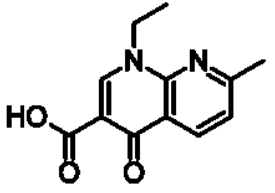
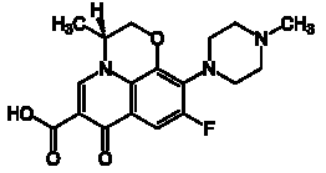
Quinolones

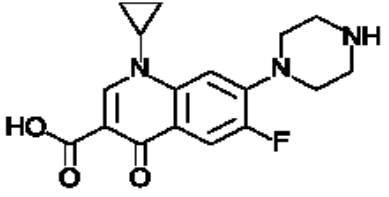
28. Oct.



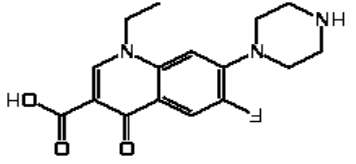
(Nalidixic acid) 1st



(Levofloxacin) 3ed



(Ciprofloxacin) 2nd



(Norfloxacin) 2nd

The important quinolones are synthetic fluorinated analogs of nalidixic acid. منشان هيك هاد موكتير مستخدم.

Fluorinated quinolones: greater potency, broader spectrum of antimicrobial activity, better safety profile

(First - line) هدول هم

لعلاج UTI

Quinolones MOA

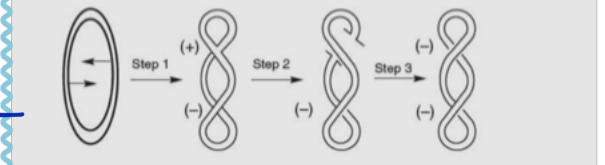
- Enter the bacterium by passive diffusion through porins in the outer membrane
- Inhibit the replication of bacterial DNA by interfering with the action of DNA gyrase (topoisomerase II) and topoisomerase IV during bacterial growth and reproduction.
  - Inhibition of DNA gyrase prevents the relaxation of positively supercoiled DNA that is required for normal transcription and replication.
  - Inhibition of topoisomerase IV interferes with separation of replicated chromosomal DNA into the respective daughter cells during cell division.

[MOA] ← اول شي بيدخل الدوا عن طريق (Passive diffusion) من خلال (Porins)، وبثبط عملية (replication) لـ (DNA) عن طريق
Topoisomerase II ← (DNA . gyrase) تثبيط
Topoisomerase IV ←

هاديه من سلايدات المبيو بس لنفهم اكتر المكتوب

MOA

- Irreversible inhibitors of DNA gyrase and topoisomerase IV, key enzymes involved in DNA-dependent RNA polymerase (DDRP).



A. View from the top: Step 1. Stabilize positive node. Step 2. Break both strands of the back segment. Step 3. Pass unbroken segment through the break and reseal on the front side.

Antimicrobial activity

- Fluoroquinolones were originally developed because of their excellent activity against gram-negative aerobic bacteria; they had limited activity against gram-positive organisms.
- Several newer agents have improved activity against gram-positive cocci.
- This relative activity against gram-negative versus gram-positive species is useful for **classification** of these agents.

هون بيحكي انه بالأصل لما صنّعوا دول الأدوية لـ (G-ve) بكن بعدين طوروهم وصار
عنّا 1st الجيل الاول ، 2nd و ... وصاروا ضد (G+ve) كمان

Classification

- Fluoroquinolones are classified by "generation" based on their antimicrobial spectrum of activity

➢ 1st genenration: Nonfluorinated quinolone (ex. nalidixic acid): narrow spectrum, usually confined to the urinary tract infections by aerobic G-ve.

➢ 2nd generation (ex. Ciprofloxacin and norfloxacin): excellent gram-negative activity, moderate to good activity against gram-positive bacteria and atypical bacteria.

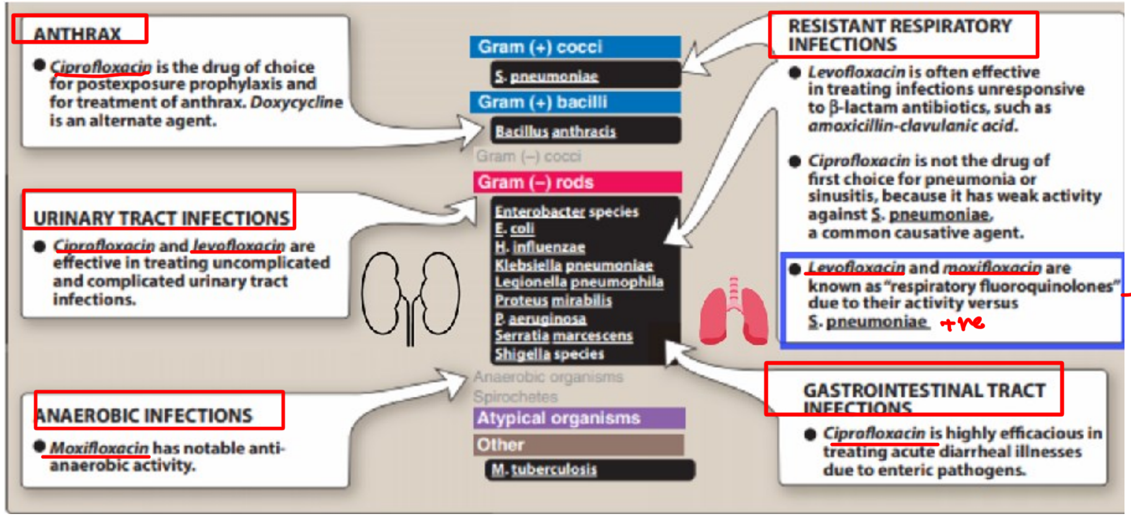
➢ 3rd generation (ex. Levofloxacin): G-ve, increased activity against G+ve

➢ 4th generation (ex. Moxifloxacin): G-ve, active against anaerobic & G+ve

· Narrow Spectrum. · G-ve aerobic bacteria	Nalidixic acid	1st gen
· G-ve bacteria (قطار جزء) · G+ve and atypical bacteria (متوسط)	Ciprofloxacin Norfloxacin	2nd gen
. G-ve. وبرسوز زادت فعالیتم . G+ve اکتر ضد	Levofloxacin	3rd gen
- G-ve, G+ve, anaerobic bacteria.	Moxifloxacin	4th gen

* الي تحتهم خط
هم الي شرحتهم
الدكتورة.

Typical therapeutic applications of fluoroquinolones.



Moxifloxacin has poor activity against P. aeruginosa.
It does not concentrate in urine and is not indicated for the treatment of UTIs.

عشان هيك هو الدوا
الوحيد الي ما بنستخدمه للعلاج UTI / لانه ما بيطلع عن طريق الكلى .

Clinical uses of nalidixic acid (1st generation)

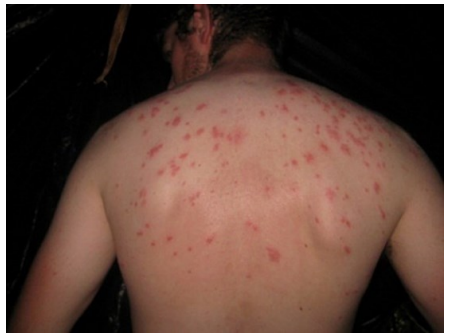
- Earlier quinolones such as **nalidixic acid** is infrequently prescribed due to poor oral bioavailability and a short half-life.
- It is effective in urinary tract infections (UTIs)

← [1st] ، دواء (nalidixic acid) هو فعّال ضد (UTI) بس هش كتير بنصرفه بسبب:

↘ poor oral BA.
↘ short half. life

Clinical uses of ciprofloxacin (2nd generation)

- Ciprofloxacin is useful for infections caused by G-ve bacilli.
- **Uncomplicated and complicated UTI** (E.coli is the most frequent cause)
- Treatment of **traveler's diarrhea** caused by E. coli (but not as prophylaxis except in certain cases)
- Ciprofloxacin is the most potent of the FQ against **P. aeruginosa** infections (used for pseudomonal infections associated with cystic fibrosis)
- Used to treat **typhoid fever** (Caused by Salmonella typhi: Fever, chills, rose spots)

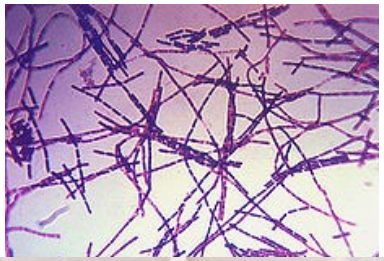


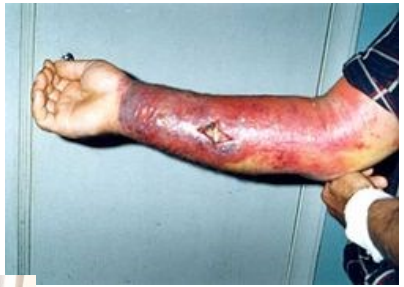
Ciprofloxacin 2nd:

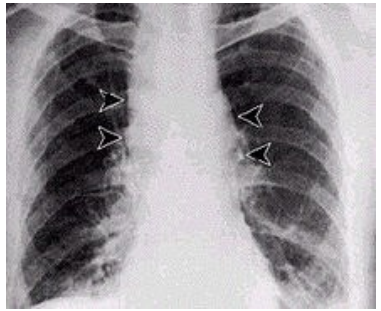
- يستخدم لعلاج [G -ve bacilli infection].
- يستخدم لعلاج [un/Complicated UTI] التي بتعلمو E. Coli.
- يستخدم لعلاج [Traveler's Diarrhea] برضو الناتجة عن E. Coli وممكن للوقاية (prophylaxis) بحالات معينة.
- يستخدم في علاج [Pseudomonal infection] التي بتعلمو بكتيريا (P. aeruginosa) خصوصًا عن مرضى (Cystic Fibrosis)
- تستخدم في علاج [Typhoid fever] الناتج عن بكتيريا (Salmonella typhi)

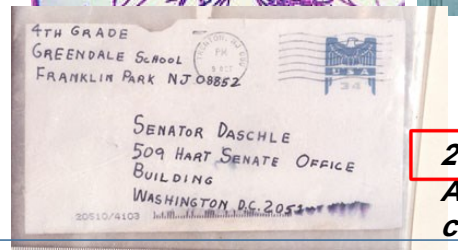
Clinical uses of ciprofloxacin (2nd generation)

- Anthrax
  - Bacillus anthracis, G+ve, biological weapon
  - Pulmonary, cutaneous, GIT symptoms : اعراضها
- Ciprofloxacin is the drug of choice for prevention and treatment of anthrax.









هون اول مرة اكتشفت

2001 Anthrax attack:
A letter sent to Senate Majority Leader Tom Daschle containing anthrax powder killed two postal workers

G +ve
(Bacillus anthracis) بكتيريا الي بتعلها [Anthrax] تستخدم لعلاج -
وهي تستخدم ك سلاح بيولوجي

Norfloxacin (2nd gen.)

- infrequently prescribed due to poor oral bioavailability and a short half-life.
- Used for complicated and uncomplicated UTIs
- Prostatitis (preferred over trimethoprim)
- Traveler's diarrhea

Nor Flox acin 2nd:

- UTI.
- Prostatitis → (trimethoprim) بنستخدمه في بعض الحالات بدلًا من
- Traveler's Diarrhea.

* تقريبًا بنفس استخدامات Cipro
لكن استخداماته محدودة بسبب:

- poor oral BA.
- short half-life.

Levofloxacin (3rd generation)

- Used in the treatment of prostatitis due to E. coli and sexually transmitted diseases, but not syphilis.
- **UTI**
- **Respiratory infections**
  1. Acute sinusitis
  2. Acute exacerbation of chronic bronchitis
  3. Community-acquired and hospital-acquired pneumonia
- Excellent activity against S. pneumoniae respiratory infections.
  - Levofloxacin and moxifloxacin are known as "respiratory fluoroquinolones", effective and used increasingly for treatment of upper and lower respiratory tract infections.

Levofloxacin 3rd:

- يستخدم في علاج [Prostatitis] الناتج عن E.Coli وبعض STD لكن مش (Syphilis).
- UTI.
- يستخدم في علاج [Respiratory Infection] الناتج عن بكتيريا S. pneumoniae

Respiratory Fluoroquinolones بنسميهم: Levofloxacin + Moxifloxacin ⇐

لانهم فعالين بعلاج (lower + upper) respiratory infection.

Moxifloxacin (4th generation)

- Enhanced activity against G+ve (ex: S. pneumoniae)
- Excellent activity against many anaerobes (resistance rates as high as 57 percent for *B. fragilis* have been reported more recently)
- Poor activity against P. aeruginosa
- Does not concentrate in urine and is not indicated for the treatment of UTIs (i.e not all of FQs are used for UTI)

Moxifloxacin 4th.

- هون زادت الفعالية ضد G+ve مثل S.pneumoniae ، و
وبرضو anaerobic لكن منجيد وجمعا انه B.Fragilis صاد عنها
مقاومة وصلت 57%.

- لسا فعاليتهم ضعيفة ضد P.aeruginosa

- وما بنستخدمه في علاج UTI لانه بيطلع إفراج
عن طريق الكبد على عكس الادوية اللي فوق.

// tetracyclines هون نتذكر //
تقريبًا نفس الخلاصة

Pharmacokinetics of FQs

- After oral administration, the fluoroquinolones are well absorbed (bioavailability of 80–95%).

الي عليهم شحنة +2 : Mg^{+2}, Ca^{+2}

- Oral absorption is impaired by divalent and trivalent cations, including those in antacids. Therefore, oral fluoroquinolones should be taken 2 hours before or 4 hours after any products containing these cations.

الي عليهم شحنة +3 Al^{+3}

- IV of ciprofloxacin & levoflxacin are available.

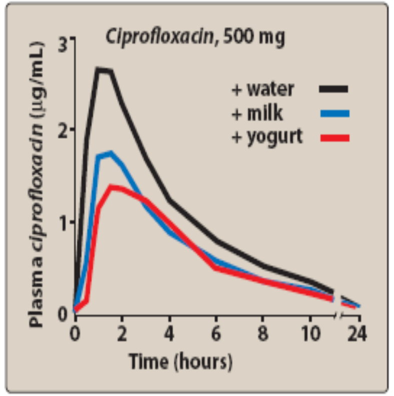


Figure 33.6
Effect of dietary calcium on the absorption of *ciprofloxacin*.

Absorption : امتصاصه منيح orally.

Cation Interaction : بوجود الأيونات الي عليهم شحنة +2 , +3 (الموجودين في مشتقات الألبان وأدوية antacid ، لذلك بنأخذها قبل بساعتين أو بعد بـ 4 ساعات.

IV : Ciprofloxacin و Levofloxacin .

Pharmacokinetics of FQs

- All the FQs distribute well into all tissues and body fluids
  - Levels are high in bone, urine (except moxifloxacin), kidney, and prostatic tissue
  - Concentrations in the lung exceed those in serum (used or respiratory tract infections)
  - Penetration into CSF is low (except ofloxacin = 90% of serum conc.)
- Most fluoroquinolones are eliminated by renal mechanisms, either tubular secretion or glomerular filtration (except moxifloxacin)

Distribution: كل الانواع ما عدا Moxifloxacin بكون تركيزهم منيح ومرتفع في bone, urine, kidney, prostat، وبضل تركيزهم في lung بكون اعلى من (serum) من شان هيك بنستخدم في RS infection

فقط الي بكون تركيزه في CSF %90 (ofloxacin)

Elimination: كلهم بيطلعوا عن طريق (tubular secretion) أو عن طريق (glomerular filtration) ما عدا (Moxifloxacin)

Side effects

- FQs are generally well tolerated. Their side effects are:

1. **Gastrointestinal**: nausea, vomiting, and diarrhea (most common)
2. **CNS problems**: headache and dizziness
3. **Phototoxicity:** patients should be advised to use sunscreen and avoid excess exposure to sunlight. If phototoxicity occurs, discontinuation of the drug is advisable.

Side effects

يعني بتخزب كهربا القلب

4. **Prolongation of the QT_c interval:** thus, should not be used in patients who are predisposed to arrhythmias or those who are taking other medications that cause QT prolongation.

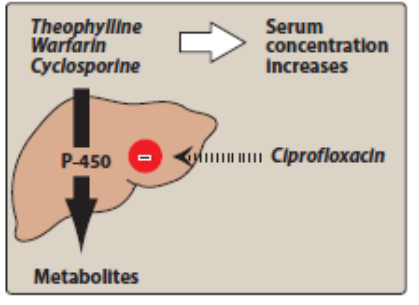
5. **Connective tissue problems**: may damage growing cartilage and cause an arthropathy (articular cartilage erosion) and tendonitis. Thus, these drugs are not routinely recommended for patients under 18 years of age.

- However, the arthropathy is reversible, and there is a growing consensus that fluoroquinolones may be used in children in some cases (eg, for treatment of pseudomonal infections in patients with cystic fibrosis).

- **CAUTIONS:** These agents should be **avoided** in pregnancy and lactation and in children under 18 years of age

Drug-drug interaction

- *Ciprofloxacin* can increase serum levels of *theophylline* by inhibiting its metabolism.
- *Ciprofloxacin* may also raise the serum levels of *warfarin*, *caffeine*, and *cyclosporine*.
- Antacids and minerals decrease fluoroquinolones absorption.



Metronidazole

- **Antiprotozoal** drug that also has potent **antibacterial** activity.
- Metronidazole is indicated for treatment of:
  1. **anaerobic** or mixed intra-abdominal infections
  2. vaginitis (trichomonas infection, bacterial vaginosis)
  3. *Clostridium difficile* infection
  4. brain abscess.

هون نتذكر طبيب الأسنان

- Adverse effects include nausea, headache, dry mouth and a metallic taste in the mouth occur commonly. Peripheral neuropathy with prolonged use.
- Dark brown urine discoloration has also been documented

هاد اللي بيستخدموا من بيطلعوا احسان الكحول وبيبين اعراض انسحابية

- Metronidazole has a disulfiram-like effect, and patients should be instructed to avoid alcohol.

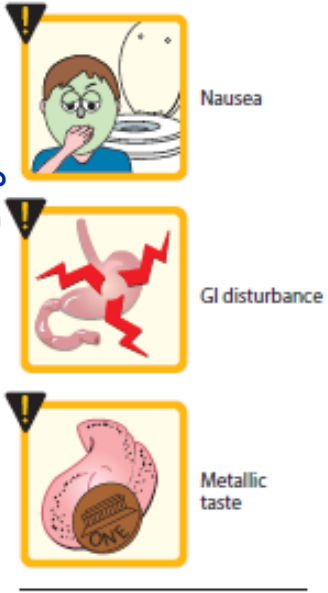


Figure 43.3
Adverse effects of *metronidazole*.