In The Name of God

Fluoroquinolones

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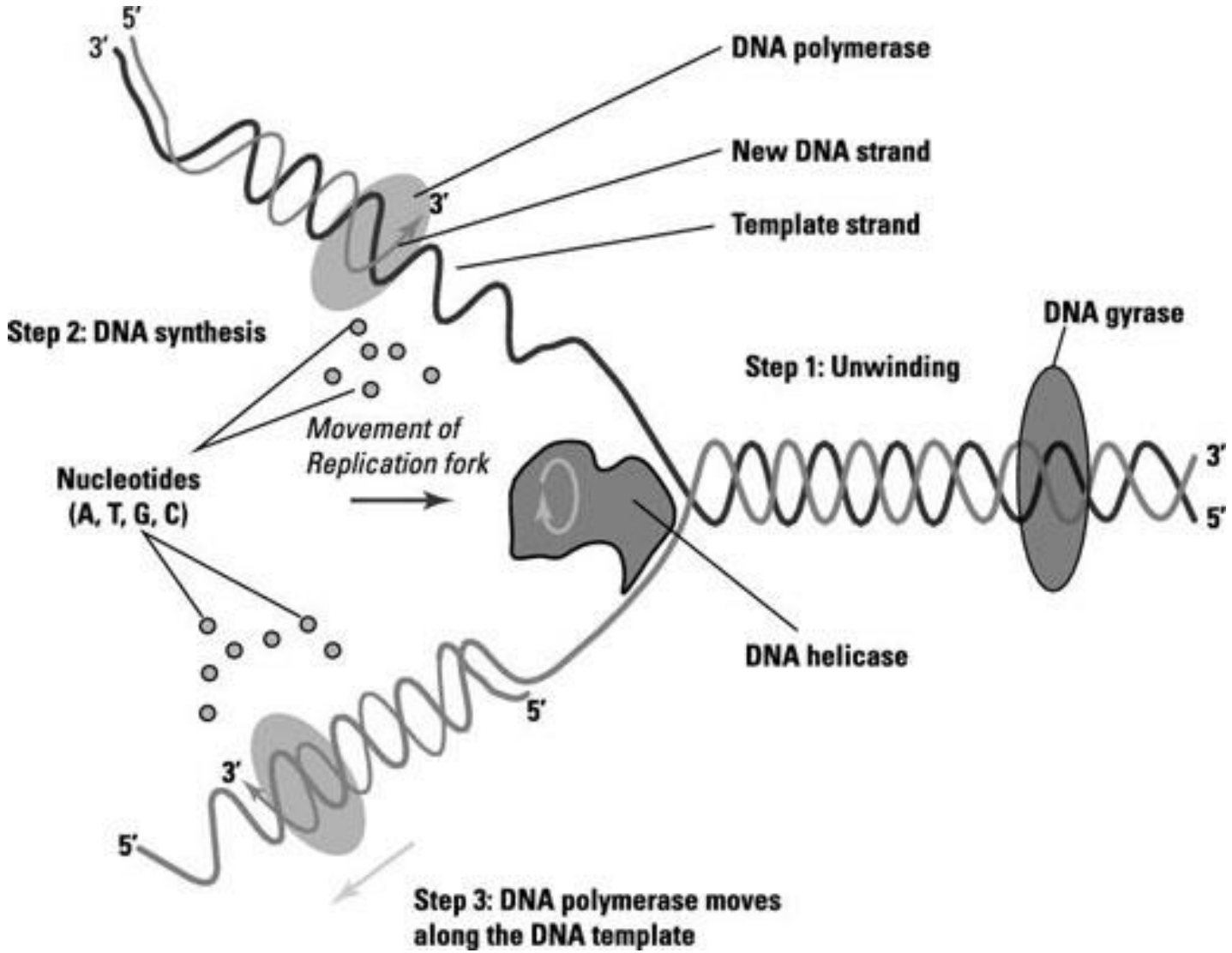
MECHANISMS OF ACTION

- Fluoroquinolones are bactericidal antibiotics that directly inhibit bacterial DNA synthesis.
- bind to complexes of DNA with each of two enzymes that are essential for DNA replication, DNA gyrase and DNA topoisomerase IV, and this binding generates DNA cleavage.
- fluoroquinolone generation of DNA cleavage complexes results in cessation of DNA replication, DNA damage, and, ultimately, cell death.



1. Aerobic gram-negative bacilli (rods): Most fluoroquinolones are highly active against Enterobacterales (*Escherichia coli, Klebsiella* spp, *Proteus* spp).

✓ Ciprofloxacin has the most potent activity against these organisms.

Pseudomonas spp: Ciprofloxacin > Levofloxacin and Delafloxacin > Moxifloxacin

2. Respiratory pathogens:

Levofloxacin and moxifloxacin: Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and intracellular or cell wall-deficient bacteria (ie, Legionella spp, Mycoplasma spp, and Chlamydia pneumoniae).

Ciprofloxacin has lesser activity against gram-positive organisms (eg, S. pneumoniae). Has potent activity against aerobic gram-negative respiratory pathogens (eg, H. influenza, M. catarrhalis).

3. Gram-positive organisms:

Levofloxacin, moxifloxacin, and delafloxacin: Staphylococcus aureus, some streptococci, and strains of coagulase-negative staphylococci.

Delafloxacin is also active against MRSA, a unique feature among fluoroquinolones.

Ciprofloxacin, norfloxacin, ofloxacin, and prulifloxacin has limited or no activity against gram-positive organisms.

4. Anaerobes:

Only moxifloxacin has sufficient activity and appears to be similarly effective as ampicillin-sulbactam for anaerobic lung infections (eg, aspiration pneumonia or lung abscess).

5. Mycobacteria:

Second-line agents in the setting of resistance and/or intolerance to first-line agents against Mycobacterium tuberculosis.

✓ Moxifloxacin and Levofloxacin are preferred over other fluoroquinolones because of their greater potency.

Activity against M. avium complex is fair to poor.

✓ Moxifoxacin and ofloxacin are active against M. leprae.

6. Other organisms: Among first-line options for the treatment of susceptible infections caused by Bacillus anthracis, Francisella tularensis, and typhoid.

PHARMACOKINETICS

- Bioavailability
- Dietary Considerations
- Drug concentrations in serum and other sites
- Half-lives of the drugs
- Routes of elimination

PHARMACOKINETICS

High oral bioavailability and a large volume of distribution.

Oral bioavailability:

- 70% for ciprofloxacin,
- 86% for moxifloxacin
- >95% for ofloxacin and levofloxacin

Peak serum concentrations: usually attained within 1 to 3 hours of administering an oral dose.

Food does not substantially reduce fluoroquinolone absorption but may delay the time to reach peak serum concentrations

- ✕ dairy, antacids, multivitamins containing zinc, sucralfate, and divalent cations (aluminum, magnesium, calcium) can substantially decrease absorption.
- ✕ Concurrent use should be avoided or should be given several hours apart from the fluoroquinolone to avoid interaction.

ADVERSE REACTIONS

- **Gastrointestinal**
  - 3-17 %, Anorexia, nausea, vomiting, and abdominal discomfort
- **Nervous system**
  - mild headache and dizziness, insomnia, alterations in mood, Seizer (especially with Theophylline and NSAID)
  - Neuromuscular blocking activity
  - Sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, weakness: last for months to years after the drug is stopped or be permanent
- **Rash and other allergic manifestations**
- **Arthropathy**
- **Tendinopathy and tendon rupture**
- **QT interval prolongation and arrhythmia**
  - Moxifloxacin > Levofloxacin > Ciprofloxacin
- **Hypoglycemia and hyperglycemia**
  - Moxifloxacin appears to confer the highest risk of both hyperglycemia and hypoglycemia.
- **Hepatoxicity**
  - Moxifloxacin (aOR 2.20) and Levofloxacin (aOR 1.85) were associated with an increased risk of acute liver injury within 30 days of receiving a prescription compared with use of clarithromycin.
  - No increased risk was observed for ciprofloxacin compared with clarithromycin.

DRUG INTERACTIONS

- With other QT-prolonging medications.
- Ciprofloxacin inhibits hepatic CYP1A2, impairs the elimination of clozapine, tizanidine, theophylline, caffeine, and methylxanthines.

✕ Ciprofloxacin should be avoided for patients taking these medications or dosing of substrate drugs should be reduced.

✓ Other fluoroquinolones do not inhibit or induce cytochrome P450 enzymes or xanthine metabolism to a clinically relevant extent.

- NSAIDs may lower the seizure threshold. Patients receiving both classes of drugs should be cautioned about and monitored for these adverse effects.
- Rifampin and the long-acting rifamycin, rifapentine, lower the plasma concentration of moxifloxacin. An important consideration when formulating treatment regimens for tuberculosis and other mycobacterial infections.

FQs in VAP,HAP

- An antipseudomonal fluoroquinolone such as ciprofloxacin (400 mg IV every 8 hours) or levofloxacin (750 mg IV daily) is preferred if *Legionella* is likely. *These agents may be administered orally when the patient is able to take oral medications. The dose of levofloxacin is the same when given intravenously and orally, while the dose of ciprofloxacin is 750 mg orally twice daily.*
- In many institutions, addition of a FQ adds minimal additional in vitro activity against local pathogens.
- The IDSA/ATS guidelines recommend either an antipseudomonal FQ or an AG for the second agent for gram-negative bacilli and they also state that AG should be avoided if alternative agents with adequate activity against gram-negative bacilli are available.
- However, we (uptodate) generally prefer an AG over a FQ if there is not concern for *Legionella,* as AG are more likely to have in vitro activity against gram-negative bacilli in those with risk factors for resistance

Recommendations in the specific FQ:

- Moxifloxacin, levofloxacin, and gemifloxacin are recommend to be avoided in patients with known QT interval prolongation or other risk factors for torsades de pointes, such as **hypokalemia**, **hypomagnesemia**, or the use of class IA (**quinidine, procainamide**) or class III (**amiodarone, sotalol**) antiarrhythmic drugs .
- The prescribing information for moxifloxacin further suggests caution in use by patients with hepatic insufficiency-associated metabolic disturbances, which may lead to QT prolongation

Pharmacokinetics and drug interactions of systemic fluoroquinolones in adults

Agent	Bioavailability	Clearance	Metabolism	Inhibition or induction of metabolism	Elimination half-life	Notes
Ciprofloxacin	70% (range 50 to 85%). Avoid taking with most antacids, mineral supplements, and certain oral medications: Decreased bioavailability in some cases by >90%.* May be taken with most foods or on an empty stomach. However, avoid taking with milk or dairy products: Decreased bioavailability up to 40%. [1]	Oral administration: ■ 30 to 50% renally cleared ¶ ■ 15% metabolized ■ 30% presystemic clearance (hepatobiliary and fecal) IV administration: ■ 70% renally cleared ¶ ■ 10% metabolized	Hepatic metabolism is poorly characterized; some metabolites are active.	Inhibitor of CYP1A2. Can increase blood levels of CYP1A2 substrate drugs (eg, clozapine, erlotinib, ibrutinib, ropinirole, theophylline, tizanidine); refer to Lexicomp drug interactions program for detail.	3 to 5 hours. Prolonged in older adults and in renal impairment (up to 8 hours in advanced chronic kidney disease).	Some drug interactions require dose adjustment or avoidance of certain combinations; refer to Lexicomp drug interactions program for detail.

Agent	Bioavailability	Clearance	Metabolism	Inhibition or induction of metabolism	Elimination half-life	Notes
Gemifloxacin[Δ] (oral only)	71%. Avoid taking with most antacids, mineral supplements, and certain oral medications: Decreased bioavailability in some cases by >90%.* May be taken with or without food.	Oral administration: ■ 36% renally cleared[¶] ■ <10% metabolized ■ 61% fecal clearance	Does not undergo CYP450 metabolism. Metabolized via glucuronidation.	Does not inhibit or induce hepatic CYP450 enzymes.	7 hours (range 4 to 12 hours). Prolonged in renal impairment.	
Levofloxacin	99%. Avoid taking with most antacids, mineral supplements, and certain oral medications: Decreased bioavailability in some cases by >90%.* May be taken with or without food.	Oral/IV administration: ■ 87% renally cleared[¶] ■ <1% metabolized ■ <4% fecal clearance	Does not undergo CYP450 metabolism. Minimally metabolized via glucuronidation.	Does not inhibit or induce hepatic CYP450 enzymes.	6 to 8 hours. Prolonged up to 35 hours in advanced chronic kidney disease.	

Agent	Bioavailability	Clearance	Metabolism	Inhibition or induction of metabolism	Elimination half-life	Notes
Moxifloxacin	90%. Avoid taking with most antacids, mineral supplements, and certain oral medications: Decreased bioavailability in some cases by >90%.* May be taken with or without food.	Oral/IV administration: ■ 20% renally cleared ■ 52% metabolized ■ 25% fecal clearance	Does not undergo CYP450 metabolism. Metabolized via glucuronidation and sulfate conjugation.	Does not inhibit or induce hepatic CYP450 enzymes.	10 to 14 hours.	

Agent	Bioavailability	Clearance	Metabolism	Inhibition or induction of metabolism	Elimination half-life	Notes
Norfloxacin[Δ] (oral only)	30 to 40%. Avoid taking with most antacids, mineral supplements, and certain oral medications: Decreased bioavailability in some cases by >90%.* May be taken with most foods or on an empty stomach, but food may delay absorption. However, avoid taking with milk or dairy products: decreased bioavailability up to 40%. [2]	Oral administration: ■ 30% renally cleared[¶] ■ 5 to 8% metabolized ■ 30% fecal clearance	Undergoes modest hepatic metabolism; however, its metabolism has not been well characterized.	Can increase blood levels of theophylline. [3] May alter cyclosporine levels; monitoring suggested. [4] Refer to Lexicomp drug interactions program for detail.	3 to 4 hours. Prolonged up to 6.5 hours in advanced chronic kidney disease.	Some drug interactions require dose adjustment or avoidance of certain combinations; refer to Lexicomp drug interactions program for detail.

Agent	Bioavailability	Clearance	Metabolism	Inhibition or induction of metabolism	Elimination half-life	Notes
Ofloxacin	>90%. Avoid taking with most antacids, mineral supplements, and certain oral medications: Decreased bioavailability in some cases by >90%.* May be taken with or without food.	Oral/IV administration: ■ 80% renally cleared ¶ ■ 4% metabolized ■ 4 to 8% fecal clearance	Does not undergo CYP450 metabolism. Metabolized via glucuronidation.	Does not inhibit or induce hepatic CYP450 enzymes.	5 to 7.5 hours. Prolonged in renal impairment.	


Thanks for your attention