Pharmacology

Subject :

Lec no : 28

Done By : Raneem Azzam

وَقُل رَّبِّ زِدْنِي عِلْمًا

Quinolones and Folic Acid Antagonists

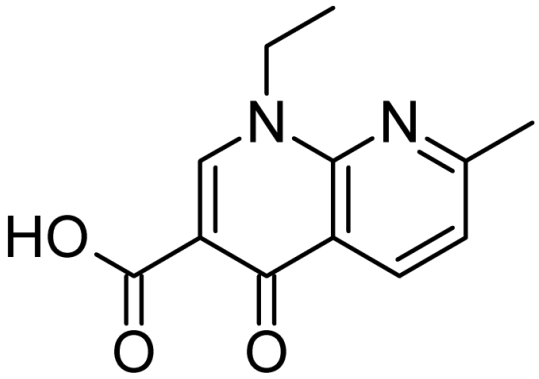
Pharmacology and Toxicology
General Pharmacology
Second Year Medical Students
Tareq Saleh
Faculty of Medicine
The Hashemite University

Textbook: Chapter 31 pp 400-412

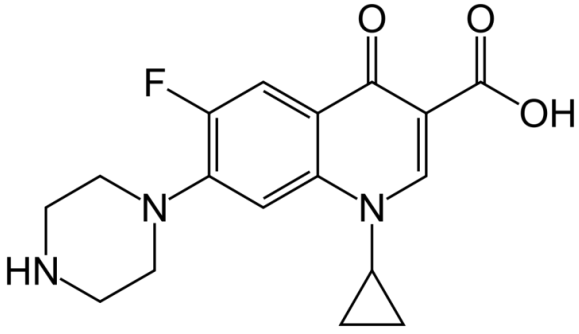
Compound that interfere with the DNA synthesise and prevents the bacteria from successfully synthesising its DNA,these drugs can also result in DNA damage in the form of DNA double strand breaks

Fluoroquinolones

Quinolones



Nalidixic acid



Ciprofloxacin

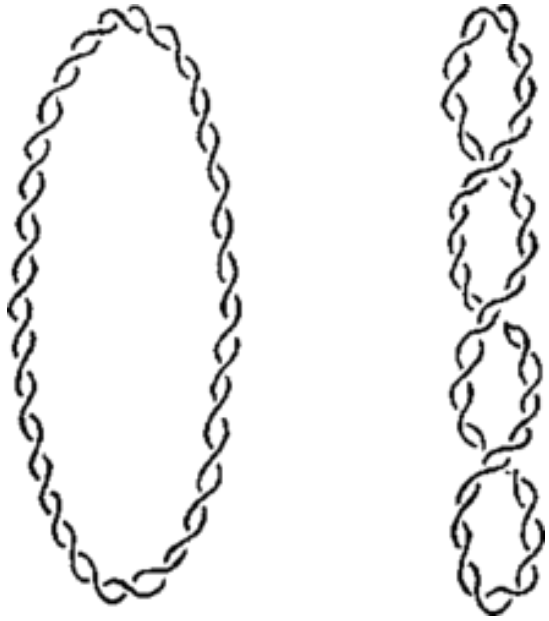
FLUOROQUINOLONES

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

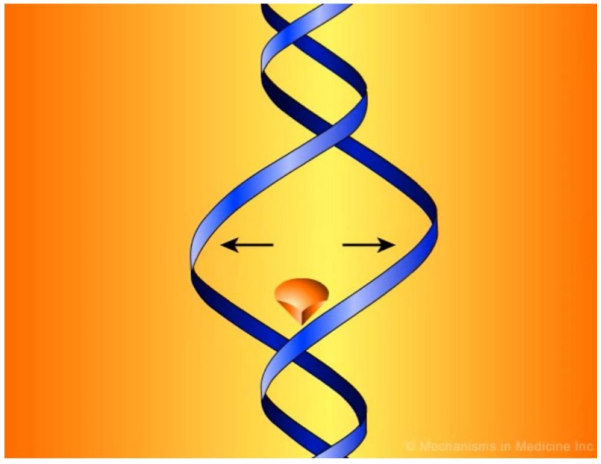
بعدين بلشنا نفرل ← عليه ← regenerate

more powerful, more broad spectrum antibiotices

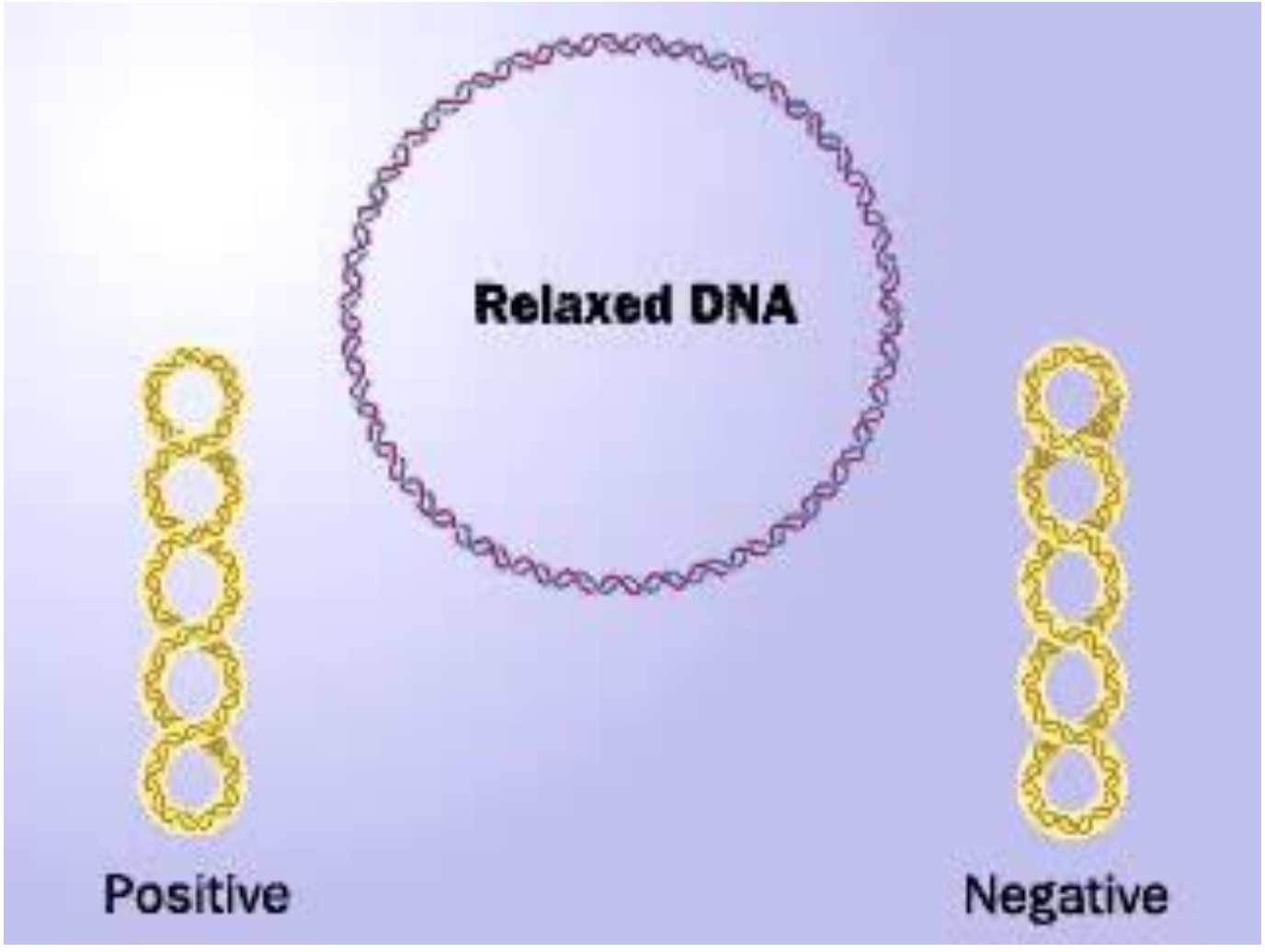
DNA Supercoiling



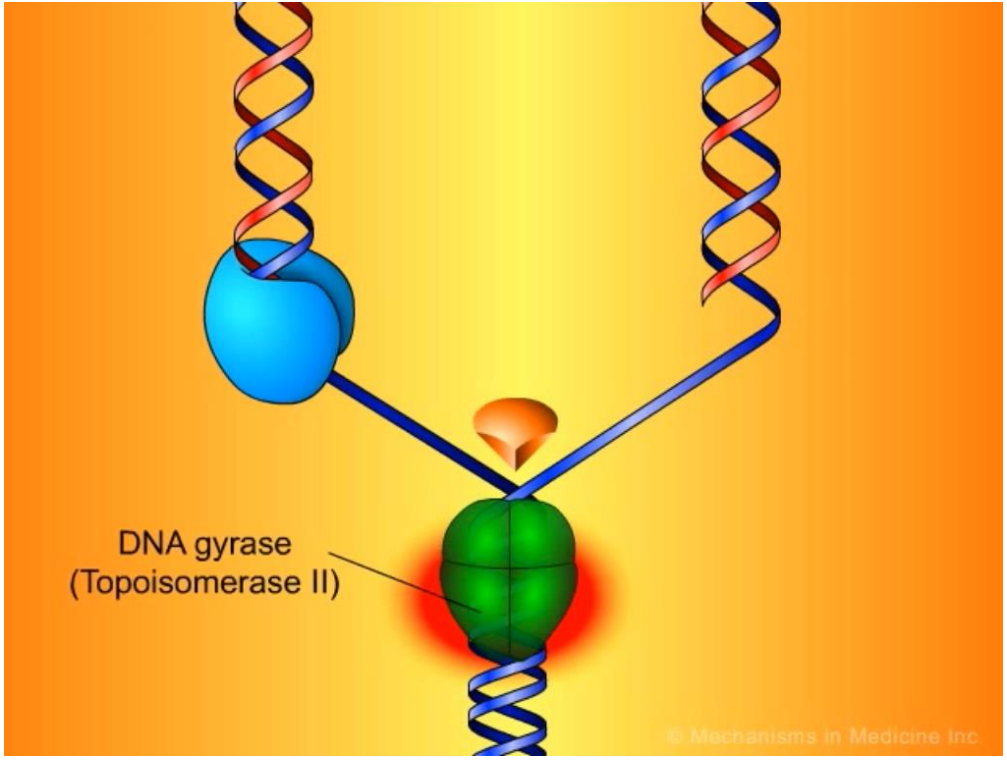
DNA Helicase



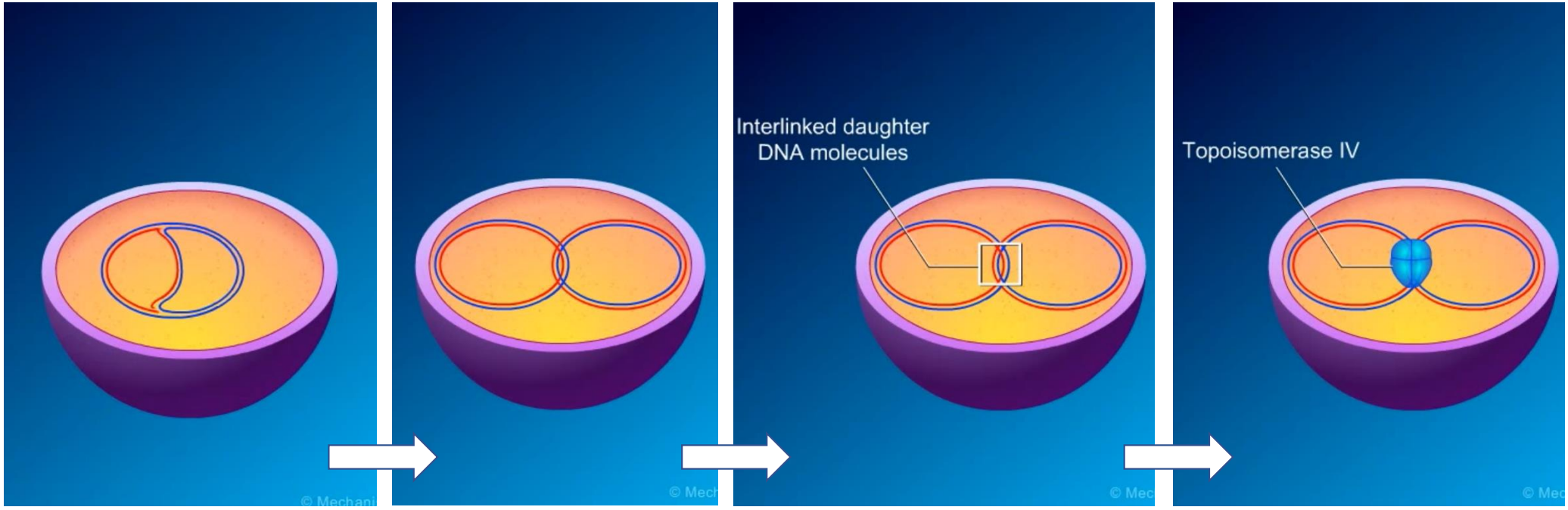
Bacteria start or attempted to initiate DNA synthesis,the first step would be to separate DNA double strand from each other
و الانزيم الي بساعدها بالفصل هو ال helicase
By breaking hydrogen bonds,+ to allow for DNA polymerase to start synthesising DNA,,it introduced super coils distal to the replication fork and that coiling that happens to the DNA is due to the separation process itself which introduces torsion force to the DNA molecules →the DNA molecules accumulates these super coils then it will not be helicase be able to separate them from each other it's like a knot (عقدة) in a thread you have to get rid of the super coils before moving forward further with DNA synthesis (لازم نفك هاي العقد)
مشان هيك في انزيم رح يساعدني نحلها :
DNA gyrase also called topoisomarase 2,this enzyme is essential for relieving super coils and it does that through introducing negative supper unwind the DNA and the way it relieves supper coils by cutting and ligase (يقص ويلحم)
So DNA has nuclease function (بتقص) and then ligating the DNA molecules one more time



DNA Gyrase



Topoisomerase IV



Another problem that happens specifically in bacteria because bacteria has circulated DNA so when it synthesis a new chromosome and reliving the super coils by using DNA gyrase the newly forming DNA molecules will be connected by the end of DNA replication to the parent DNA molecule,,,and these molecules need to be separated in order for the bacteria to divide and to relieve this connection or this coiling another topoisomerase very similar to DNA gyrase called topoisomerase 4 relieves the two daughter DNA molecules from each other

و بتعملها زي ما بتعمل ال gyrase

relieving the two ring from each other and then ligating again

* حكينا حكون ال Topoisomerase I ↔ II حكينا للبكتيريا حتى تصنع DNA

← حكيت شو بالنسبة لل Florquinon شو بتعمل ؟

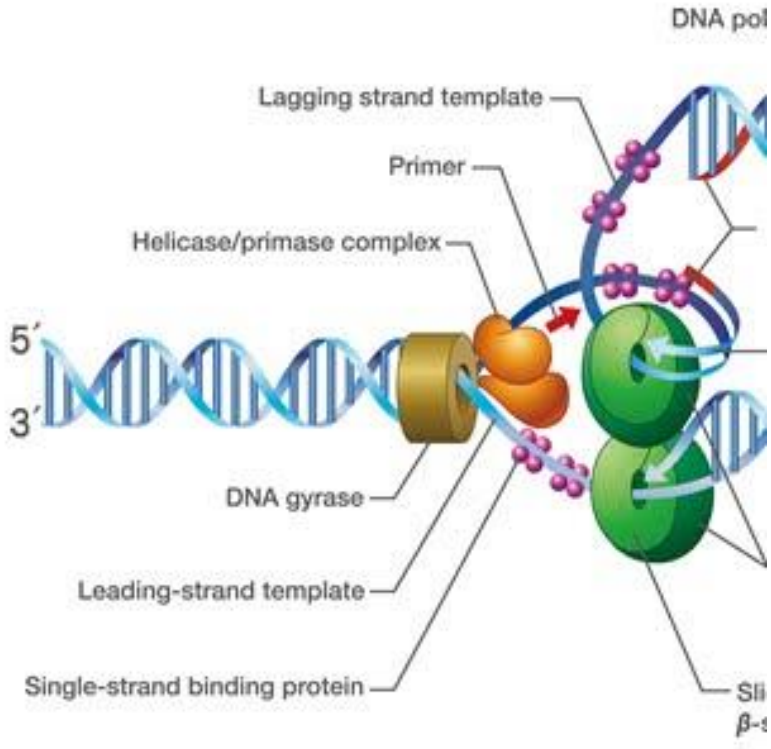
They don't interfere with nucleas function of the enzyme but they bind to bacterial DNA gyrase and topoisomerase 4 and inhibits their ligation step

يعني هي رح تخلي الانزيم يقطع طبيعي زي ما بتعمل بسسس خطوة تلزيق الي قطعو رح تمنعها

If the ligation doesn't occur, this will create a broken DNA.
**Any break in the dna is considered lethal ,if this break occurs ,the bacteria will undergo cell death.

Quinolones

- **Mechanism of action**
  - Inhibit ligation step of bacterial DNA gyrase and bacterial topoisomerase IV
- -Inhibition of gyrase: increases the number of permanent chromosomal breaks
- -Inhibition of topo IV: interferes with the separation of newly replicated DNA



→ both events are lethal to bacteria] → cause that these compound are bactericidal

Quinolones

Mechanism of action

In gram-negative: inhibition of gyrase>topo IV

In gram-positive: inhibition of topo IV>gyrase

What does that mean?

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

May be , there is some differences between the different member of the floroquinolones famiy in their selectivity to either gyrase of topoisomerase depending on the type of the bacteria and the type of the drug.

This statement refers to the mechanism of action of certain antibiotics on gram-negative and gram-positive bacteria.

Gram-negative bacteria have a double-layered cell wall structure, which includes an outer membrane. The inhibition of gyrase, a type of enzyme involved in DNA replication and repair, is more effective in targeting gram-negative bacteria. Inhibition of gyrase disrupts the bacterial DNA structure and function, leading to cell death.

On the other hand, gram-positive bacteria have a single-layered cell wall structure without an outer membrane. In gram-positive bacteria, the inhibition of another type of enzyme called topoisomerase IV is more effective. Topoisomerase IV is also involved in DNA replication and repair. Inhibition of topoisomerase IV disrupts the DNA structure and function in gram-positive bacteria, ultimately leading to cell death.

In summary, the statement suggests that certain antibiotics target gyrase more effectively in gram-negative bacteria, while topoisomerase IV is the primary target in gram-positive bacteria. Understanding these differences allows for the development of antibiotics that specifically target different types of bacteria based on their cell wall structures.

معلومة خارجية بس للعلم

Quinolones

Antibacterial spectrum

- Bactericidal
- Time-dependent killing
- Effective against gram-negative (including E.coli and Pseudomonas), atypical, gram-positive (strep), mycobacteria….
- Levofloxacin: excellent activity against *S. pneumoniae*

Quinolones

Antibacterial spectrum

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

-narrow-spectrum

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

سيب نور

ciprofloxacin → used in the treatment of urinarytract infections . + first line retreat

-gram-negative (pseudomonas, H.influenzae) and atypical

- **Third-generation: levofloxacin**

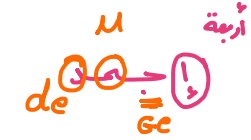
The most common cause of pneumonia or community acquired pneumonia is streptococcus pneumonia , so it is the 1 st line treatment of community acquired pneumonia

-gram-negative, atypical and gram-positive (including S. pneumoniae and MSSA) → No MRSA

- **Fourth-generation: moxifloxacin, Gemifloxacin, delafloxacin**

-enhanced gram-positive effects including staph and strep + coverage of gram-negative Enterobacteriaceae + they are not very good against pseudomonas

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



من تنويغ فاخترها من الكتاب

5. **Delafloxacin**: *Delafloxacin* [del-a-FLOX-a-sin] has improved activity against gram-positive cocci, including MRSA and Enterococcus spp. Due to its spectrum of activity, it is an option for managing acute bacterial skin and skin structure infections. It is available as an intravenous and oral formulation.

Nalidixic acid is mainly against gram -ve bacteria.

*Its use is not very common.

**Ciprofloxacin is one of the drugs which are used in the treatment of urinarytract infections .

**Levofloxcin is now commonly used to treat gram -ve and +ve infections ,e.g urinary tract infections and respiratory infections caused by streptococcus pneumonia.

** The most common cause of pneumonia or community acquired pneumonia is streptococcus pneumonia , so it is the 1 st line treatment of community acquired pneumonia .

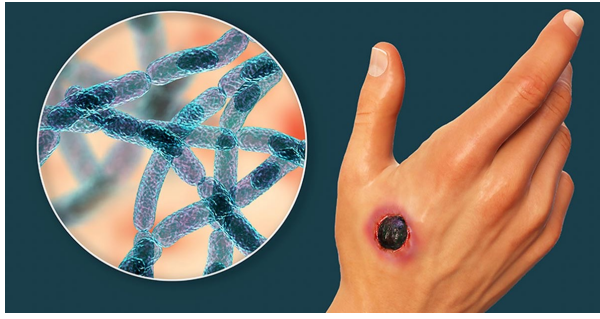
Examples of Clinically Useful Fluoroquinolones

Ciprofloxacin

- Effective against gram-negative including P. aeruginosa
- Clinical indications:

1. Gastroenteritis e.g., traveler's diarrhea
2. Typhoid fever (Salmonella)
3. Anthrax (drug of choice)
4. Urinary tract infections

→ (high dose for pseudomonal infections)



Examples of Clinically Useful Fluoroquinolones

Covers all gram -ve bacteria that is covered by ciprofloxacin.
* Have a very good effect against gram +ve bacteria such as streptococcus and methicillin sensitive staph.aureus .
*In addition to its first line usage, it is also uses for the treatment of urinary tract infections .
* Community aquifer pneumonia is commonly caused by gram +ve bacteria such as streptococcus pneumonia..

Levofloxacin

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

First-line therapy for community acquired-pneumonia

First line : especially when the penicillin types are resistant .
*Most of penicillins (beta lactate) cover gram +ve bacteria , if there is resistance of simple amoxicillin and ampicillin as in JORDAN (high resistance) ,then the levofloxacin is the 1 st line therapy for acquired pneumonia.

Examples of Clinically Useful Fluoroquinolones

Moxifloxacin

TB

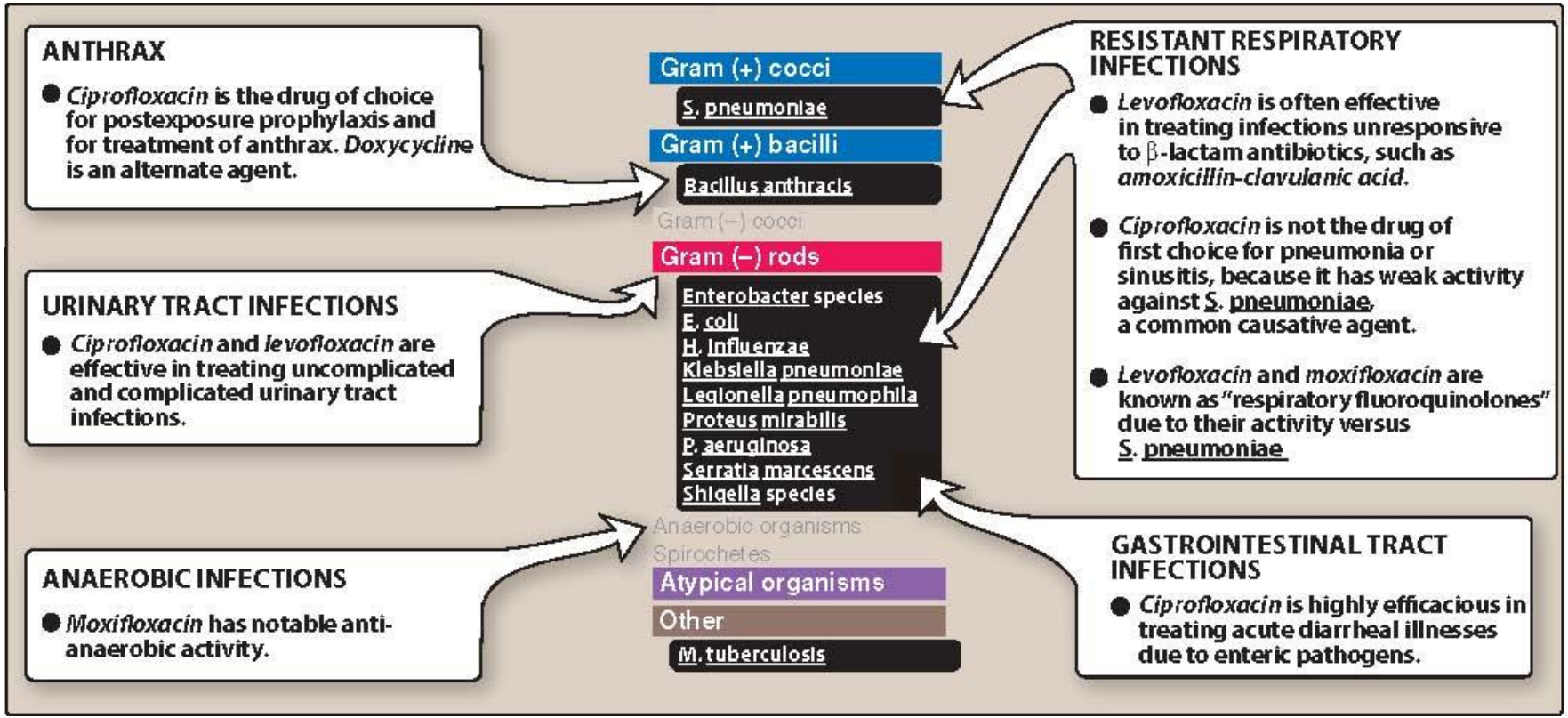
- Effective against gram-negative, S. pneumonia and mycobacterium
- Clinical indications:

1. For community-acquired but not nosocomial pneumonia (weak against pseudomonas)
2. Second-line for TB

The most common cause of community acquired pneumonia is streptococcus pneumonia also there are other causes like gram -\+ but the commonest is streptococcus pneumonia

Nosocomial pneumonia , when patient stay at hospital for about 1 month , it is caused by resistant bacteria Kline MRSA and pseudomonas “main cause of pneumonia “

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".

Flora imbalance

صار عنا first line و second بسبب خطر ال resistance + عنا resistance في الاردن لل Ciprofloxacin

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

Fluoroquinolones

Mechanisms of resistance

-mainly chromosomal

1. **Altered target:**

-mutations in *gyrA* or *parC*

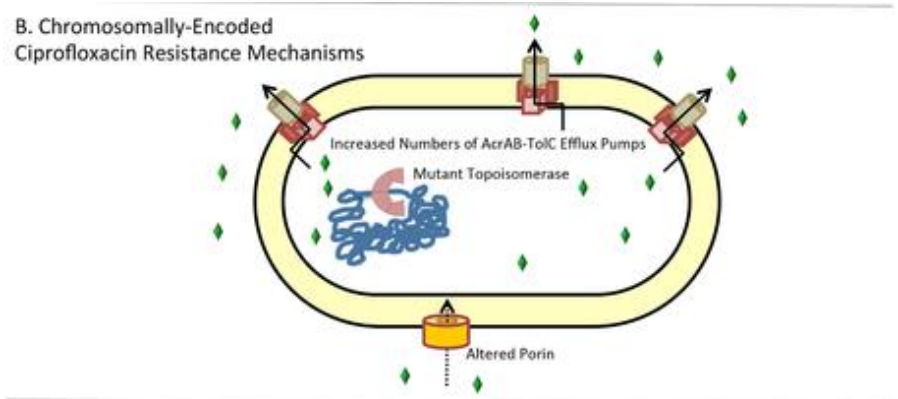
2. **Decreased accumulation**

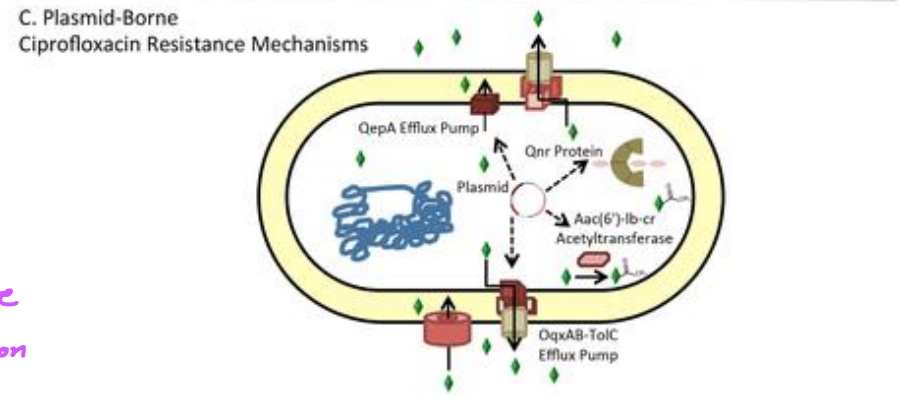
-porin channels

-efflux pumps

3. **Fluoroquinolone degradation**

- Cross-resistance because they share the same mechanism of action





The targets are gyrase (topo 1) and topo 4

this bacteria can use this mutation , alter the structure of the 2 enzymes in the way that decreases their affinity to floroquinilones and this is the main mechanism of resistance against floroquinolones (alteration of the targets of the drug) in the same way that the MRSA alter the structure penicillin binding proteins "target for beta lactams".

chromosomal. Why?! Because it contains genes that encode for topo 2\4.
→ parC: produces topo 4.
→gyrA: produces gyrase.

-porin channels

These compound need to be internalised within the cell to reach topoisomerase in DNA they have to cross through porin channels in gram-,so som of gram- reduce the permeability of their channels to these compounds

Fluoroquinolones

Pharmacokinetics

- **Absorption**

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

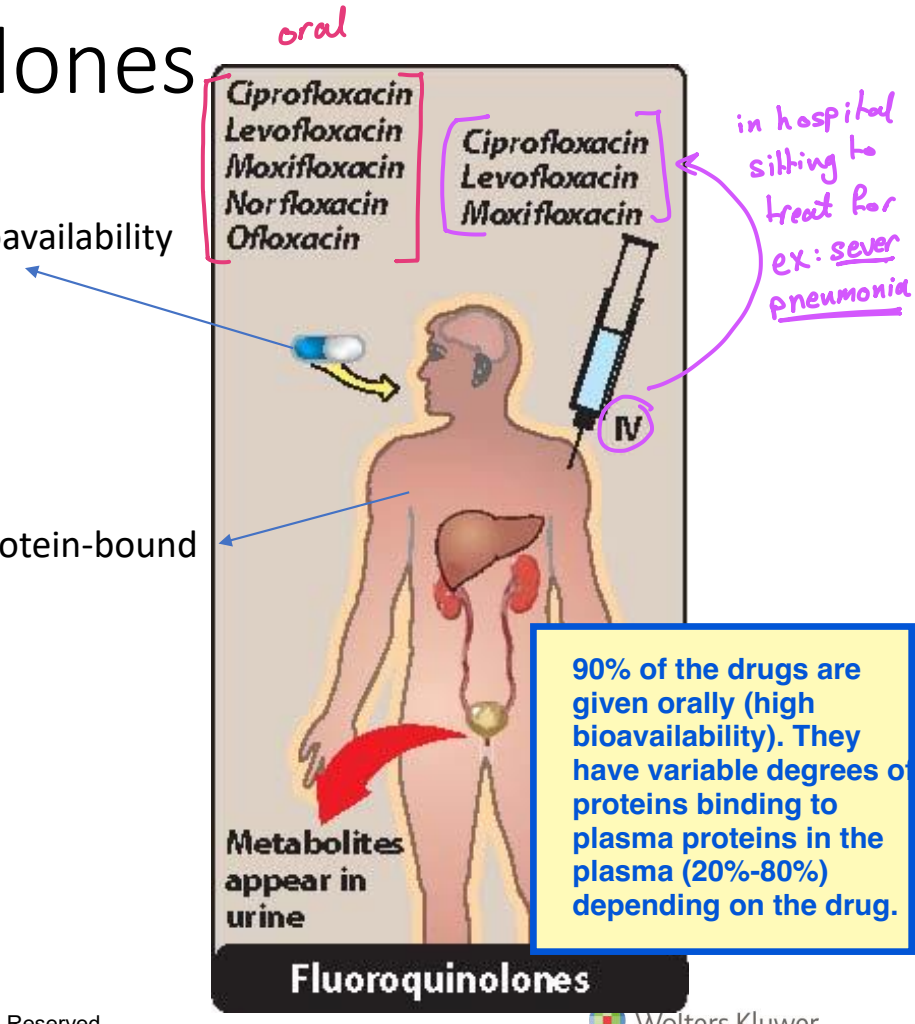
-food, Ca^{++}, Al^{+3} and Mg^{++} interfere with absorption → similar to tetracyclines

- **Distribution**

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

-good CSF distribution

-concentrate in macrophages and neutrophils very good for treatment atypical bacteria



90% of the drugs are given orally (high bioavailability). They have variable degrees of proteins binding to plasma proteins in the plasma (20%-80%) depending on the drug.

Fluoroquinolones

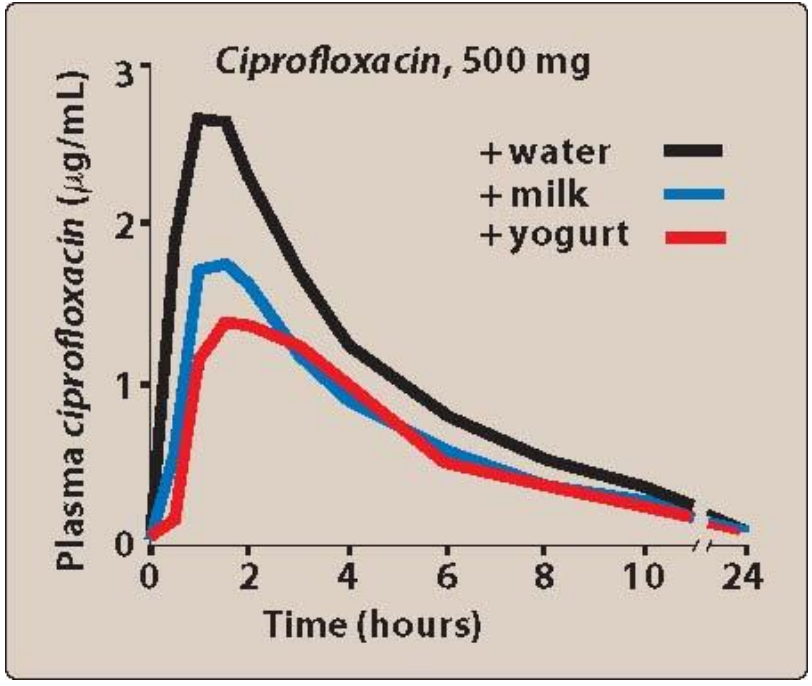
Pharmacokinetics

It is very well-absorbed with water.

It is less-absorbed with milk .

It is definitely concentrated in the urine that is why they are given for the treatment of urinary infections , also they can distribute to the lung fluid that is why they are also given for the treatment of respiratory infections .

§ It can concentrate immune cells , mostly in macrophages and neutrophils .



Fluoroquinolones

Pharmacokinetics

- **Elimination**

-most fluoroquinolones are excreted renally

-Moxifloxacin is excreted by liver (can be used in patients with renal impairment) because it doesn't depend on kidny elimination

Similar to the elimination of the cell wall inhibitors

Quinolones

Adverse effects

-generally well-tolerated

- **N/V/D** Nausea / Vomting / Diarrhea
- **Headache and dizziness**
- **Peripheral neuropathy and glucose dysregulation** Glucose dysregulation is similar to what happens in diabetes.
- **Phototoxicity**
- **(boxed warning) Articular cartilage erosion, tendinitis, tendon rupture**
- **QT prolongation** Qt prolongation (cardiac toxicity) :can cause cardiac arrhythmia

common

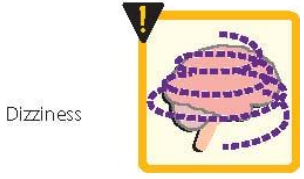
rare

black

very rare

for any sever life threating ADE

Quinolones have 1 boxed warning

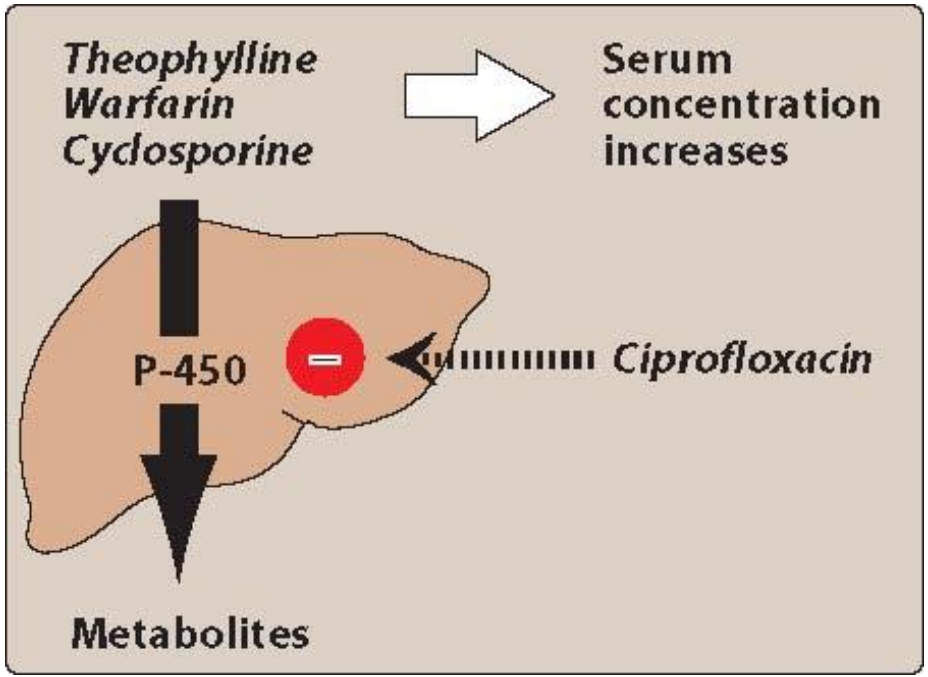


Quinolones

Drug-drug interaction

- Cipro can inhibit metabolism of theophylline, others
- Quinolones can raise serum warfarin

زيها أخذنا قبل



Ciprofloxacin inhibit the metabolism of warfarin resulting in the increase of the warfarin concentration in the plasma