CHEMOTHERAPY

Fluoroquinolone Drugs (FQ I & FQ II) for Chemotherapy Course **Drugs**
– Chemotherapy Course

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Chemotherapy PHAR 5

Semester Two

Week number 7 and 8

27/3/2025

Learning Objectives

- **Learning Objectives**
- By the end of this lecture, students should be able to:

1. **Understand the classification** of fluoroquinolones into **FQ I** and **FQ II**, and their differences in spectrum and clinical use.
2. **Describe the mechanism of action** of fluoroquinolones, including how they inhibit **DNA gyrase** and **topoisomerase IV** in bacterial cells.
3. **Identify the common indications** for fluoroquinolones and understand when to use first-generation versus second-generation drugs.
4. **Evaluate the pharmacokinetics** of fluoroquinolones, including their **absorption**, **distribution**, **metabolism**, and **excretion**, as well as their clinical implications.
5. **Recognize and manage the potential adverse effects** of fluoroquinolones, including risks for **tendonitis**, **QT prolongation**, and **CNS toxicity**, and their clinical consequences.

Learning Outcomes

◦ After completing this lecture, students should be able to:

1. **Explain the classification** of fluoroquinolones and the role of **FQ I** and **FQ II** in treating a wide range of bacterial infections.
2. **Demonstrate an understanding of the mechanism of action** of fluoroquinolones and their impact on bacterial DNA replication, transcription, and repair.
3. **Identify the key clinical uses** of fluoroquinolones in the treatment of **respiratory**, **urinary**, **gastrointestinal**, and **skin infections**.
4. **Assess the pharmacokinetic properties** of fluoroquinolones, including bioavailability, tissue penetration, and elimination routes, and apply this knowledge to clinical practice.

5. Discuss the adverse effects and contraindications of fluoroquinolones, providing appropriate recommendations for patient management based on risk factors like age, renal function, and comorbidities

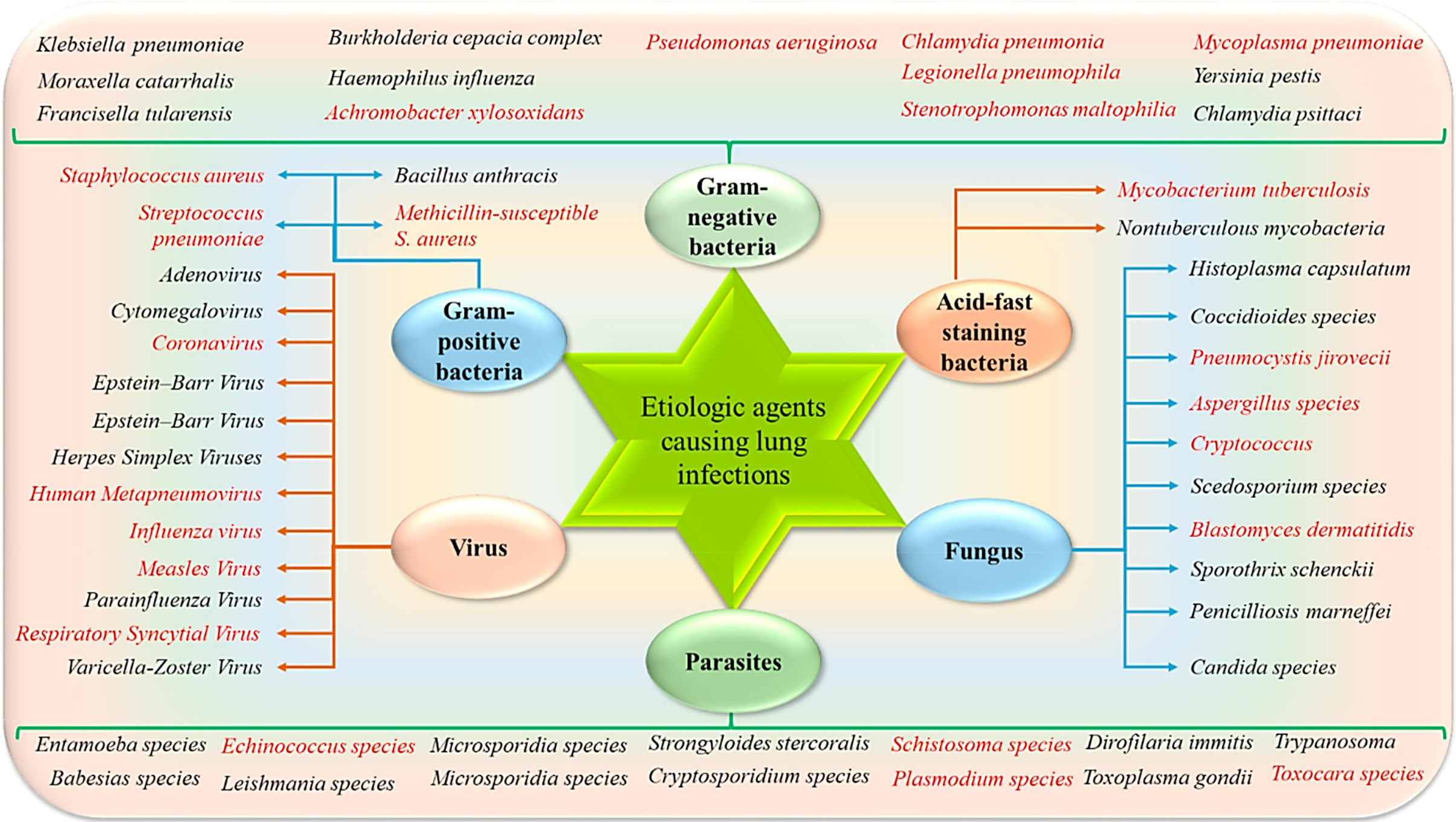
Introduction to Fluoroquinolones

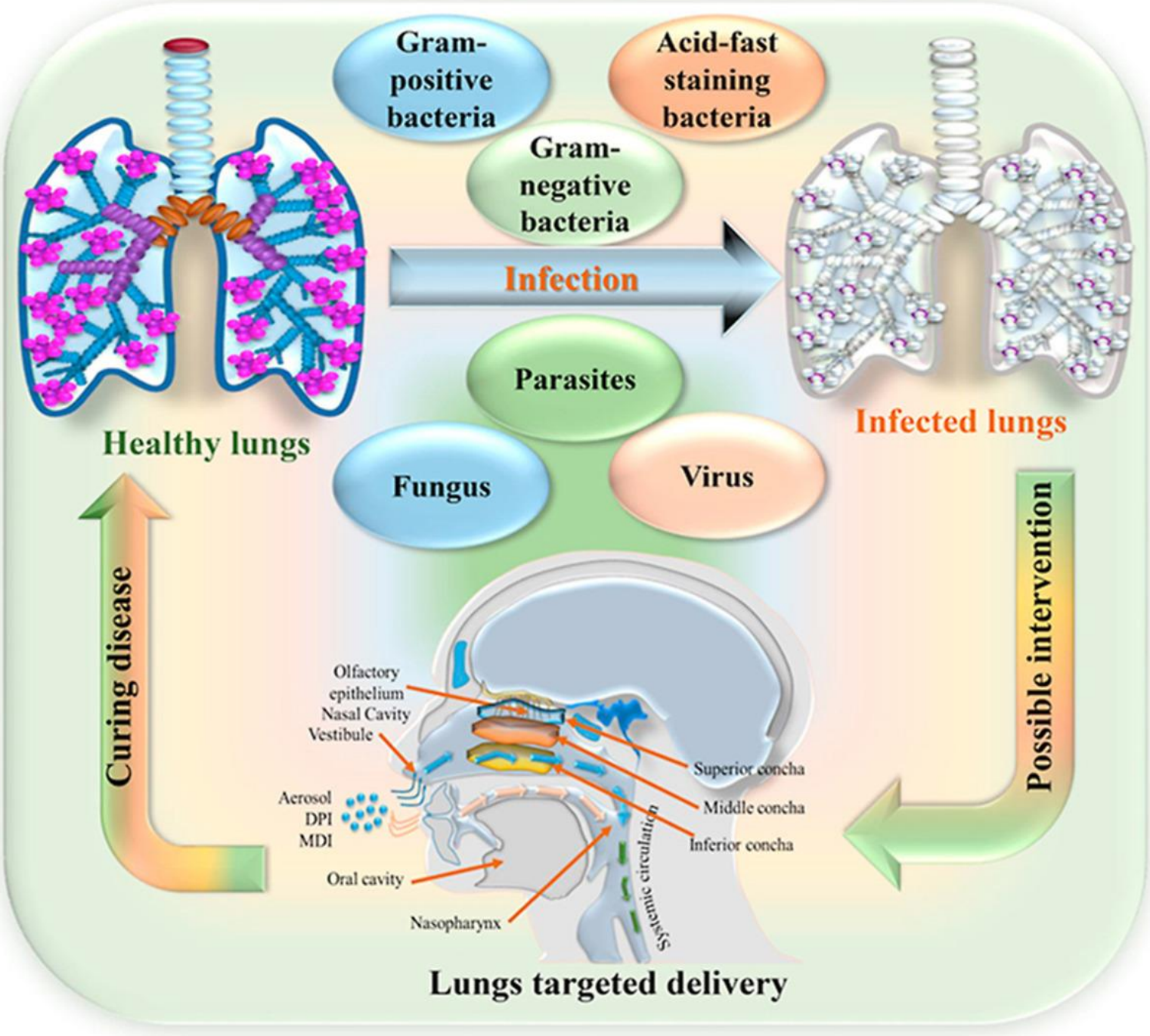
- Fluoroquinolones are a class of **synthetic antibacterial agents** that are widely used for treating a variety of **bacterial infections**. These drugs are a subclass of **quinolones**, which are characterized by their **fluorine** atom attached to the 6th position of the **quinolone ring** structure

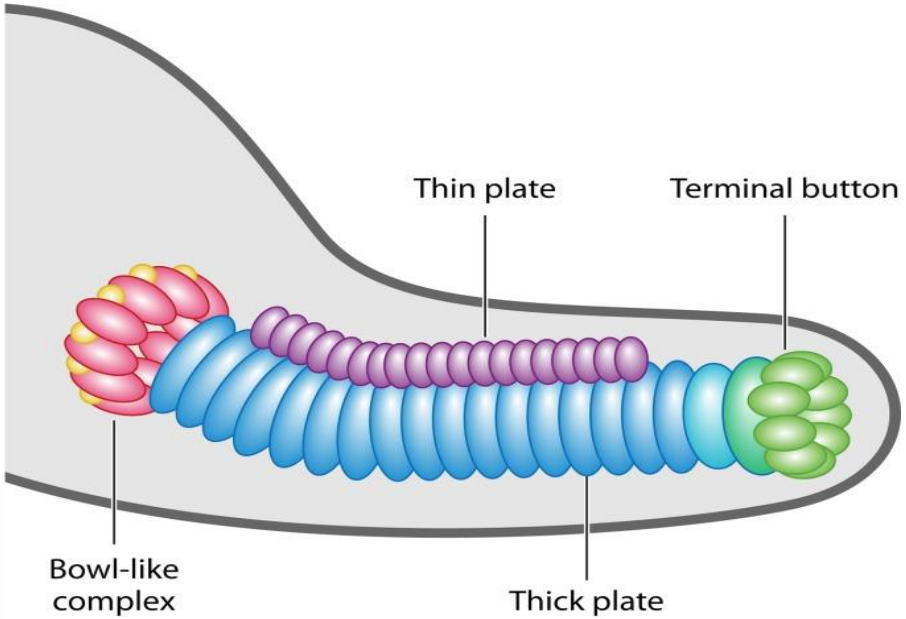
1. Overview of Fluoroquinolones

- Mechanism of Action: Fluoroquinolones inhibit DNA gyrase and topoisomerase IV, which are essential enzymes for bacterial DNA replication, transcription, and repair.
- Broad-spectrum activity: They are effective against gram-negative and gram-positive bacteria, including some atypical pathogens (e.g., Mycoplasma pneumoniae and Chlamydia).

Gram-positive and Gram-negative bacteria


Klebsiella pneumoniae
Moraxella catarrhalis
Francisella tularensis
Burkholderia cepacia complex
Haemophilus influenza
Achromobacter xylosoxidans
Pseudomonas aeruginosa
Chlamydia pneumonia
Legionella pneumophila
Stenotrophomonas maltophilia
Mycoplasma pneumoniae
Yersinia pestis
Chlamydia psittaci
Gram-negative bacteria
Staphylococcus aureus
Streptococcus pneumoniae
Bacillus anthracis
Methicillin-susceptible S. aureus
Gram-positive bacteria
Adenovirus
Cytomegalovirus
Coronavirus
Epstein–Barr Virus
Epstein–Barr Virus
Herpes Simplex Viruses
Human Metapneumovirus
Influenza virus
Measles Virus
Parainfluenza Virus
Respiratory Syncytial Virus
Varicella-Zoster Virus
Virus
Etiologic agents causing lung infections
Acid-fast staining bacteria
Mycobacterium tuberculosis
Nontuberculous mycobacteria
Fungus
Histoplasma capsulatum
Coccidioides species
Pneumocystis jirovecii
Aspergillus species
Cryptococcus
Scedosporium species
Blastomyces dermatitidis
Sporothrix schenckii
Penicilliosis marneffei
Candida species
Parasites
Entamoeba species
Babesias species
Echinococcus species
Leishmania species
Microsporidia species
Microsporidia species
Strongyloides stercoralis
Cryptosporidium species
Schistosoma species
Plasmodium species
Dirofilaria immitis
Toxoplasma gondii
Trypanosoma
Toxocara species





Mycoplasma pneumoniae from the Respiratory Tract and Beyond.

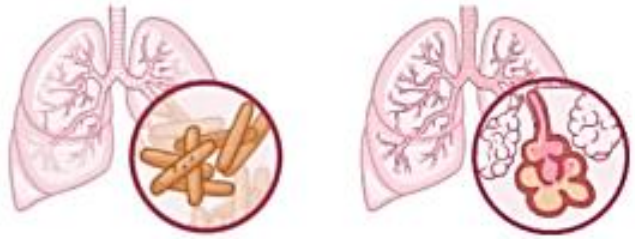
1. Overview of Fluoroquinolones

- Oral and parenteral administration: Fluoroquinolones can be taken orally and also administered intravenously, which makes them highly versatile for outpatient and inpatient settings.

FLUOROQUINOLONES

* EYE INFECTIONS
  - BACTERIAL CONJUNCTIVITIS

* CHEST INFECTIONS
  - TUBERCULOSIS
  - PNEUMONIA

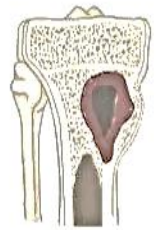


* GI
  - SHIGELLOSIS

* UTIs

* GENITAL INFECTIONS
  - GONORRHEA

* BONE & JOINT INFECTIONS



Classification of Fluoroquinolones

- Fluoroquinolones are classified into **two generations** based on their spectrum of activity, pharmacokinetics, and clinical indications:

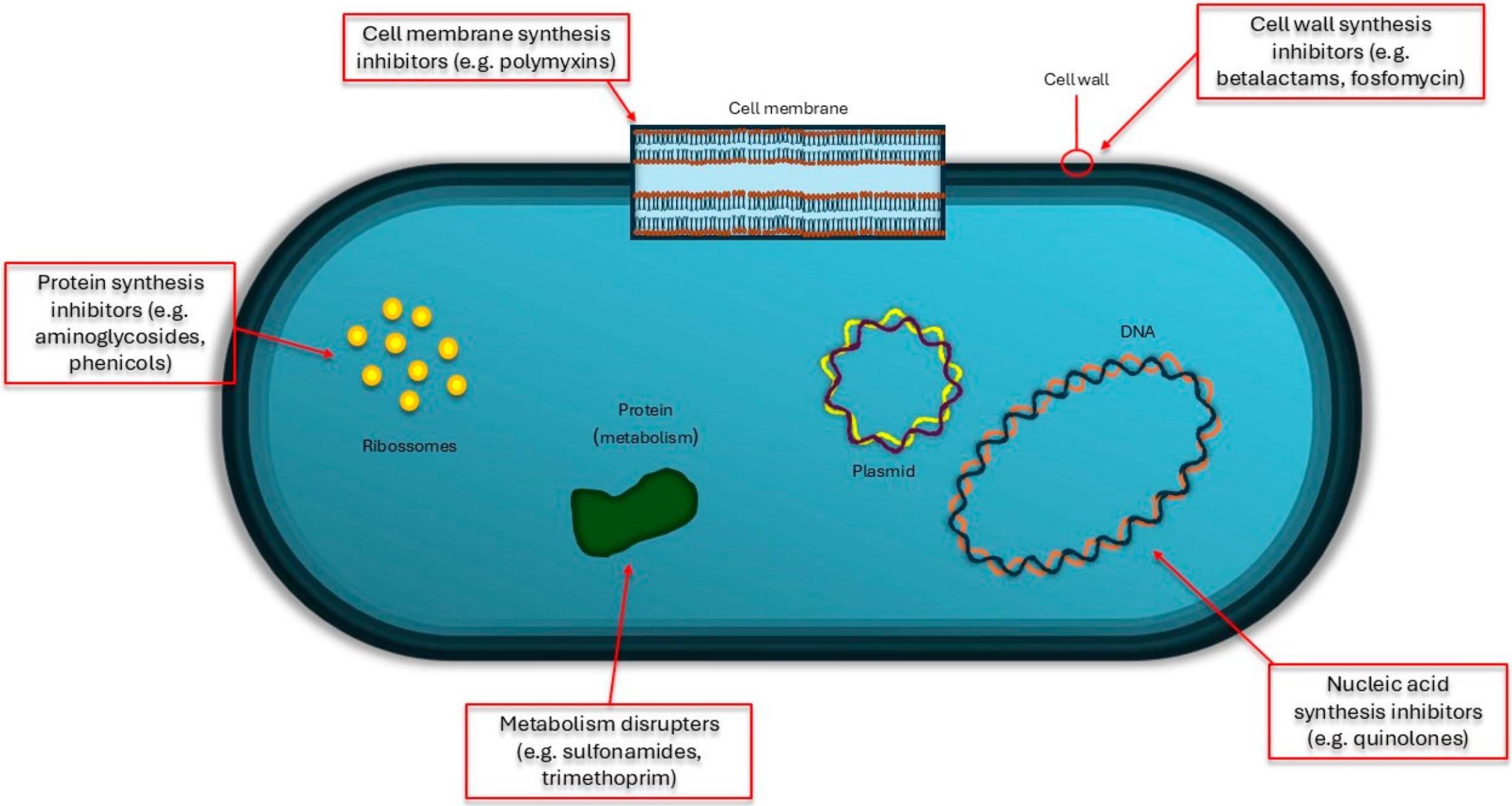
- 1. Fluoroquinolones (FQ I) – First Generation
- First-generation fluoroquinolones were developed for **gram-negative bacterial infections** and have limited activity against **gram-positive bacteria**.

- ***Examples of FQ I Drugs:***
- ***A.*** **Norfloxacin**
- **Ofloxacin**

Key Features of FQ I:

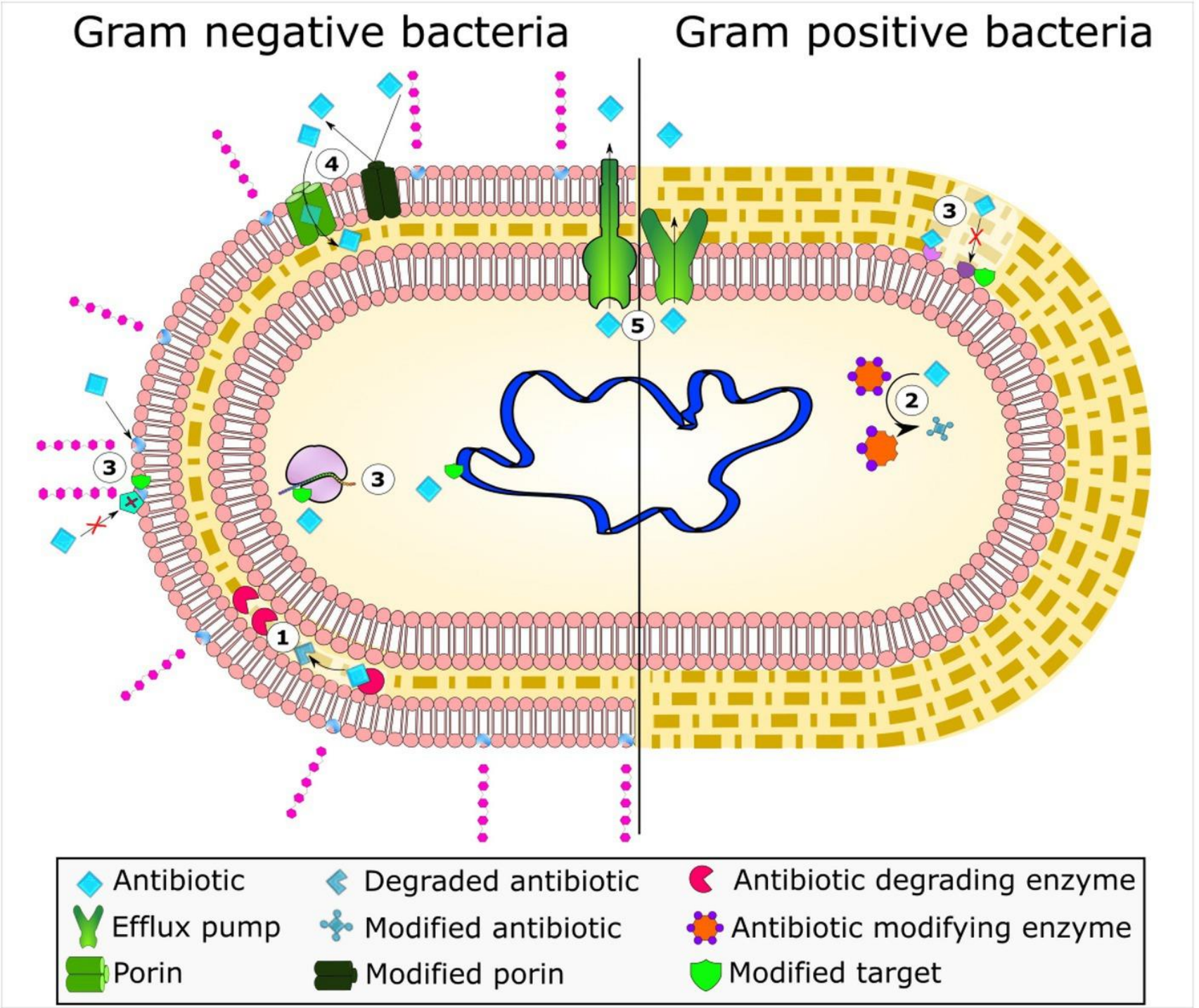
◦ ***Key Features of FQ I:***

- **Activity:** Primarily effective against **gram-negative** organisms, including **Enterobacteriaceae** (e.g., *E. coli*, *Klebsiella spp.*).
- **Limited gram-positive activity:** Less effective against **Streptococcus pneumoniae** and **Staphylococcus aureus**.
- **Clinical Uses:** Often used to treat urinary tract infections (UTIs), **gastrointestinal infections**, and **prostatitis**.
- **Pharmacokinetics:** Generally, these drugs have good **oral bioavailability** and are excreted through the kidneys.



The Figure showing the Depicts the action of the main antibiotics that are used on Klebsiella spp.

Bacterial mechanisms of resistance to antimicrobial agents. The frequent mechanisms of antibiotic resistance observed in bacteria include enzymatic hydrolysis (1), enzymatic antibiotic modifications through group transfer and redox process (2), alterations to antibiotic targets (3), decreased antibiotic permeability through porin alteration (4), and active antibiotic extrusion via membrane efflux pumps (5).



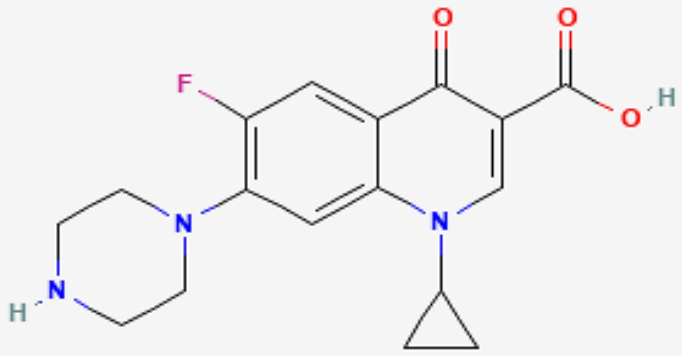
2. Fluoroquinolones (FQ II) – Second Generation and Beyond

- Second-generation fluoroquinolones and those developed later have **broader antimicrobial activity** than first-generation agents, including enhanced activity against **gram-positive bacteria** and **atypical pathogens**.

2. Fluoroquinolones (FQ II) – Second Generation and Beyond

- ***Examples of FQ II Drugs:***

1. Ciprofloxacin (widely used for **gram-negative infections**)

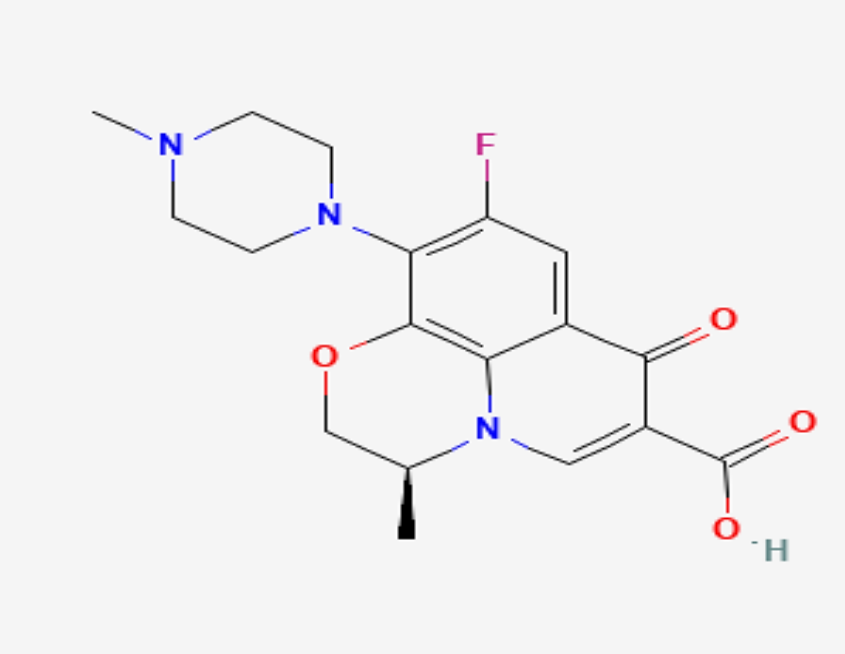


$C_{17}H_{18}FN_3O_3$

2. Fluoroquinolones (FQ II) – Second Generation and Beyond

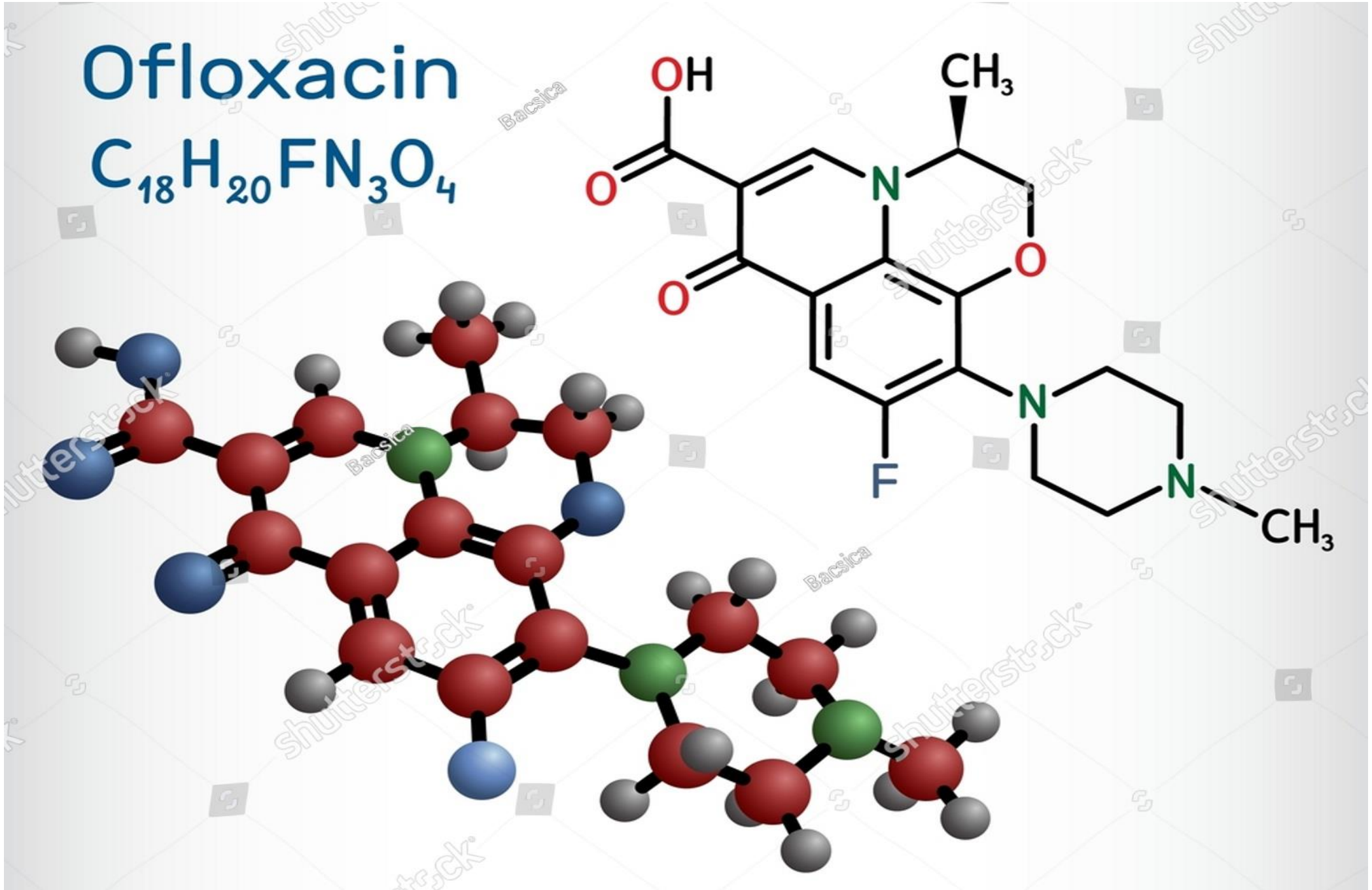
- ***Examples of FQ II Drugs:***

2. Levofloxacin (a **L-isomer** of ofloxacin with better gram-positive activity)



Ofloxacin

$C_{18}H_{20}FN_3O_4$



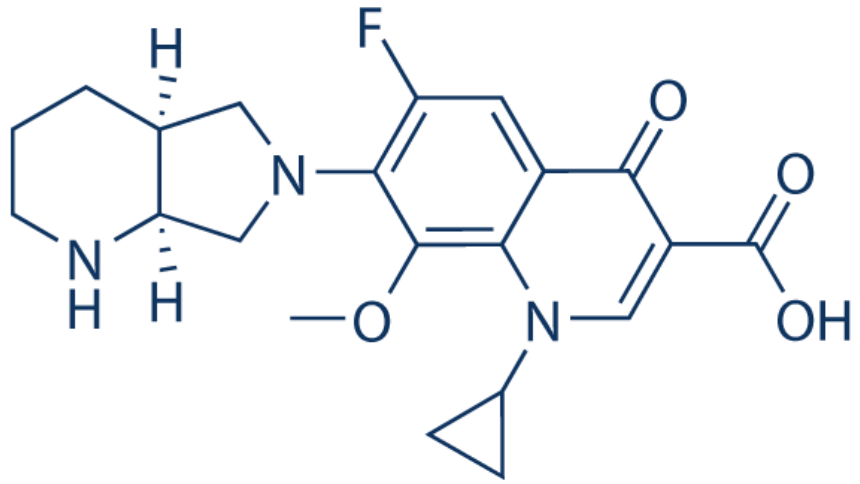
Levofloxacin

- **Levofloxacin** is a third-generation fluoroquinolone and is the pure L-enantiomer of ofloxacin. Fluoroquinolones are broad spectrum bactericidal agents with activity against many of the important corneal pathogens including staphylococci, Neisseria gonorrhoea, Haemophilus influenzae, Enterobacteriaceae, and Pseudomonas aeruginosa.

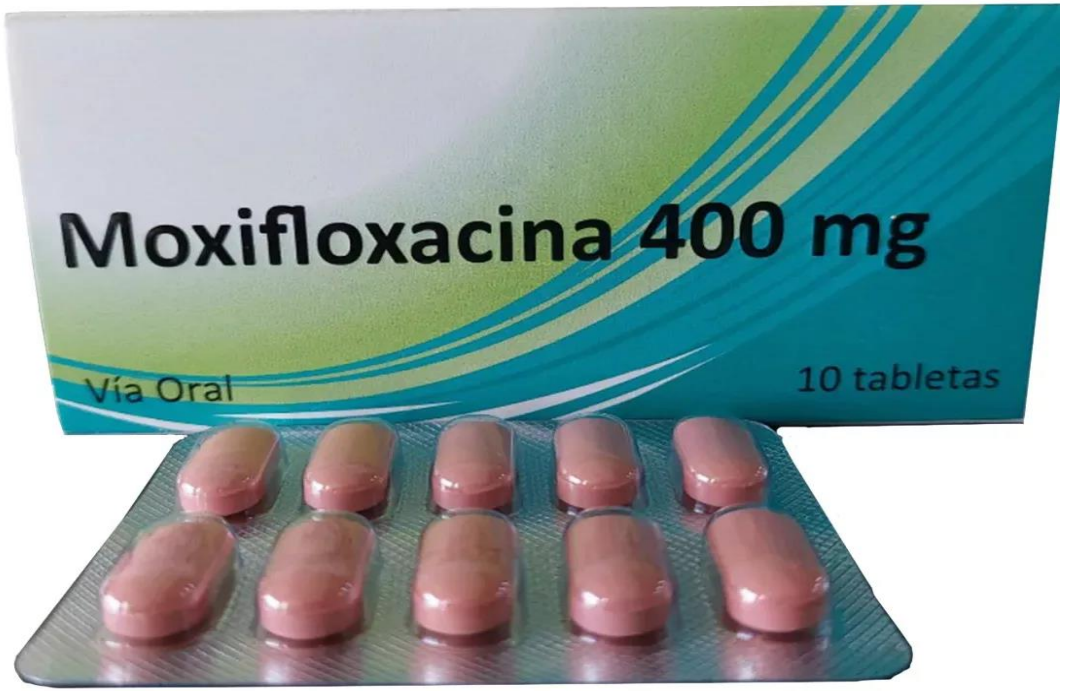
2. Fluoroquinolones (FQ II) – Second Generation and Beyond

- ***Examples of FQ II Drugs:***

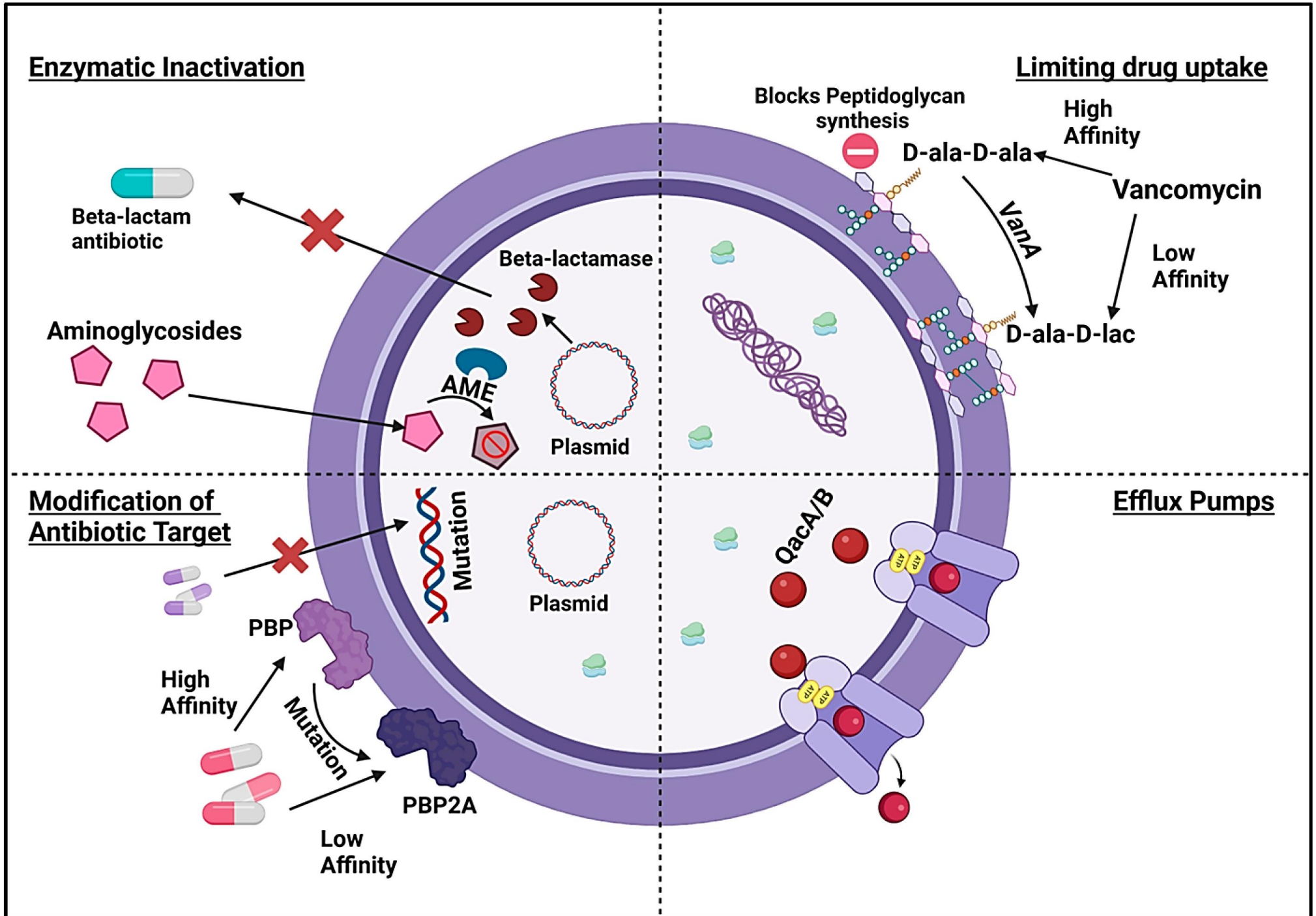
3. **Moxifloxacin** (greater activity against **gram-positive organisms** and **atypical bacteria**)



C21H24FN3O4



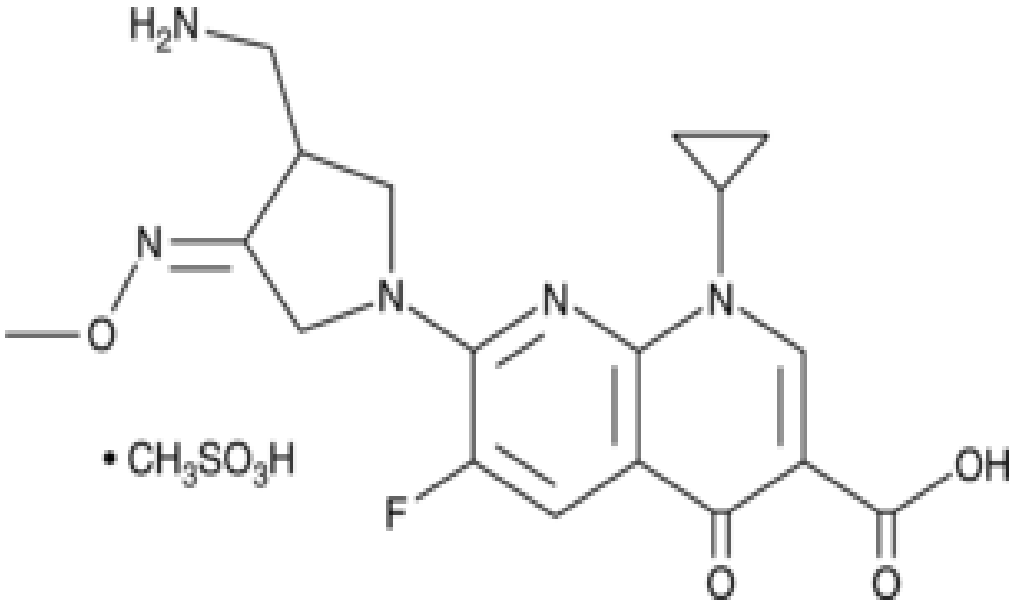
Resistance mechanisms of Gram-positive bacteria. The figure showing depicts four major resistance mechanisms discussed in the review, including beta-lactamase action, AMEs inactivating aminoglycosides, a mutation in the ribosomal binding site, PBP alteration, efflux pump, and cell wall modification. (Figure created using Biorender, https://www.biorender.com/).



2. Fluoroquinolones (FQ II) – Second Generation and Beyond

- ***Examples of FQ II Drugs:***

4. **Gemifloxacin** (similar to moxifloxacin but with slightly more activity against **Streptococcus pneumoniae**)



Key Features of FQ II:

- **Broader Spectrum of Activity:**
  - Effective against **gram-negative** bacteria (e.g., *Pseudomonas aeruginosa*, *Enterobacteriaceae*).
  - Strong activity against **gram-positive bacteria** (e.g., *Streptococcus pneumoniae*).
  - Excellent activity against **atypical pathogens** (e.g., *Mycoplasma pneumoniae*, *Chlamydia spp.*, *Legionella*).
- **Clinical Uses:**
  - **Respiratory infections** (e.g., **community-acquired pneumonia**, **chronic obstructive pulmonary disease (COPD) exacerbations**).
  - **Urinary tract infections** (UTIs), **skin infections**, **abdominal infections**, and **bone and joint infections**.
  - Treatment of **tuberculosis** in combination therapy (especially **Moxifloxacin**).

Key Features of FQ II:

- **Pharmacokinetics:** They have **excellent oral bioavailability** and are often available in both oral and IV formulations. They are primarily excreted in the **urine** (except **moxifloxacin**, which is eliminated via **hepatic metabolism**).

Mechanism of Action of Fluoroquinolones

◦ Fluoroquinolones work by inhibiting two crucial enzymes involved in bacterial DNA replication and repair:

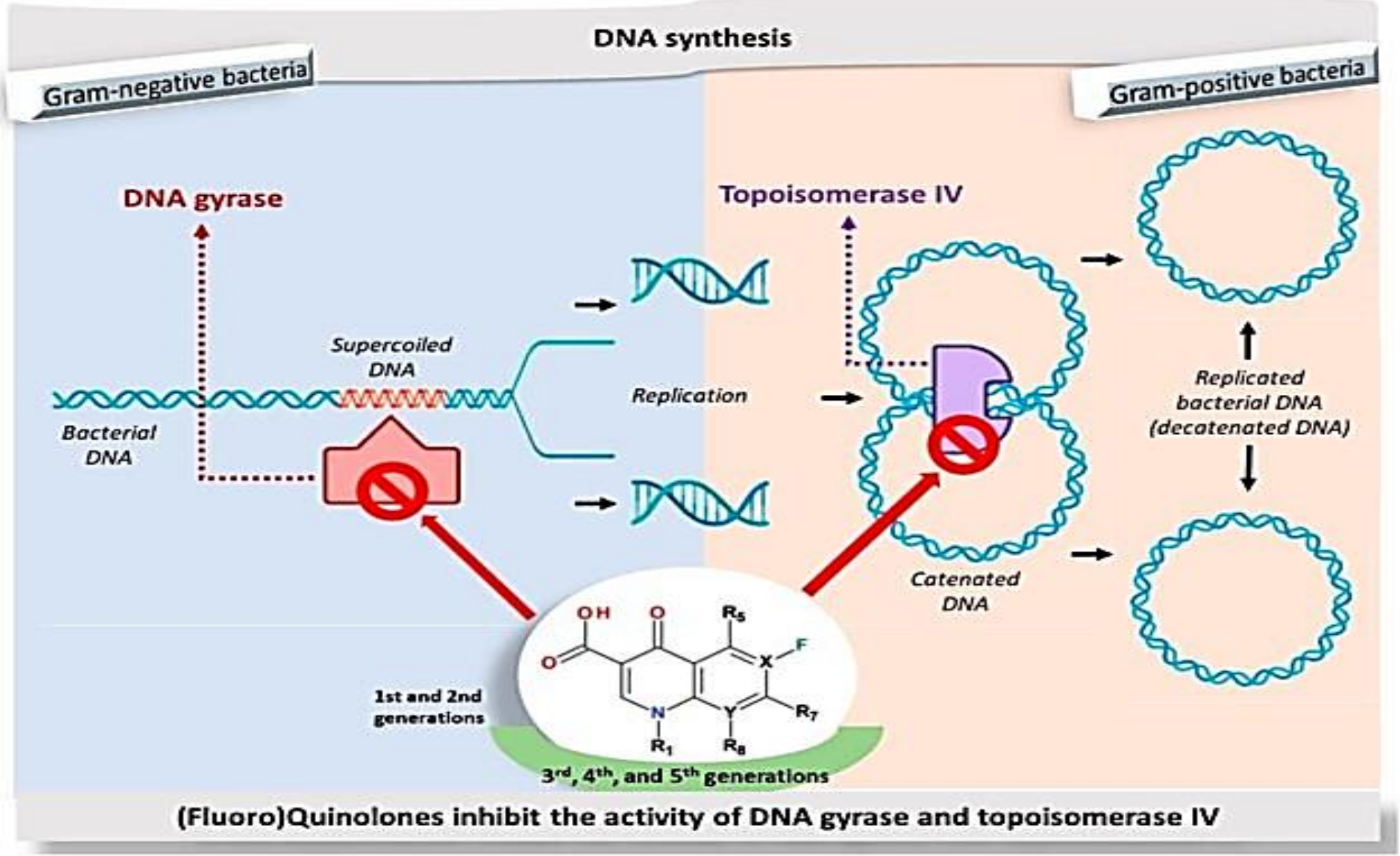
◦ 1. DNA Gyrase Inhibition:

- DNA gyrase is essential for relieving the **supercoiling** tension that occurs during **DNA replication**. Inhibition of DNA gyrase by fluoroquinolones prevents **DNA unwinding**, leading to the inability of the bacteria to replicate its DNA.

◦ 2. Topoisomerase IV Inhibition:

- **Topoisomerase IV** is involved in the separation of **daughter DNA strands** after DNA replication. Fluoroquinolones also inhibit this enzyme, disrupting the final stages of **DNA segregation**.

◦ The result is **DNA damage** and **cell death** due to the accumulation of **double-strand breaks** in the bacterial chromosome.



(Fluoro)Quinolones inhibit the activity of DNA gyrase and topoisomerase IV

Clinical Uses of Fluoroquinolones

- Fluoroquinolones are used to treat a wide variety of infections, and their choice depends on the **susceptibility of the pathogen** and the **generation** of fluoroquinolone.
- 1. Respiratory Tract Infections:
  - **Ciprofloxacin**: Effective for **Pseudomonas aeruginosa** in cases of **bronchitis** and **pneumonia**.
- **Levofloxacin** and **Moxifloxacin**: Used for **community-acquired pneumonia** (CAP), **COPD exacerbations**, and **sinusitis**

Clinical Uses of Fluoroquinolones

◦ 2. Urinary Tract Infections (UTIs):

- **Norfloxacin**, **Ofloxacin**, and **Ciprofloxacin**: These are commonly prescribed for **complicated UTIs** and **pyelonephritis**.

◦ 3. Gastrointestinal Infections:

- **Ciprofloxacin**: Effective against **salmonella**, **shigella**, and **Campylobacter** species, often used for **gastroenteritis**.

◦ 4. Skin and Soft Tissue Infections:

- **Levofloxacin** and **Moxifloxacin**: Used for **skin infections**, **wound infections**, and **cellulitis**.

◦ 5. Bone and Joint Infections:

- **Ciprofloxacin**: Used for **osteomyelitis** caused by **gram-negative bacteria** (e.g., *Pseudomonas aeruginosa*).

Adverse Effects of Fluoroquinolones

◦ While fluoroquinolones are generally well-tolerated, they can cause **serious side effects**, particularly with prolonged use.

◦ 1. Common Adverse Effects:

- **Gastrointestinal symptoms**: Nausea, vomiting, diarrhea, abdominal pain.
- **Headache, dizziness**: Common neurological side effects.
- **Tendonitis and tendon rupture**: Especially in patients >60 years, those on **steroids**, or with **renal failure**.
- **QT interval prolongation**: Particularly with **Moxifloxacin**, leading to potential arrhythmias.

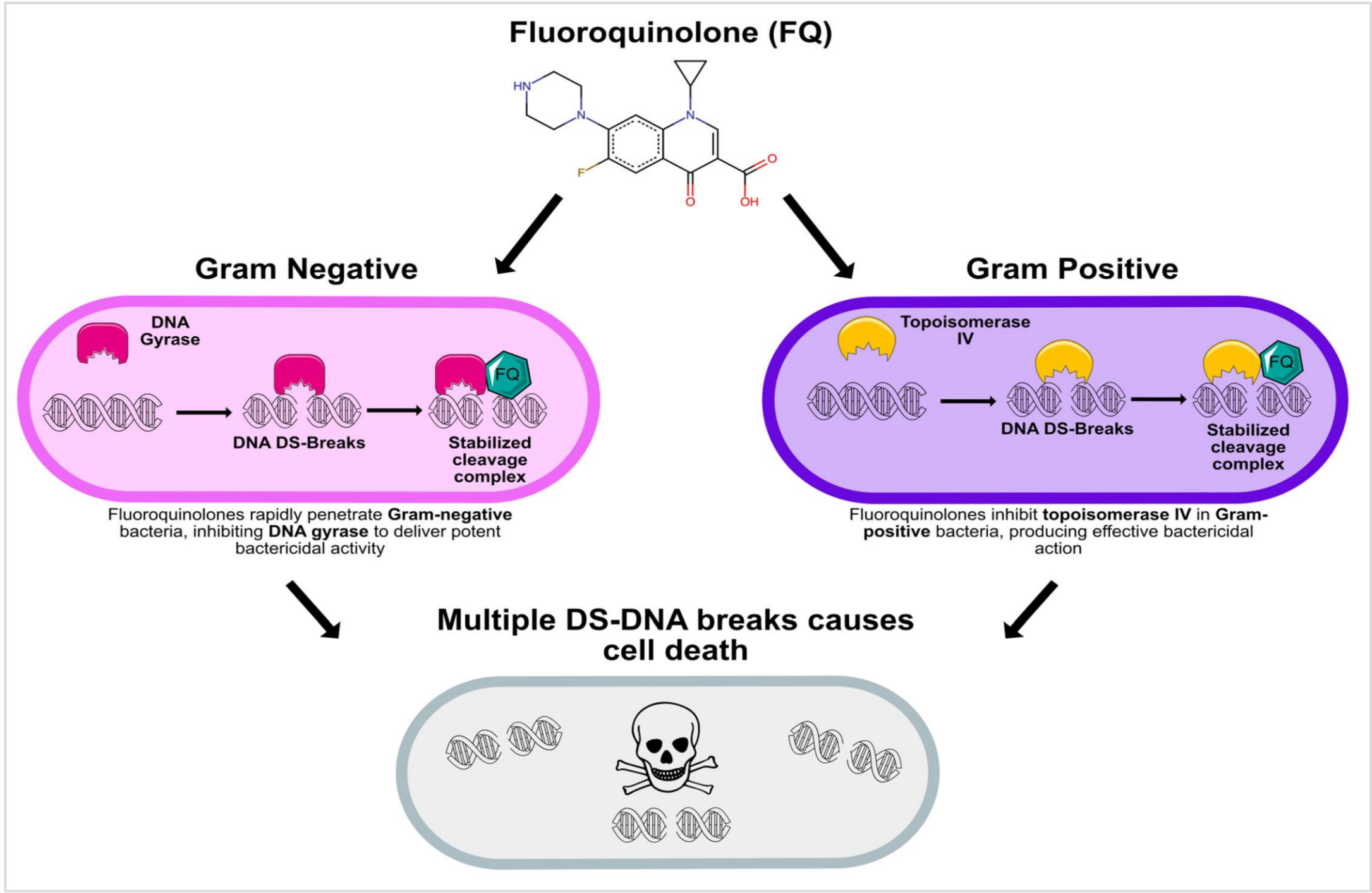
Rare but Serious Adverse Effects:

- **Central nervous system (CNS)**: Seizures, confusion, hallucinations (particularly in elderly patients).
- **Cardiotoxicity**: **Moxifloxacin** and **Levofloxacin** have been associated with **QT prolongation** and potential arrhythmias.
- **Peripheral neuropathy**: Can occur, especially with **long-term use**.
- **Hypersensitivity reactions**: Skin rash, anaphylaxis.

◦ 3. Contraindications:

- **Pregnancy**: Fluoroquinolones are generally contraindicated in pregnancy due to potential effects on fetal cartilage.

◦ **Pediatric use**: Should be avoided in children unless absolutely necessary, due to potential **joint toxicity**.


Fluoroquinolone (FQ)
HN
N
N
F
O
O
OH
Gram Negative
DNA Gyrase
FQ
DNA DS-Breaks
Stabilized cleavage complex
Fluoroquinolones rapidly penetrate **Gram-negative** bacteria, inhibiting **DNA gyrase** to deliver potent bactericidal activity
Gram Positive
Topoisomerase IV
FQ
DNA DS-Breaks
Stabilized cleavage complex
Fluoroquinolones inhibit **topoisomerase IV** in **Gram-positive** bacteria, producing effective bactericidal action
Multiple DS-DNA breaks causes cell death

. Contraindications:

- 3. **Pregnancy**: Fluoroquinolones are generally contraindicated in pregnancy due to potential effects on fetal cartilage.
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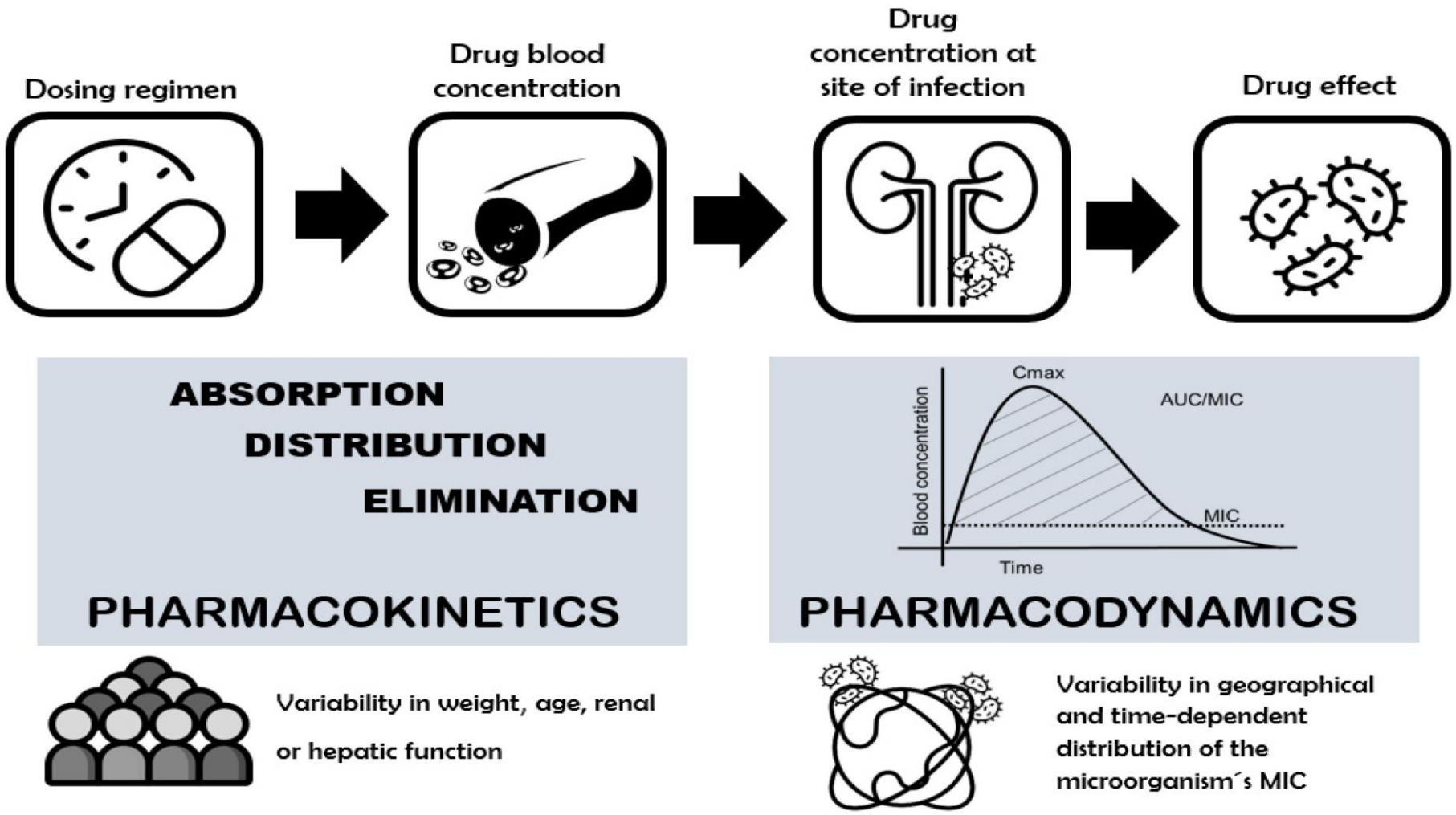
Pharmacokinetics of Fluoroquinolones



Pharmacokinetic/Pharmacodynamic factors affecting the dose-antimicrobial response relation. Cmax: peak plasma concentration, AUC: area under the plasma drug concentration-time curve from tim centration-time curve from time, MIC: minimum inhibitory concentration of an antibiotic against a bacterial pathogen.

Pharmacokinetics of Fluoroquinolones

- Fluoroquinolones are well-absorbed after **oral administration**, with good **bioavailability** (especially **Ciprofloxacin** and **Levofloxacin**). They distribute widely in body tissues, including the **lungs**, **kidneys**, **bone**, and **urine**, making them effective for a variety of infections.

Pharmacokinetics of Fluoroquinolones

- Absorption: Good oral absorption, although divalent and trivalent cations (e.g., calcium, magnesium) can impair absorption.
- Distribution: High tissue penetration, especially into the urinary tract and respiratory system.
- Metabolism: Some fluoroquinolones (e.g., Moxifloxacin) undergo hepatic metabolism, while others (e.g., Ciprofloxacin) are primarily excreted unchanged in the urine.
- Excretion: Mostly renal, with dose adjustment required in renal impairment.

Summary

- **Fluoroquinolones** are an important class of **broad-spectrum antibiotics** with excellent activity against both **gram-negative** and **gram-positive** bacteria.
- They are **classified into two generations**: **FQ I** (first generation) with activity mainly against **gram-negative** organisms and **FQ II** (second generation) with enhanced activity against **gram-positive

References

1. Goodman & Gilman’s: The Pharmacological Basis of Therapeutics
- 13th Edition. McGraw-Hill Education, 2018.

(Chapter on Antimicrobial Chemotherapy, including Fluoroquinolones)
ISBN: 978-1259584732
✅ A comprehensive pharmacology textbook that provides in-depth details on the mechanism of action, clinical use, and side effects of fluoroquinolones.

2. "Basic and Clinical Pharmacology."
15th Edition. McGraw-Hill Education, 2020.
ISBN: 978-1260452310
✅ A well-known pharmacology textbook with a dedicated section on fluoroquinolones, their mechanisms, uses, and pharmacokinetics.

- **3.** Benedict, S. T., et al.
- **"Fluoroquinolones: Mechanisms of Action and Resistance."**

Clinical Microbiology Reviews, 2001; **14(4): 678-707.**
DOI: 10.1128/CMR.14.4.678-707.2001
✅ A detailed review article that explores the mechanisms of action, resistance patterns, and clinical applications of fluoroquinolones.

References

◦ **4.** Harris, P. A., et al.

◦ **"Fluoroquinolones: A Review of Their Pharmacology, Clinical Use, and Safety Profile."**

Pharmacology & Therapeutics, 2020; **45(1): 1-16.**

DOI: 10.1002/prp2.1550

✅ A peer-reviewed paper that provides an in-depth look at the pharmacological properties, clinical uses, and adverse effects of fluoroquinolones.

◦ **5.** World Health Organization (WHO).

◦ **"Antimicrobial Stewardship: Fluoroquinolones."**

World Health Organization, 2019.

https://www.who.int/medicines/areas/rational_use/antimicrobial-stewardship/en/

✅ Provides information on the role of fluoroquinolones in antimicrobial stewardship, including their clinical uses and concerns related to resistance.