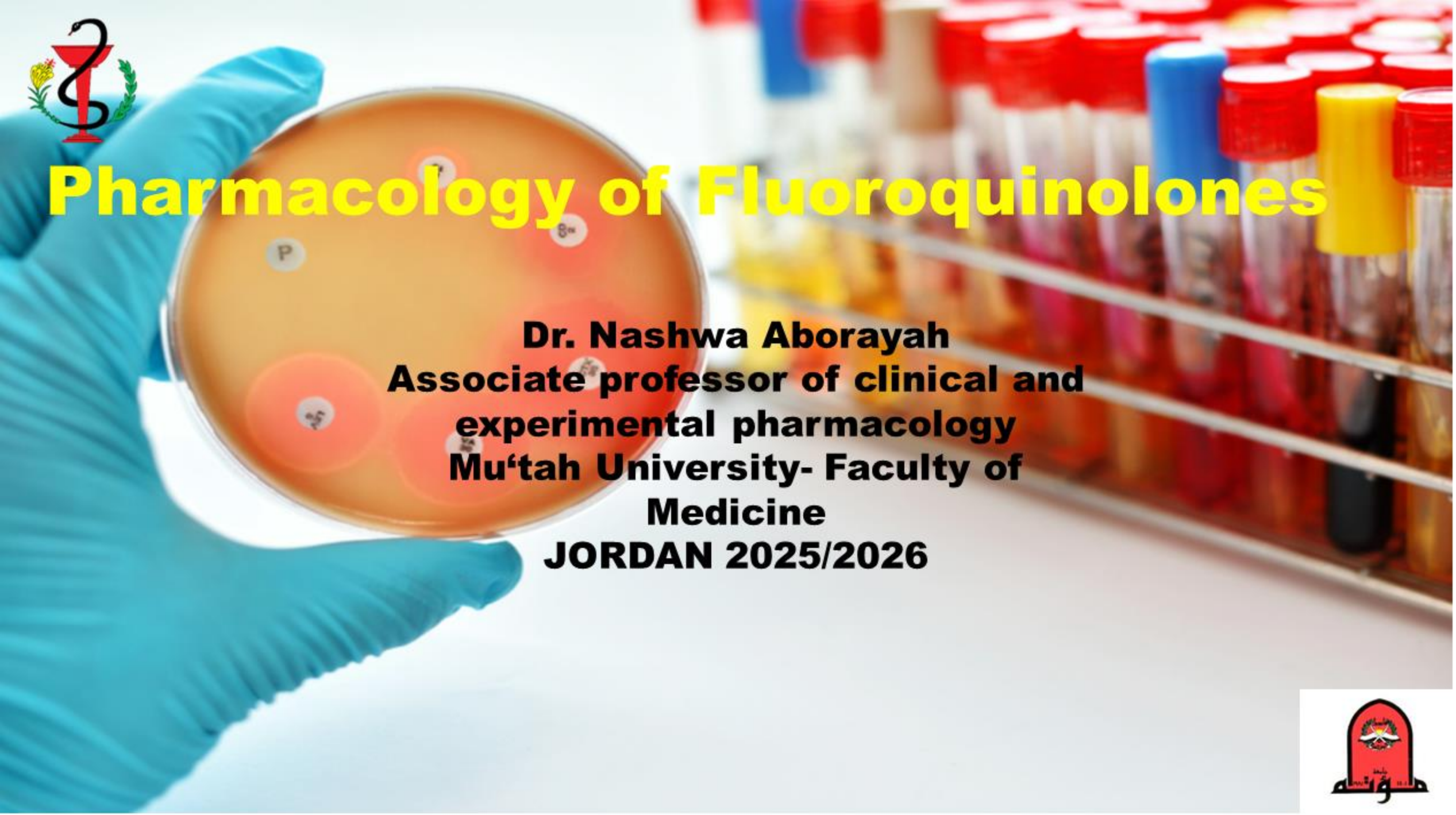

Pharmacology of Fluoroquinolones

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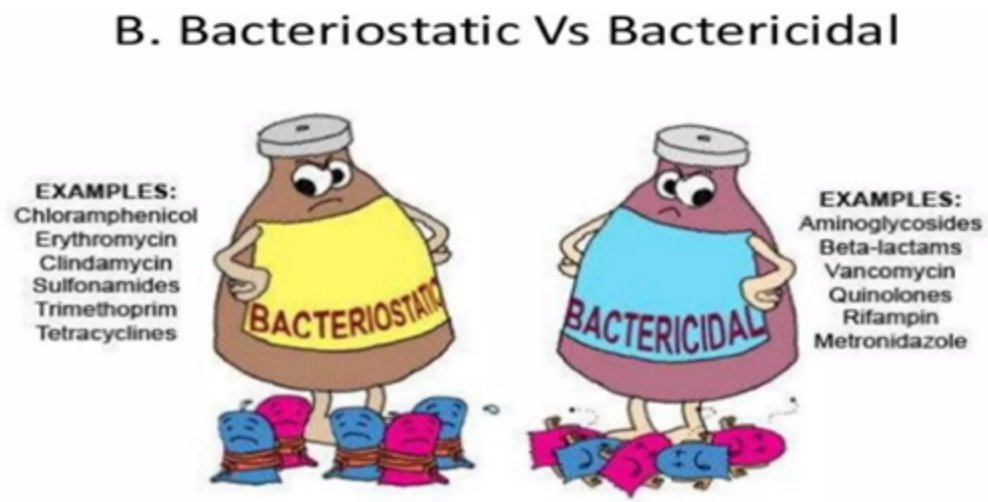
Objectives

- What are fluoroquinolones?
- Nalidixic acid: *prototype* of fluoroquinolones
- Fluoroquinolones:
- Generations
- Spectrum
- Advantages
- Mechanism of action
- Resistance
- Uses
- Adverse effects and contraindications

Quinolones

- Synthetic antimicrobials
- Bactericidal
- Primarily gram-negative bacteria



Nalidixic acid

- **First member**: prototype
- **Characteristics :**
- **1- Cover G-negative bacteria**: **narrow-spectrum quinolone** antibiotic
- **2- Rapidly excreted in urine: (t1/2: 1-2.5 hours)** in concentrations enough for **treatment of UTIs (active metabolite: hydroxynalidixic acid)**

Disadvantages of nalidixic acid

- 1- Concentration of free drug in plasma & most tissues is **non-therapeutic** for **systemic infections**
- 2- Narrow spectrum
- 3- Rapid development of bacterial resistance

Limited therapeutic use

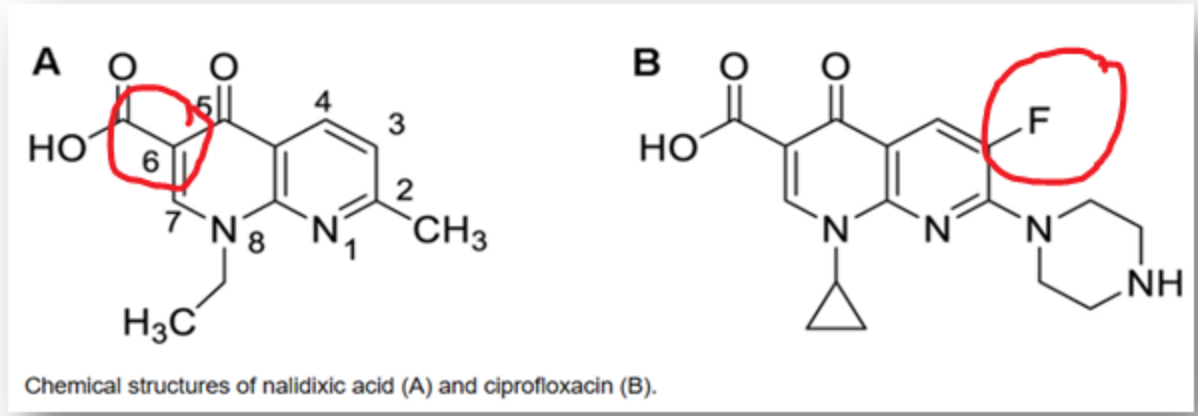
Fluoroquinolones

•Quinolones are molecules **structurally derived from the heterobicyclic aromatic compound quinolone.**

•**Fluorination (addition of fluorine atom) of quinolone structure at position 6** resulted in derivatives called **fluoroquinolones**

- The key structural difference **between nalidixic acid and fluoroquinolones** is the addition of a **fluorine atom at position C6** of the chemical structure.

- This modification significantly **broadens the antibacterial spectrum** and **increases the potency of fluoroquinolones** compared to the original nalidixic acid.

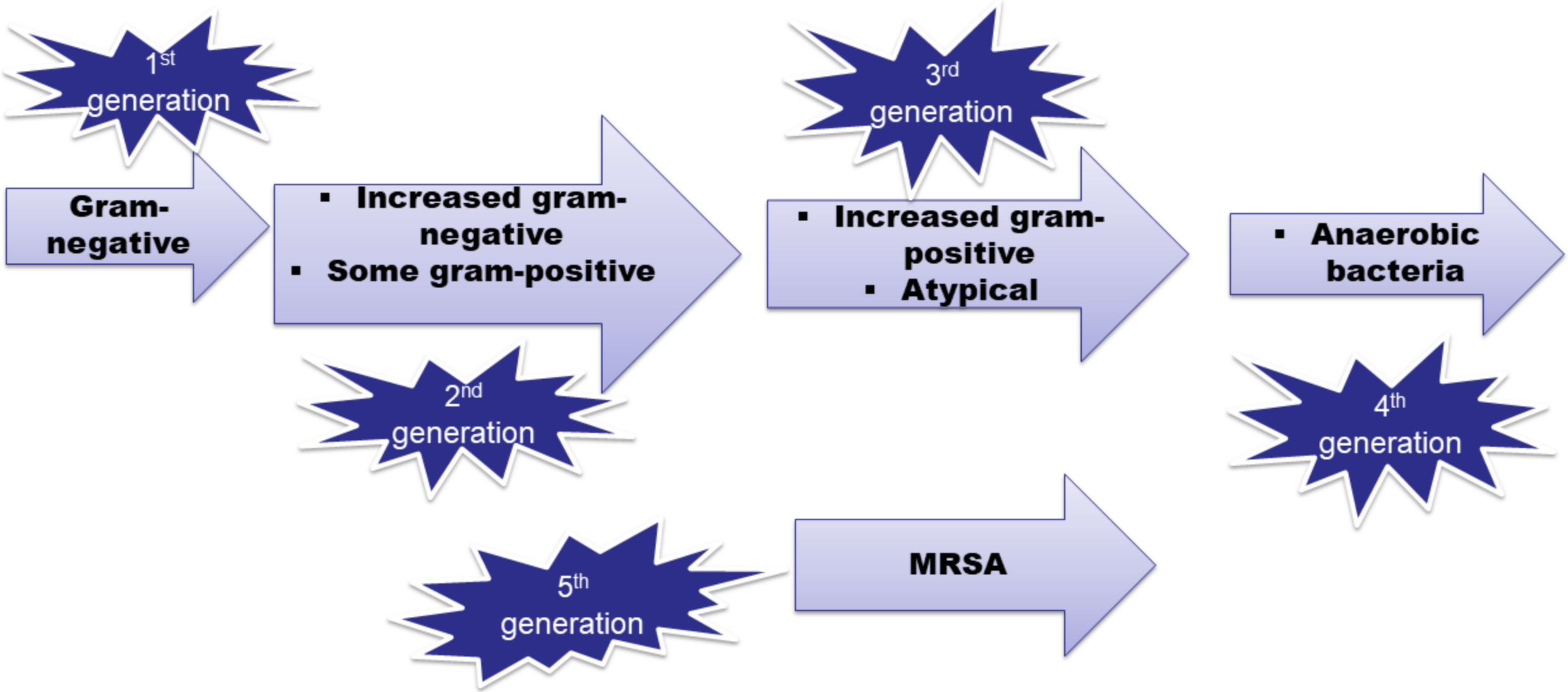


Chemical structures of nalidixic acid (A) and ciprofloxacin (B).

Generations & Spectrum (floxacin-ending)

Generation	Spectrum	Examples
First	Gram-negative bacteria	Nalidixic acid
Second	Enhanced gram-negative activity, including Pseudomonas aeruginosa, and some gram-positive activity	Ciprofloxacin, norfloxacin, ofloxacin.
Third	Increased activity against gram-positive bacteria, including Streptococcus pneumonia, as well as atypical pathogens	Levofloxacin, **sparfloxacin.**
Fourth	Added significant activity against anaerobic bacteria	Moxifloxacin, gemifloxacin, **trovafloxacin**
Fifth	improved activity against resistant bacteria **(like MRSA)** broader spectrum (Gram-positive/negative) better tissue penetration	Delafloxacin Nadifloxacin

Spectrum of fluoroquinolones



Advantages of fluoroquinolones

1- Potency: High

2- Antimicrobial spectrum: Broad

4- Tissue penetration: Good

5- Duration of action: Long

3- Development of resistance: Slow

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

Pharmacokinetics of fluoroquinolones

Item	Effects
Absorption	❑ **Rapid** and **complete** oral absorption ❑ **Avoid with food** (or drugs) containing Al, Ca, Iron and minerals (magnesium, zinc, selenium, phosphorus, ……)
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
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

- Fluoroquinolones kill bacteria by inhibiting crucial enzymes:
- DNA gyrase (gram-negative) and topoisomerase IV (gram-positive) which are essential for DNA replication, repair, and transcription.
- This mechanism leads to:
- Disruption of DNA synthesis, transcription , and cell division.
- DNA Gyrase: Adds negative supercoils to DNA, preventing tangles during replication.
- Topoisomerase IV: Separates interlinked daughter DNA strands after replication.
- Inhibition of these enzymes leading to:
- "over winding" / excessive positive supercoiling of DNA leads to faulty protein synthesis and bacterial death.

•**Selective toxicity:**

•**In mammalian cells (human cells):**

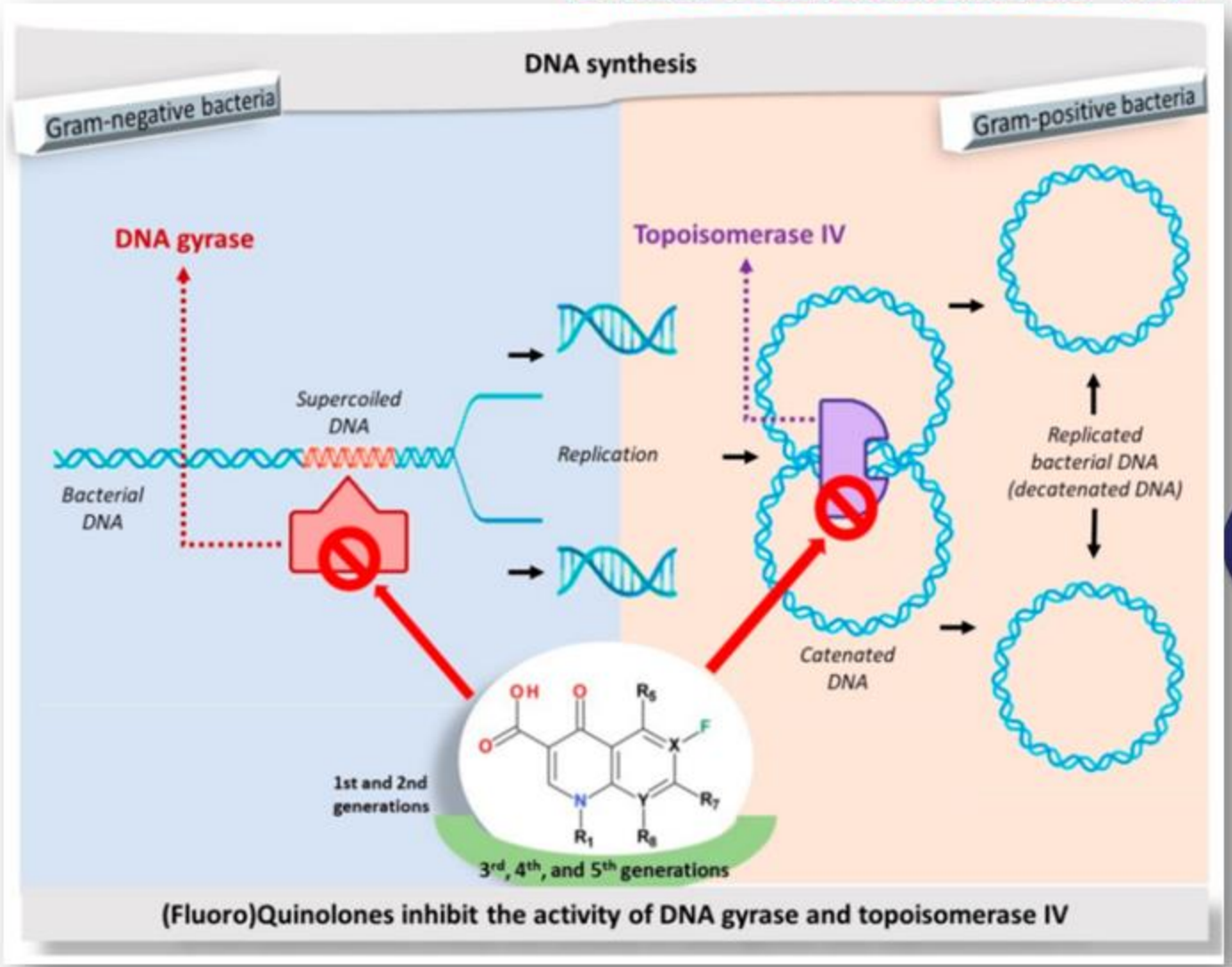
Topoisomerase II

1- Low affinity for fluoroquinolones

2- Inhibited by quinolones only at much higher concentrations.

Low toxicity to host cells

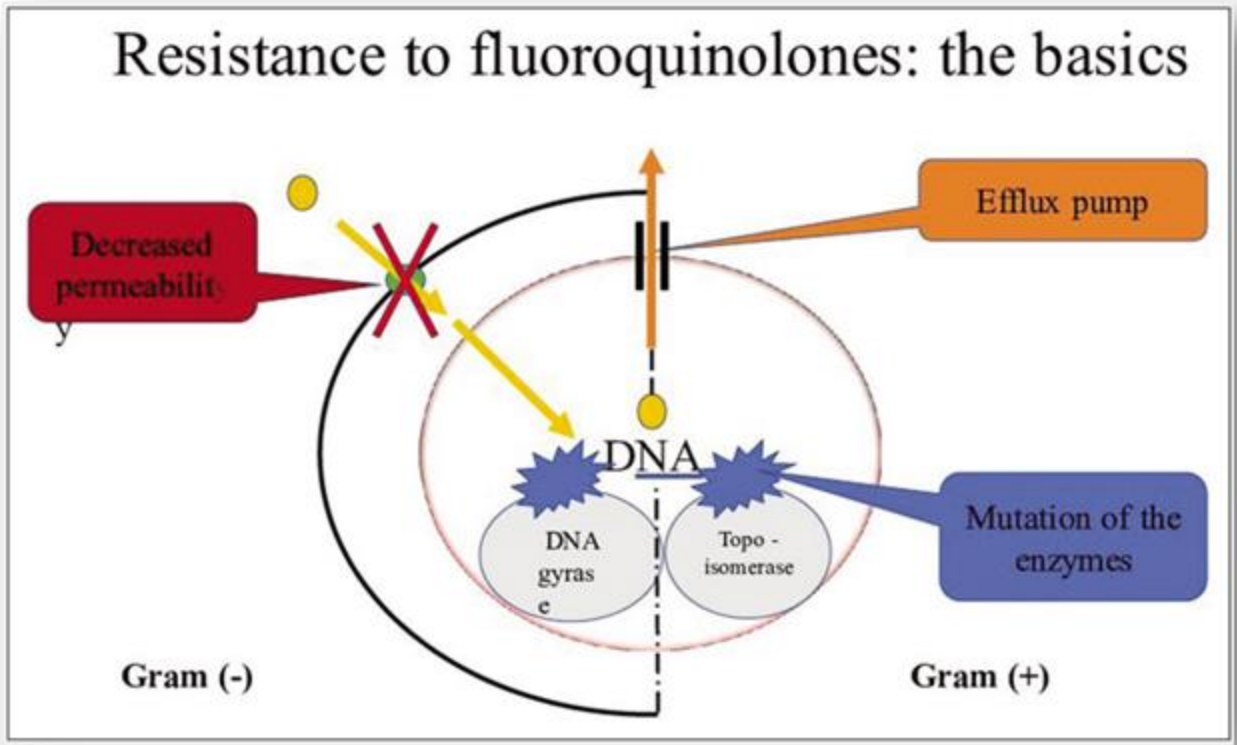
Mechanism of action

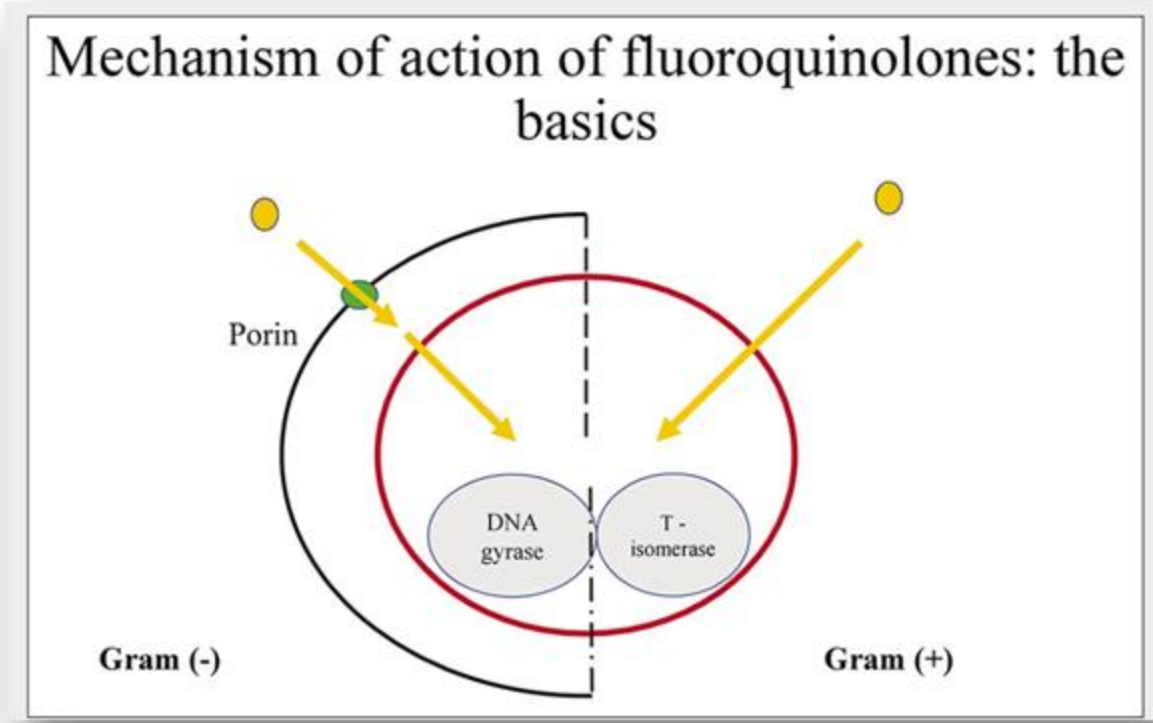


Catenated DNA:

two or more circular DNA molecules interlinked like chain links, forming a topological knot, rather than being attached end-to-end

Mechanism of resistance





Mechanism of resistance

- **1- Chromosomal mutation:**

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

- **2- Drug efflux (pump):** across bacterial membranes
- **3- Decreased permeability**

Resistance is slow to develop

Therapeutic indications

1- Urinary tract infections: UTIs

- **Most commonly used antimicrobials for UTI**
- **Very effective against Gram negative bacilli like:**
  E.coli, Proteus, Enterobacter , Pseudomonas

❑ **Ciprofloxacin 500 mg twice daily**

2- Salmonella typhi infection (typhoid fever):

- **Ciprofloxacin** 500 mg twice daily for 10 days (2×10)
- Prevents carrier state

Therapeutic indications

3- Respiratory infections:

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

4-Bone and joint infections: Osteomyelitis & joint infections

5- Meningitis

6- Atypical infections

Indications of fluoroquinolones

Resk of **typhoid** and **UTIs** in **atypical** **bone** and **brain**

- **Re**: respiratory infections
- **Typhoid** fever
- **UTIs**
- **Atypical** infections
- **Bone** and joint infection
- **Brain**: meningitis

ADRs

1- Musculoskeletal:

- **Tendonitis & tendon rupture**: **ciprofloxacin**: tendinopathy of Tendo Achillis
- **Arthropathy (Joint disease)** in immature animals: (possible teratogenic)

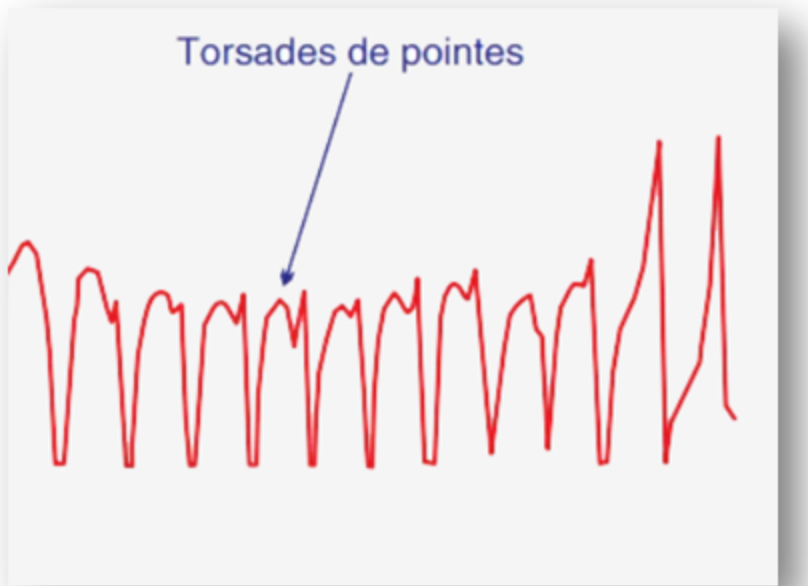
- **Contraindication**:
- Children less than 6-12 years
- Pregnancy
- During breast feeding

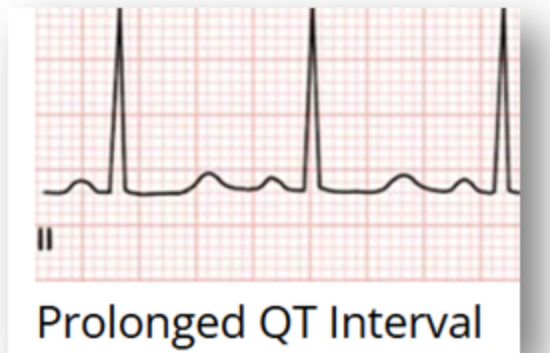
ADRs

- **2- CNS:**
- **Excitation** due to **blocking of GABA receptors**:
- Seizures have occurred predominantly in patients receiving theophylline or a NSAIDs and epilepsy patients
- **Contraindications:**
- 1- Concurrent administration of theophylline or NSAIDs
- 2- Epilepsy

ADRs

- **3- QT interval prolongation**: **sparfloxacin** withdrawn (Torssade de points).
- **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- Trovafloxacin:**
- Withdrawn worldwide in 2016: **serious hepatotoxicity** leading to liver transplant or death.





ADRs

T T L CNS and ECG

T: tendon rupture
T: teratogenic: arthoropathy
L: Liver toxicity
CNS: excitation
ECG: prolongation of QT interval

ADRs

- **5- Drug interactions:**
- **NSAIDs & theophylline** may enhance CNS toxicity of fluoroquinolones
- **Minerals (iron, calcium, zinc, magnesium in antacids/supplements)**
- Reduce absorption of quinolones
- **Corticosteroids** (increased tendon damage risk)
- **Fluoroquinolones are cytochrome p450 inhibitors:**
- **Warfarin (anticoagulant): risk of bleeding**

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THANK YOU