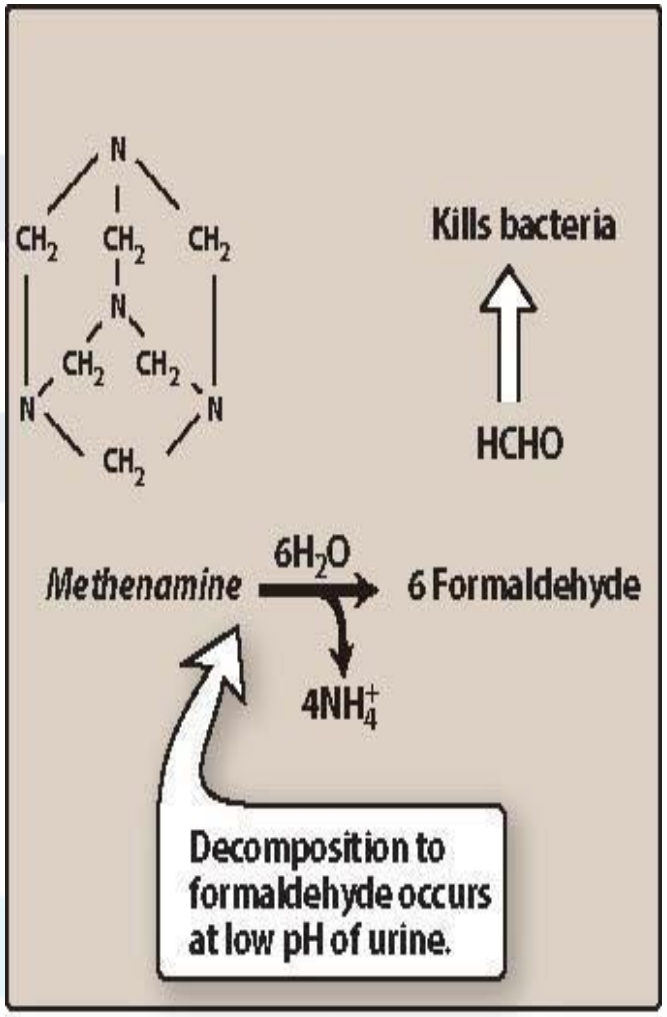
- UTIs are more prevalent in women and elderly
- Most common cause: *E. coli* (80% of uncomplicated UTIs)
- Second most common cause: *Staphylococcus saprophyticus*

**Most frequently used agents:**

1. **Nitrofurantoin**
2. Fosfomycin
3. **Cotrimoxazole**
4. **Fluoroquinolones(2nd line for uncomplicated, 1st line for complicated)**
5. **Methenamine(chronic suppressive therapy/prophylaxis)**

# Methenamine

- **MOA**: decomposes at an acidic pH of 5.5 or less in the urine → produces formaldehyde → toxic to most bacteria by denaturating proteins and nucleic acids. Methenamine is combined with a weak acid (for example, hippuric acid) to maintain urine acidity and promote production of formaldehyde
  - **Antibacterial spectrum**: used for chronic suppressive therapy to reduce UTIs(prophylaxis). Active against E.coli, enterococcus, and staph species.
  - Some activity against **Pseudomonas or Proteus spp**



# Methenamine

urine pH must be kept acidic to achieve bactericidal activity. The main benefit of methenamine is the lack of selection for resistant organisms.

**Pharmacokinetics:-**

Methenamine is orally absorbed, with up to 30% decomposing in gastric juices, unless protected by enteric coating.

It reaches the urine through tubular secretion and glomerular filtration. Concentrations are sufficient to treat susceptible organisms.

Due to ammonia formation, use should be avoided in hepatic insufficiency.

# Methenamine

**Adverse effects: -**

The major adverse effect of methenamine is gastrointestinal distress,

at higher doses, albuminuria, hematuria, and rashes may develop.

Methenamine mandelate is contraindicated in patients with renal insufficiency, because mandelic acid may precipitate. The methenamine hippurate formulation should be used instead.

[Note: Sulfonamides, such as cotrimoxazole, react with formaldehyde and must not be used concomitantly with methenamine. The combination increases the risk of crystalluria and mutual antagonism.]

# Nitrofurantoin

- Nitrofurantoin is now first-line for uncomplicated cystitis
- **MOA**: Major inhibitor of DNA and RNA synthesis(through free radicals)
- Useful against *E.coli, klebsiella,* Enterococcus spp., and Staphylococcus spp.
- Following oral administration, it is rapidly absorbed, with nearly 40% excreted unchanged in the urine.
- Common adverse events include nausea, vomiting, and diarrhea. Use of the microcrystalline formulation decreases the incidence of gastrointestinal toxicity.
- Rare complications of therapy include pulmonary fibrosis, neuropathy, and autoimmune hepatitis.
- Can also cause hemolytic anemia in patients with G6PD
- Should not be used in patients with renal impairment or term pregnant women

13. **A 33-year old healthy female presents with 2-day history of dysuria (painful urination), urinary frequoncy and urgency. Urine culture indicated that she has an uncomplicated urinary tract infection cause by E. coli. Which of the following agents will be your FIRST CHOICE for the treatment of the lady ?**

A. Bacitracin.
B. Sulfadiazine.
C. Nitrofurantoin.
D. Moxifloxacin.
E. Clotrimoxazole.

Answer:C

**48. A 49-year-old male AIDS patient showed up at the ER with altered mental state and weakness after suffering from a seizure at home. Patient record indicate that he reported sensory abnormalities primary care physician within the last month. The patient committed to his antiretroviral therapy and described to have immunodeficiency (mean CD4+ count of 40 cells/ +75 st deviation). Physical examination revealed cervical lymph, Head CT scanning showed multiple ring-enhancing lesions while blood testing confirmed the existence of Toxoplasmas Which of the following antibiotics is BEST to treat the patient symptoms?**

A. Pyrimethamine + sulfadiazine
B. Trimethoprim + sulfasalazine
C. Ampicillin + gentamicin
D. Piperacillin + tazobactam
E. Metronidazole + paromomycin

Answer:A