* DNA Synthesis inhibitors :
  - → folate antagonists
    - → sulfonamide .
    - → Trimethoprim .
    - → Trime thoprim – sulfamethoxazole mixtures .
  - → Quinolones .

* جسم البكتيريا	جسم الانسان
folic acid يصنع الـ ذاتياً	لا يصنع الـ folic acid يعتمد في الحصول عليه على مصادر خارجيه مثل السبانخ

. Dihydropteroate synthose ① → Dihydrofolic acid ② (dihydrofolate reductase) → Tetrahydrofolic acid → purines → DNA

PABA

* sulfonamide → inhibit step ① → Dihydropteroate synthase
* Trimethoprim → inhibit step ② → dihydrofolate reductase
* sulfonamide → have similas structure to (PABA)
* sulfonamide → يأثر على البكتيريا فقط بدلنه موجوده في step ① جسم البكتيريا واغير موجوده في جسم الانسان (mammals)

* PABA → Para-amino benzoic acid

* Sulfonamide: → bacteriostatic

classification

oral absorbed	oral non-absorbed	Topical
Sulfamethoxazol (oral)	Sulfasalazine (IV)	Sodium sulfacetamide mafenide acetate Silver Sulfadiazine (Topical)

→ oral sulfonamide basis on their half-lives :
- → short acting.
- → intermediate acting.
- → Long acting.

→ Distribution →
- → whole body fluids.
- → CSF.
- → placenta.
- → milk.

Sulfonamide (active) —acetylation at N4→ (inactive) : → this couse (crystalurea)

→ Elimination → by glomeruler filtration (kidney)

→ in renal failure → dosage should be reduced

oral-absorbed agents:

* sulfisoxazole + sulfamethoxazole : → short-to medium-acting.
  → for UTI (urinary tract infections)
* sulfadiazine + pryimethamine = The first line therapy toxoplasmosis.
* sulfadoxine + pryimethamine = antimabrial.

* Sulfonamide

→ Oral – nonabsorbable agents:

Sulfasalazine = sulfapyridine + 5-amino salicylic acid (5-ASA)
(in local intestinal flora)

Sulfasalazine → used for →
- ulcerative colitis.
- enteritis.
- inflamatory bowed disease

→ Topical agent:

Sodium sulfacetamide: →
- opthalmic or ointment
- for bacterial conjunctivitis
- adjunctive therapy for trachoma (eye infection)

mafenide acetate: →
- absorbed from burn sites
- inhibit carbonic anhydrase
- cause metabolic acidosis
- limits its usefulness

silver sulfadiazine: →
- less toxic sulfonamide
- better than mafenide acetate in treat wounds burn.

silver sulfadiazine > mafenide acetate
(in treat burn wounds)

* Side effect sulfonamide:

- crystalurea → reversed → hydration
  - alkalinizatio of the urin.
- Hypersensitivity:
  - rash
  - angioderma
  - steven-Johnson syndrome (SJS)
- Hematopoietic distrurbonces:
  1. granulocytopenia
  2. thrombocytopenia
  3. hemolytic reactions → بسبب ↓ glucose-6 phosphate dehydrogenase
- kernicterus:
  - in newborns
  - displaces bilirubin
  - Free bilirubin go to CNS and cause injury to brain

* sulfonamide
  - should nt given to newborns and infants → under 2 month (≥ 2 moth)
  - Shouldn't given to pregnant at term

Resistance to Sulfonamides

1. Some bacteria lack the enzymes required for folate synthesis from PABA and, like mammals, depend on exogenous sources of folate; therefore, they are not susceptible to sulfonamides.
2. Sulfonamide resistance may also occur as a result of mutations that:
   - (1) cause overproduction of PABA
   - (2) cause production of a folic acid-synthesizing enzyme that has low affinity for sulfonamides, or
   - (3) impair permeability to the sulfonamide.

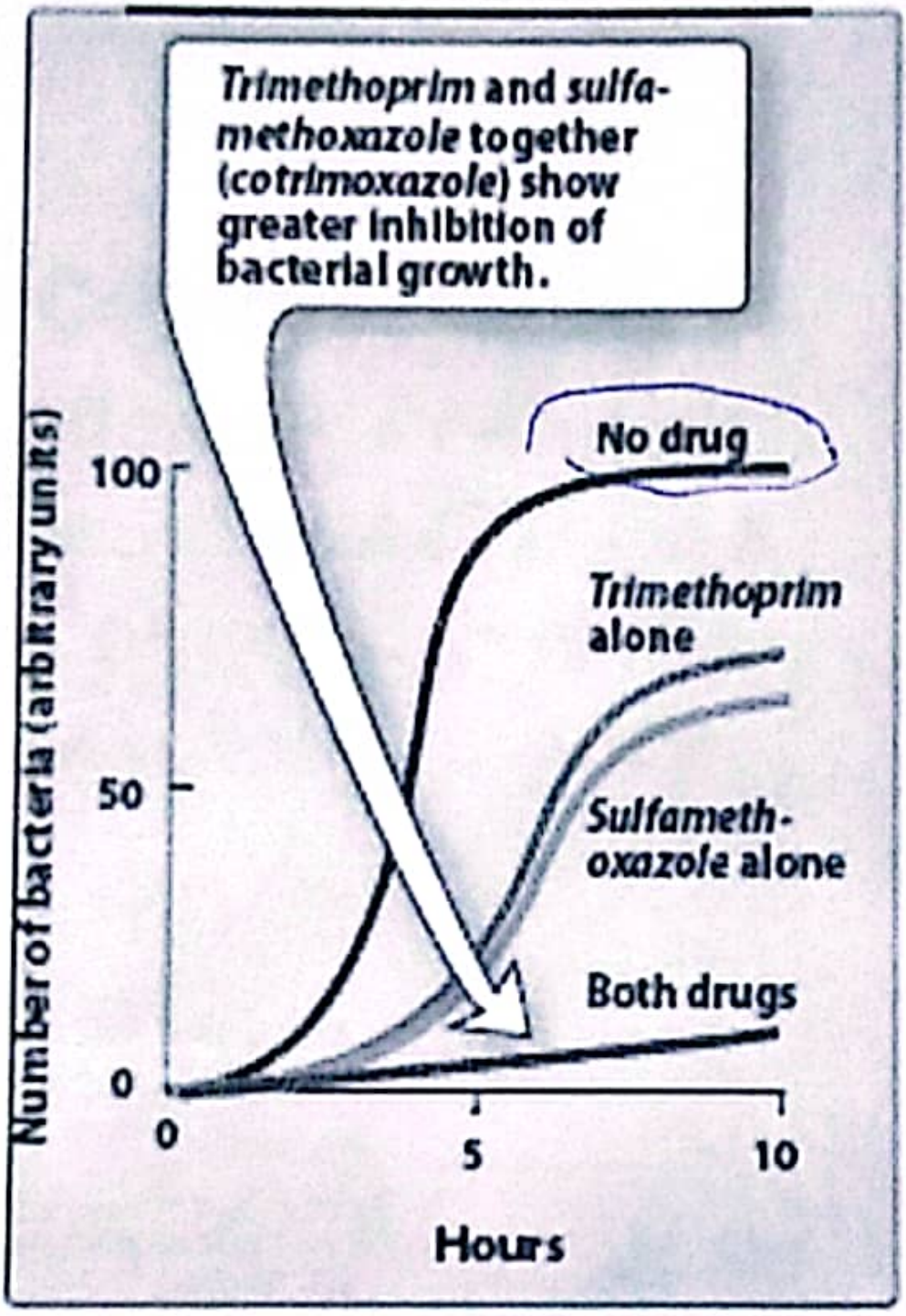


Figure 33.13
Synergism between *trimethoprim* and *sulfamethoxazole* inhibits growth of Escherichia coli.

* Trimethoprim: تأثيرها على البكتيريا اكثر من تأثيرها على الانسان
much less efficient inhibitor dihydrofolate reductase.
∴ بأثر على الـ mammalian cells (الانسان)

* Pyrimethamine: inhibit dihydrofolate reductase in protozoa

* Trimethoprim or Pyrimethamine + sulfonamide = marked enhancement (synergism)

* Trimethoprim → (oral).
* Trimethoprim + sulfamethoxazole ⇒ (IV) + (oral).
* which drug it is more active antibacterial in prostatic fluid and vaginal fluid than other drugs? (Trimethoprim)

* Trimethoprim → alone → for UTI
→ for prostatitis

* Fluoroquinolones is better than Trimethoprim → for prostatitis
Fluoroquinolones > Trimethoprim in treat bacteria prostatitis

* pryimethoamine + sulfonamide → For → toxoplasmosis.
→ antimalaria.

* Trimethoprim + sulfamethoxazole :
  - → co trim oxazole
  - → for wide variety infections
  - → for P.j.pneumonia (infections complication AIDS)
  - → are the most effective therapy:
    - → shigellosis
    - → salmonella
    - → UTI
    - → prostatitis

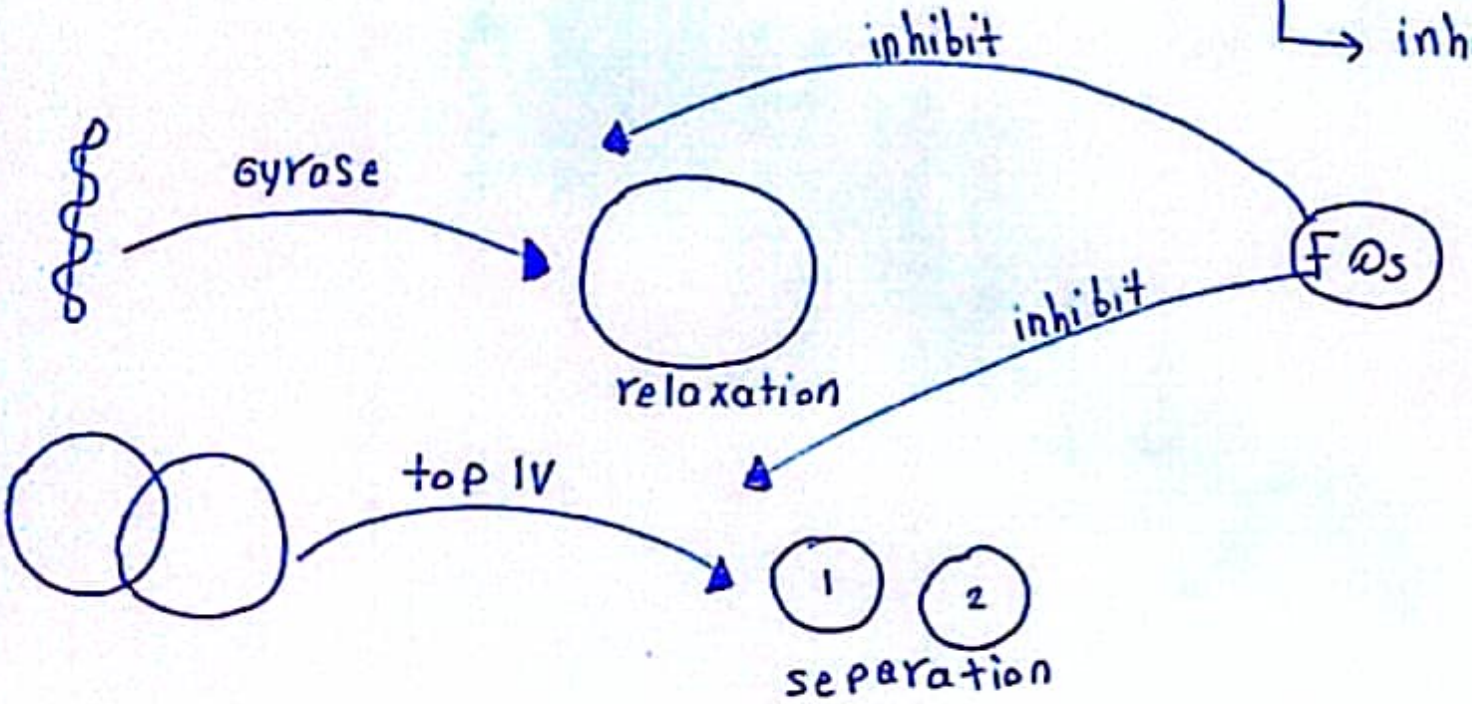
* Trimethoprim → S/E → similar to folic acid difficiency :
  - → Anemia .
  - → leukopenia .
  - → granulocytopenia .

* Fluoroquinolones(FQ) : → broad spectrum

→ MoA : → by passive diffusion through porins in outer cell membran → enter the bacterium.

→ inhibit DNA → inhibit DNA gyrase(top II).

→ inhibit (top IV).



FQs → inhibit DNA gyrase → prevents relaxation → Which required * transcription+replication

→ inhibit top IV → separation DNA into → daughter cell during cell division

FQs

- originally → (G-ve) aerobic
- newer
  - (G-ve)
  - (G+ve)
- classified into (4) generation → based on targets
- First generation :
  - non fluorinated quinolone.
  - Ex → nalidixic acid.
  - narrow → (G-ve) aerobic
  - for UTI
  - poor orall absorbed + short half live → لونها نادرا ما بوصفوها للمرضى
- Second generation :
  - Ex
    - ciprofloxacin
    - Norfloxacin
  - Excellant → (G-ve)
  - good – moderate
    - G+ve
    - Atypical bacteria
- Thired gereration :
  - Ex → Levofloxacin
  - (G-ve) + (G+ve)
- 4th generation :
  - Ex
    - moxifloxacin
    - (G-ve) + (G+ve) + anaerobic

*Ciprofloxacin: → used for

- → infection by G-ve bacilli.
- → uncomplication and complication UTI.
- → Traveler's diarrhea. → but to used for prophylaxis except in certain cases.
- → is the most potent (F ∅) for → P. aeruginosa infection.
- → for psedomonal infections with cystic fibrosis.
- → typhoid fever
  - → caused by (Salmonella typhi).
  - → symptom
    - → Fever.
    - → chills.
    - → Rose spots (بقع وردية).
- → Anthrax : الجمرة الخبيثة
  - → (G+ve)
  - → biological weapon يعتبر سلاح بيولوجي
  - → sympton on اعراض على
    - → GI
    - → cutaneous (الجلد)
    - → pulmonary

* what is drug choice for prevention and treatment Anthrax: (ciprofloxacin)

* Norfloxacin :
  - poor orall absorbition + short half live → لهيك نادراً مابوصفوه للمريض
  - used for
    - uncomplication UTI.
    - prostatitis (better than trimethoprim)
      Norfloxacin > trimethoprim
    - traveler's diarrhea.

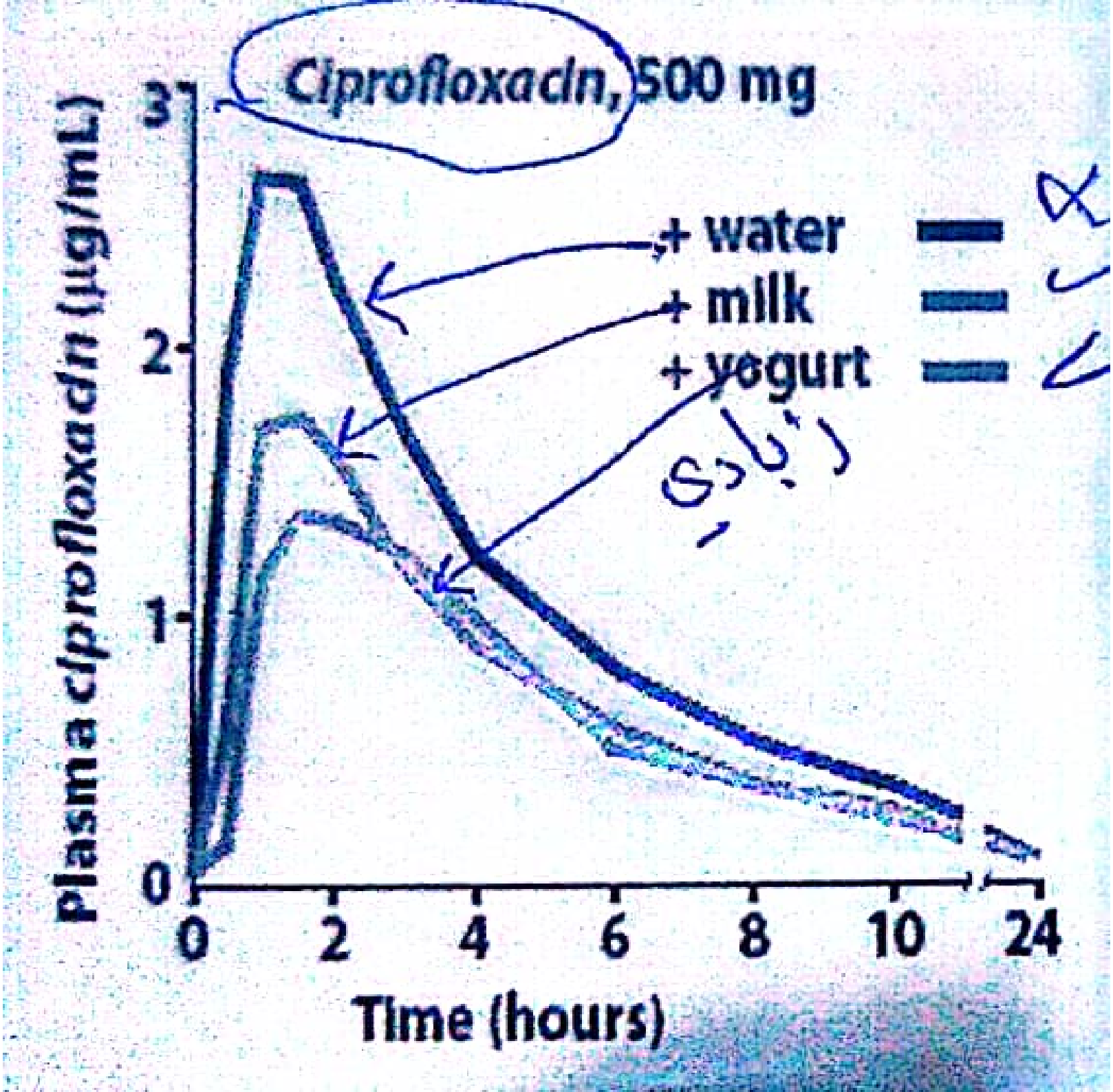
* Levofloxacin : → used for
  - protatitis
  - UTI
  - sexually transmitted diseases
  - Respiratory infection
    - Acute sinusitis
    - Acute exacerbation
    - Community and hospital acquired pneumonia
  - S. pneumoniae infection

* what are the drug that known as respiratory FDs & that effective in treat upper and lower respiratory tract infection : (Levofloxacin + moxifloxacin)

* Moxifloxacin :
  - active aganist
    - S. pneumoniae
    - anaerobes (except B. frogilis)
  - porr active
    - P. aeruginosa
    - B. frogilis
  - not elimenation by urin, → so, not used for treat (UTI)

* Metronidazole → active → B. frogilis
* fluoroquinolones + clindamycin → not active → B. Fragilis
* not all (F ⌀s) are used for UTI.
* (F⌀) → contraindication for pregnant womman.
* (F⌀)
  - (orall).
  - (IV) → ciprofloxacin / Levofloxacin
  - impaired by divalent and trivalent cation + antiacids + calcium
  - so, should taken
    - 2 hour → before
    - 4 hour → after

  → any products containing these.


Ciprofloxacin, 500 mg
+ water
+ milk
+ yogurt
Plasma ciprofloxacin (µg/mL)
3
2
1
0
0
2
4
6
8
10
24
Time (hours)

(FQs)

distribution well in tissue and body fluid

- bone
- Low CSF → Except → ofloxacin عالي الانتشار في csf
- lung
- urin → Except → moxifloxacin قليل الانتشار في الـ urin
- kidney
- prostatic tissue.

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.
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).