Nucleic synthesis inhibitors

Pharmacology 3

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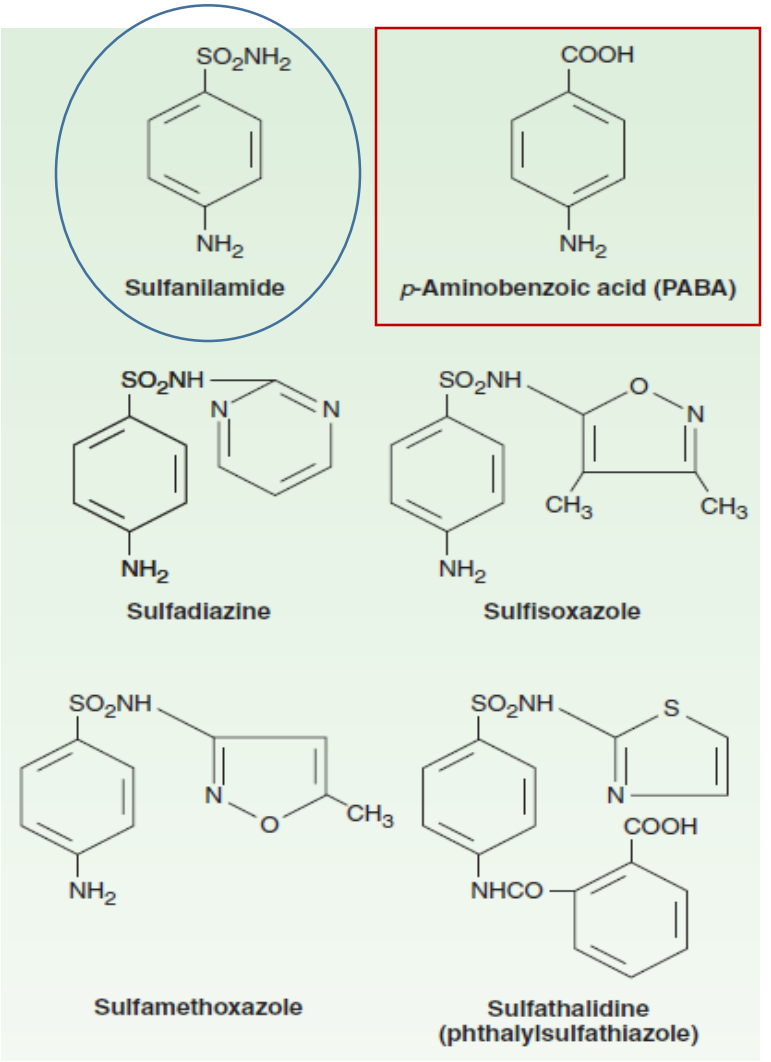
Inhibitors of NA synthesis

- Sulphonamides and trimethoprim
- Metronidazole
- Quinolones
- Rifampicin

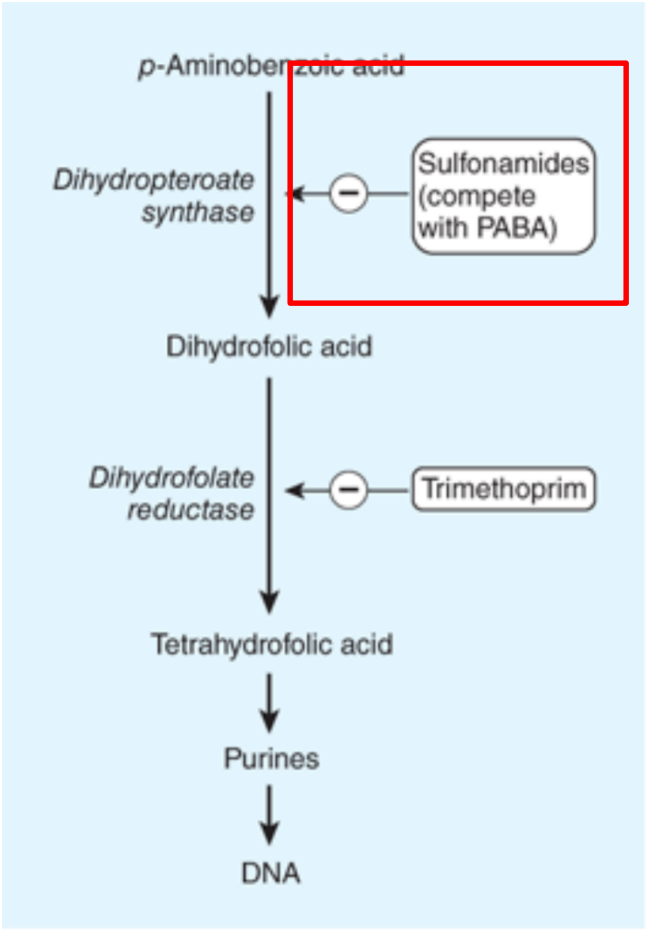
Sulfonamides

- Bacteria can not utilize external folic acid (FA) for DNA synthesis (human cell can)
- Bacteria must synthesize FA from PABA.
- Sulfonamides are structurally similar to *p*-aminobenzoic acid (PABA)



Sulfonamides Mechanism of Action

- Sulfonamide-susceptible organisms, unlike mammals, cannot use exogenous folate but must rely on their ability to synthesize folate from para-amino benzoic acid (PABA)
- This pathway is thus essential for production of purines and nucleic acid synthesis.
- As structural analogs of PABA, sulfonamides inhibit dihydropteroate synthase and folate production.
- The sulfa drugs, including cotrimoxazole, are bacteriostatic.



Source: Bertram G. Katzung, Anthony J. Trevor: Basic & Clinical Pharmacology,
www.accesspharmacy.com

Pharmacokinetics of Sulfonamides

- Sulfonamides can be divided into three major groups:

(1) oral, absorbable **(sulfamethoxazole)**

(2) oral, nonabsorbable **(Sulfasalazine)**

(3) topical **(Sodium sulfacetamide, mafenide acetate, silver sulfadiazine)**

- The oral, absorbable sulfonamides can be classified as short-, intermediate-, or long-acting on the basis of their half-lives

Drug	Half-Life	Oral Absorption
Sulfonamides		
Sulfacytine	Short	Prompt (peak levels in 1–4 hours)
Sulfisoxazole	Short (6 hours)	Prompt
Sulfamethizole	Short (9 hours)	Prompt
Sulfadiazine	Intermediate (10–17 hours)	Slow (peak levels in 4–8 hours)
Sulfamethoxazole	Intermediate (10–12 hours)	Slow
Sulfapyridine	Intermediate (17 hours)	Slow
Sulfadoxine	Long (7–9 days)	Intermediate
Pyrimidines		
Trimethoprim	Intermediate (11 hours)	Prompt
Pyrimethamine	Long (4–6 days)	Prompt

Clinical Uses

- **A. ORAL ABSORBABLE AGENTS**
- Sulfisoxazole and sulfamethoxazole are short- to medium-acting agents used almost exclusively to treat **urinary tract infections.**

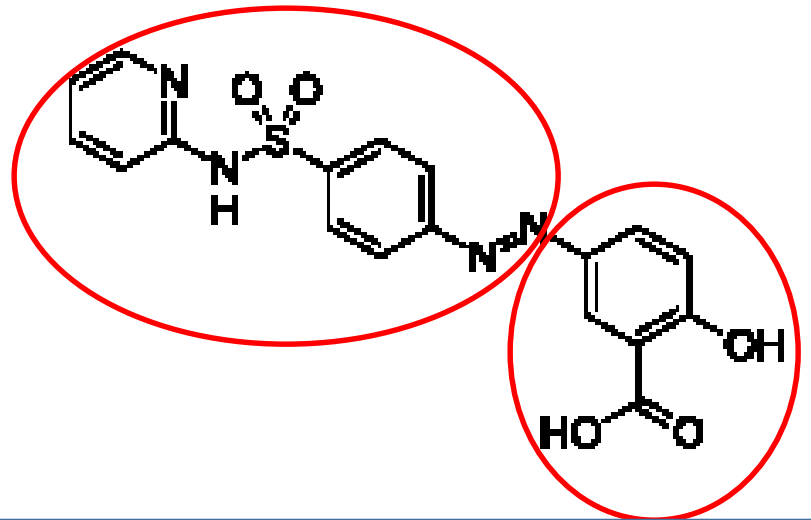
- Sulfadiazine in combination with pyrimethamine is first-line therapy for treatment of acute **toxoplasmosis.**

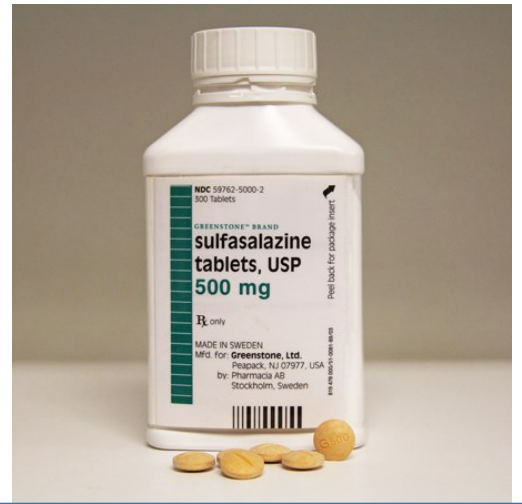
- Sulfadoxine in combination with pyrimethamine is used as an **antimalarial** drug.

Clinical Uses

- **B. ORAL NONABSORBABLE AGENTS**
- Sulfasalazine is an integrated sulfapyridine and 5-amino salicylic acid (5-ASA)

- It is widely used in ulcerative colitis, enteritis, and other inflammatory bowel disease (Local intestinal flora split sulfasalazine into sulfapyridine and 5-aminosalicylate, with the latter exerting the anti-inflammatory effect).





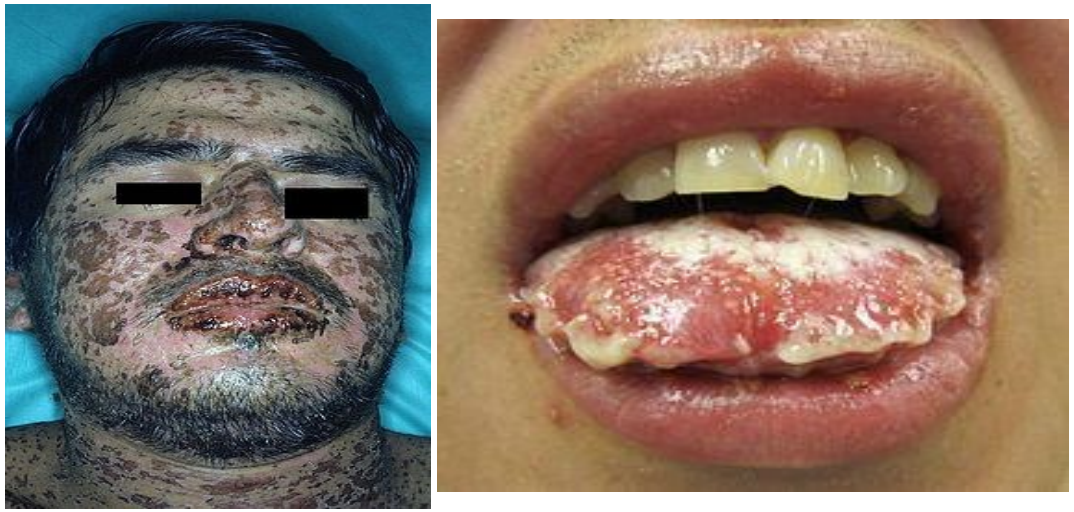
Clinical Uses

- **C. TOPICAL AGENTS**
- **Sodium sulfacetamide** ophthalmic solution or ointment is effective in the treatment of **bacterial conjunctivitis** and as adjunctive therapy for trachoma (eye infection caused by bacterium *Chlamydia trachomatis)*.

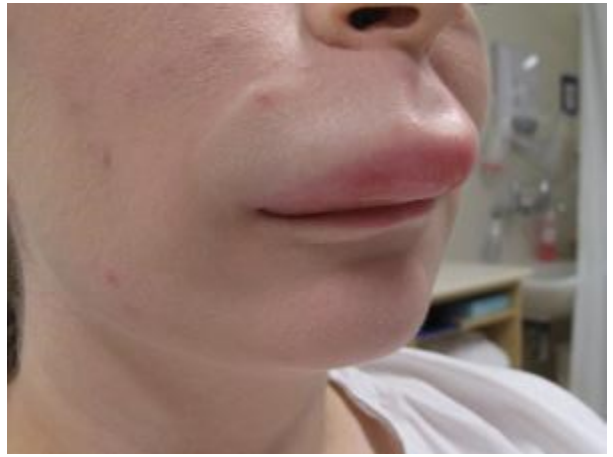
- Another sulfonamide, **mafenide acetate,** is used topically but can be absorbed from **burn** sites. The drug and its primary metabolite inhibit carbonic anhydrase and can cause metabolic acidosis, a side effect that limits its usefulness.
- **Silver sulfadiazine** is a less toxic topical sulfonamide and is preferred to mafenide for prevention of infection of **burn wounds**.

Side effects of sulfonamides

- Crystalurea due to precipitation (reversed by adequate hydration & alkalinization of the urine)
- Hypersensitivity:
  - rash
  - Angioderma
  - Steven-Johnson syndrome (SJS) which is caused by separation of the epidermis from the dermis



Steven-Johnson syndrome



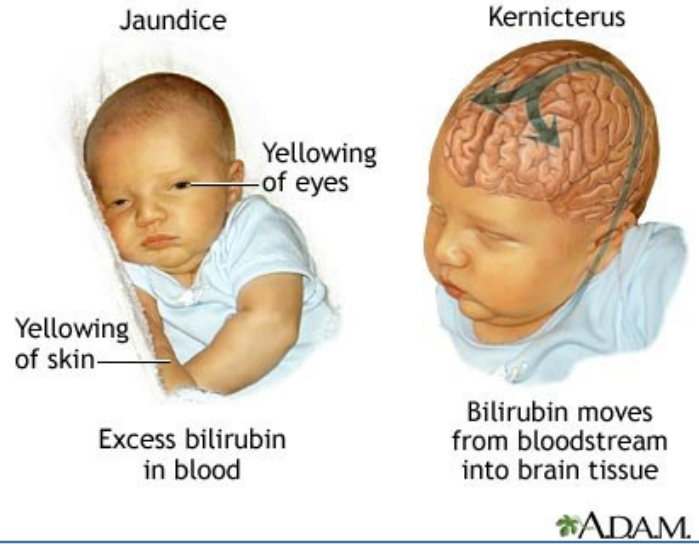
Angioderma

Side effects of sulfonamides

- **HEMATOPOIETIC DISTURBANCES**
  - Sulfonamides can cause granulocytopenia or thrombocytopenia.
  - Sulfonamides may provoke hemolytic reactions in patients with glucose-6-phosphate dehydrogenase deficiency.
- **Kernicterus**
  - Occurs in newborns
  - Sulfa drugs displaces bilirubin from serum albumin
  - Free bilirubin go to CNS and cause injury

  to brain
  - Shouldn't be given to newborns & infants

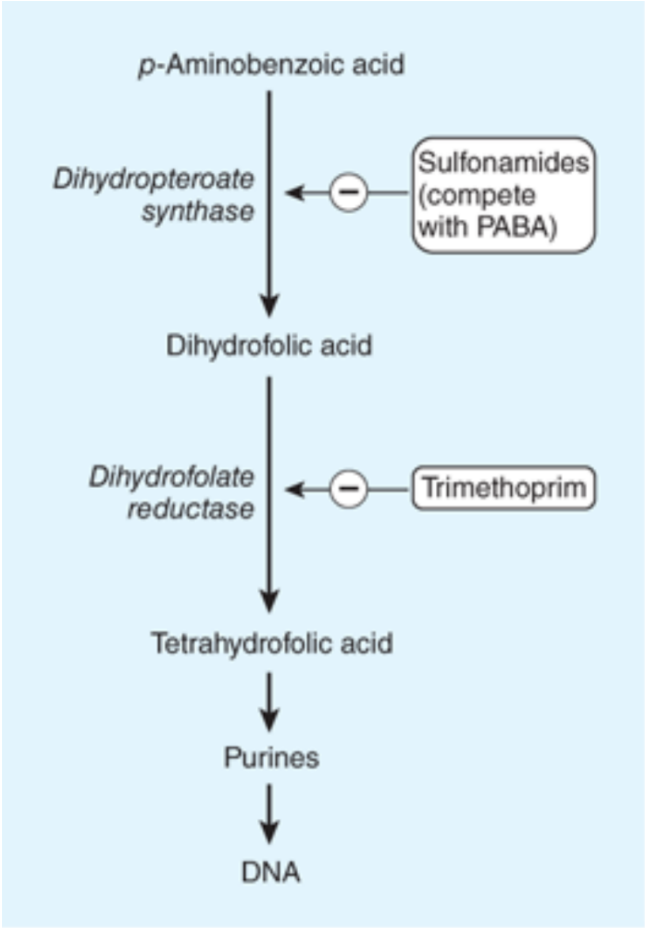
  (< 2 months) , pregnant at term



Trimethoprim & trimethoprim-sulfamethoxazole mixtures

Mechanism of Action

- **Trimethoprim**, selectively inhibits bacterial dihydrofolic acid reductase, which converts dihydrofolic acid to tetrahydrofolic acid, a step leading to the synthesis of purines and ultimately to DNA (much less efficient inhibitor of mammalian dihydrofolic acid reductase).
- **Pyrimethamine**, selectively inhibits dihydrofolic acid reductase of protozoa compared with that of mammalian cells.



Source: Bertram G. Katzung, Anthony J. Trevor: Basic & Clinical Pharm
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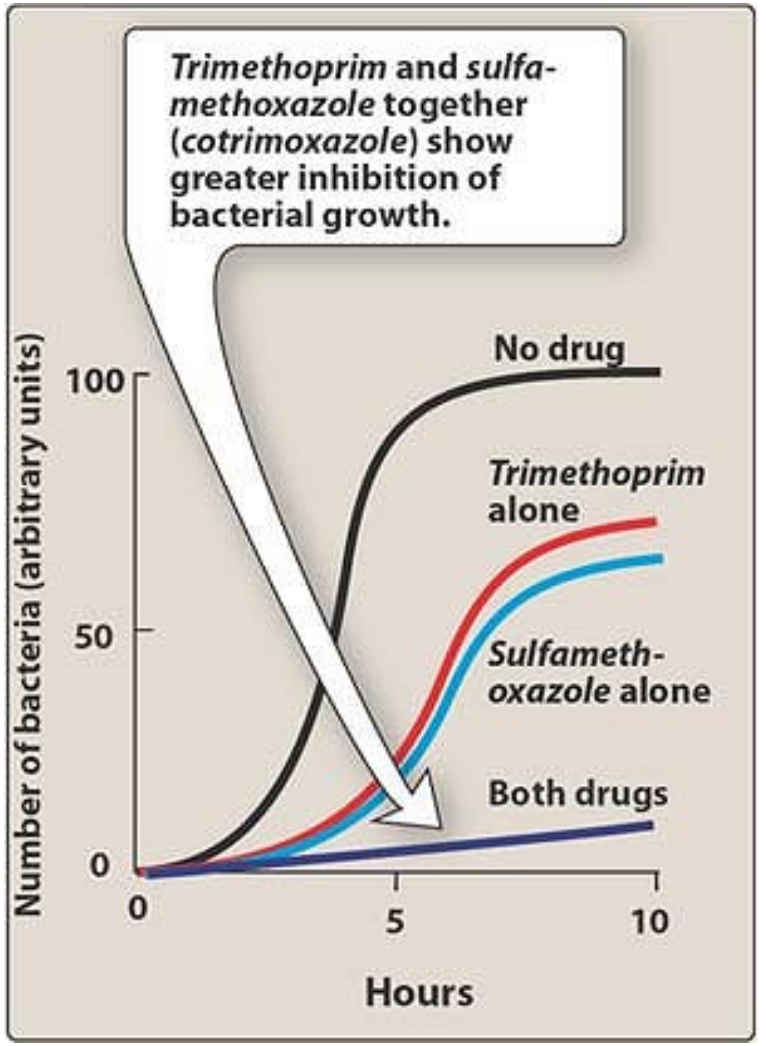
Cotrimoxazole

- Trimethoprim & trimethoprim-sulfamethoxazole mixtures
- Trimethoprim and sulfamethoxazole are rarely used alone today.
- Individually, these drugs (alone) are **bacteriostatic…..**

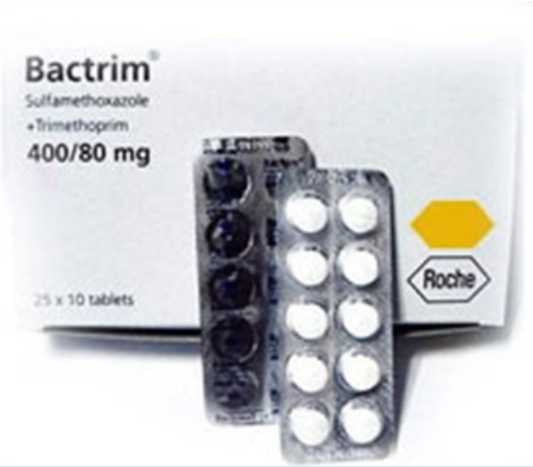
- This combination in co-trimoxazole provides a synergistic combination and **bactericidal** effect



- **Pharmacokinetics**

  - Trimethoprim is usually given orally, alone or in combination with sulfamethoxazole, which has a similar half-life. Trimethoprim-sulfamethoxazole can also be given intravenously.

  - Trimethoprim (a weak base) concentrates in prostatic fluid and in vaginal fluid, which are more acidic than plasma. Therefore, it has more antibacterial activity in prostatic and vaginal fluids than many other antimicrobial drugs.



- **Clinical Uses**

ORAL TRIMETHOPRIM

- Trimethoprim can be given alone in acute urinary tract infections and in the treatment of bacterial prostatitis (although fluoroquinolones are preferred).

ORAL TRIMETHOPRIM-SULFAMETHOXAZOLE (Cotrimoxazole)

A combination of trimethoprim-sulfamethoxazole is effective treatment for a wide variety of infections including *P jiroveci* pneumonia (This is a common opportunistic infection complicating AIDS. Cotrimoxazole is the most effective therapy), shigellosis, salmonella infections, urinary tract infections, prostatitis.

ORAL PYRIMETHAMINE WITH SULFONAMIDE

- Pyrimethamine and sulfadiazine are used in the treatment

of toxoplasmosis and falciparum malaria.

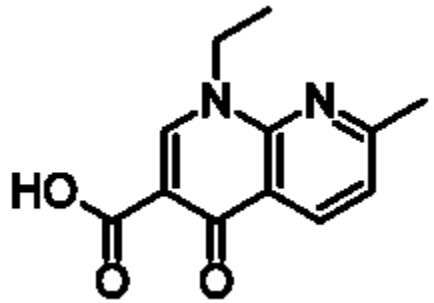
- **Side effects**

  - Similar to the effects of folic acid deficiency
  - Anemia, leukopenia, and granulocytopenia, especially in pregnant patients and those having very poor diets
  - Can be reversed by the simultaneous administration of folinic acid, which does not enter bacteria.

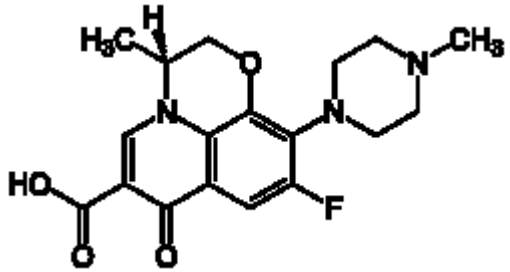
Drug Interactions

- On the basis of protien binding displacement → Potention of effect of(?)
- And on the basis of Inhibition of metabolism → Potentiation of effect of (?)

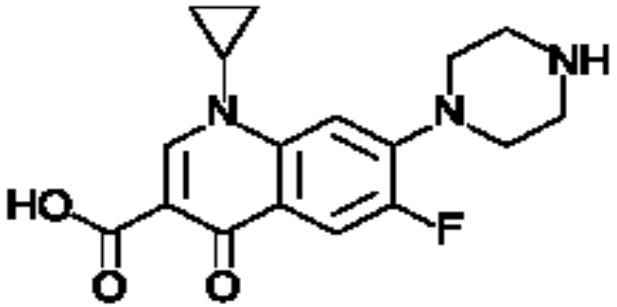
Quinolones



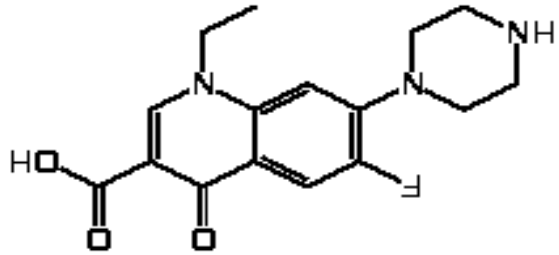
Nalidixic acid



Levofloxacin



Ciprofloxacin



Norfloxacin

The important quinolones are synthetic fluorinated analogs of nalidixic acid. Fluorinated quinolones: greater potency, broader spectrum of antimicrobial activity, better safety profile

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.

Antimicrobial activity

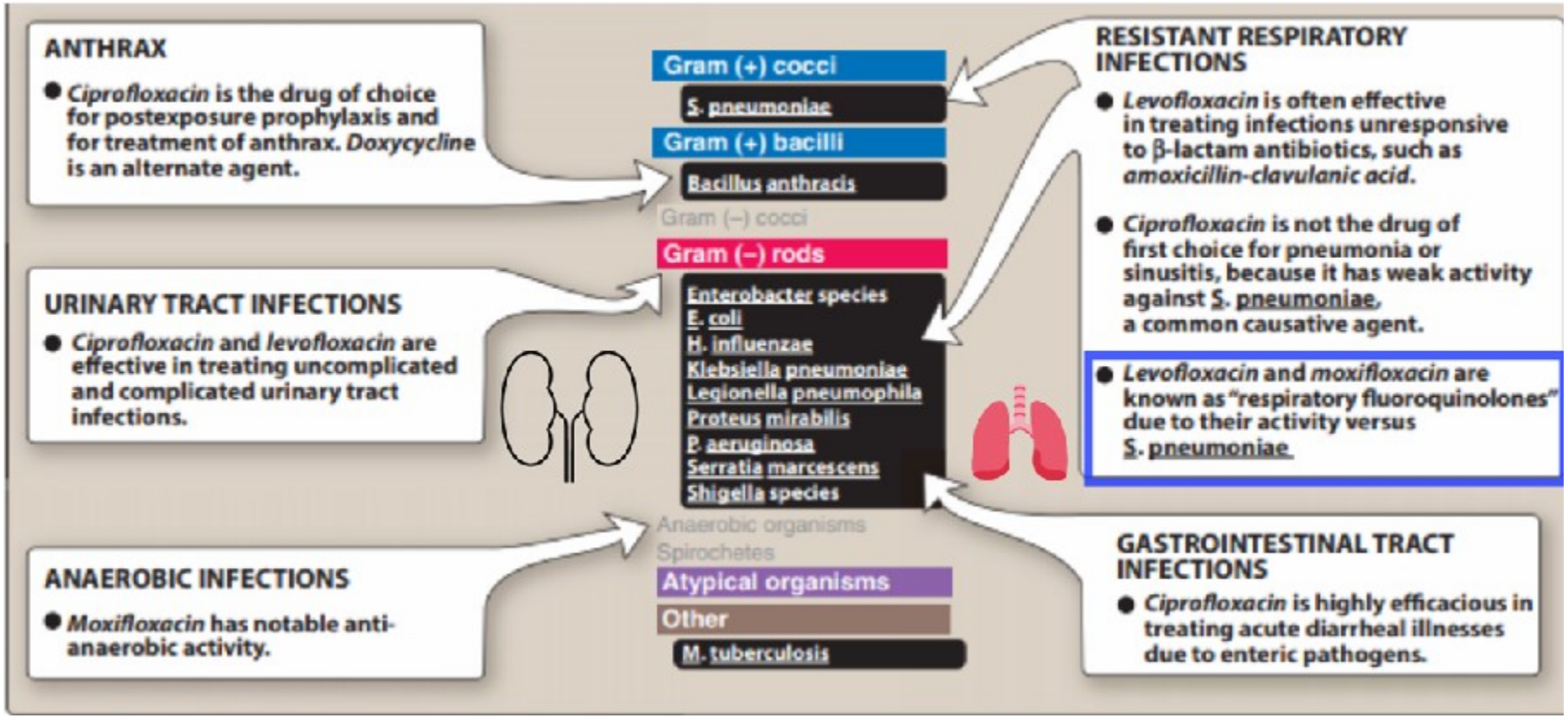
- Fluoroquinolones were originally developed because of their excellent activity against gram-negative aerobic bacteria; they had limited activity against gram-positive organisms.
- Several newer agents have improved activity against gram-positive cocci.
- This relative activity against gram-negative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

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

Typical therapeutic applications of fluoroquinolones.



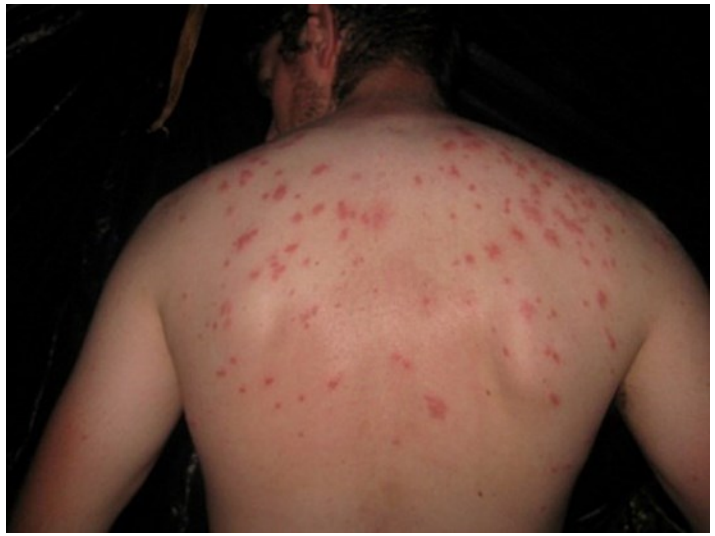
Moxifloxacin has poor activity against P. aeruginosa.
It does not concentrate in urine and is not indicated for the treatment of UTIs

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)

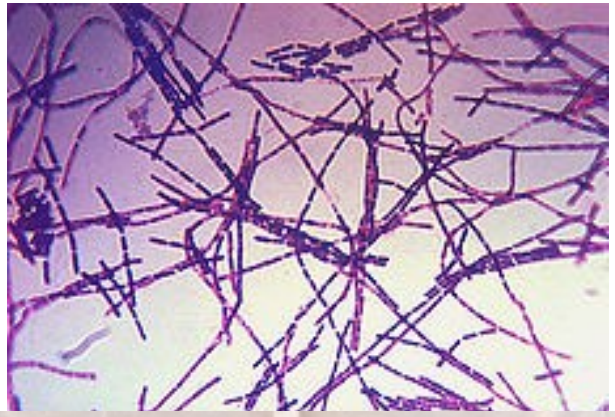
Clinical uses of ciprofloxacin (2nd generation)

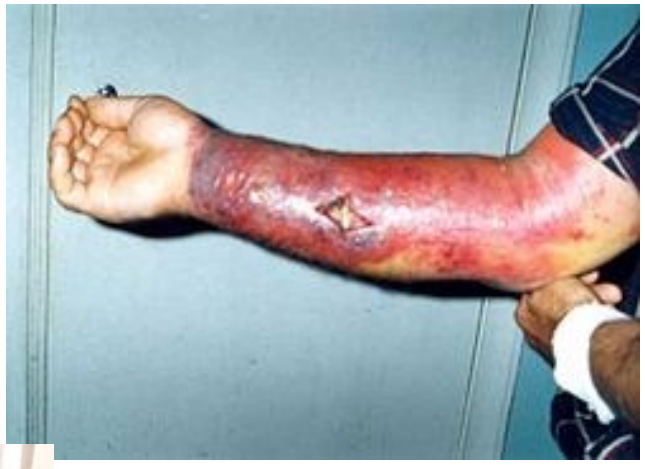
- Ciprofloxacin is useful for infections caused by G-ve bacilli.
- **Uncomplicated and complicated UTI** (E.coli is the most frequent cause)
- Treatment of **traveler's diarrhea** caused by E. coli (but not as prophylaxis except in certain cases)
- Ciprofloxacin is the most potent of the FQ against **P.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

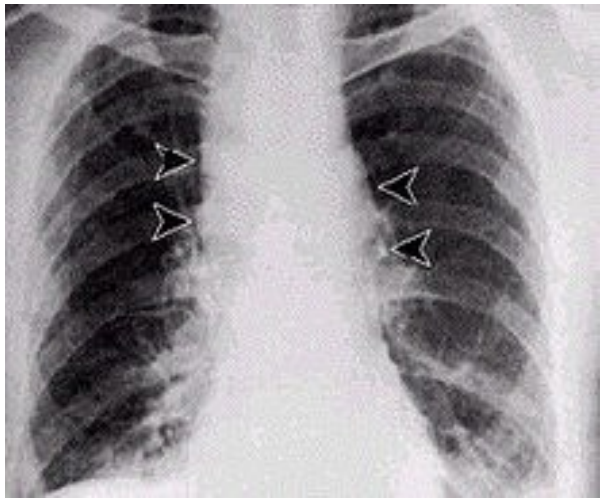


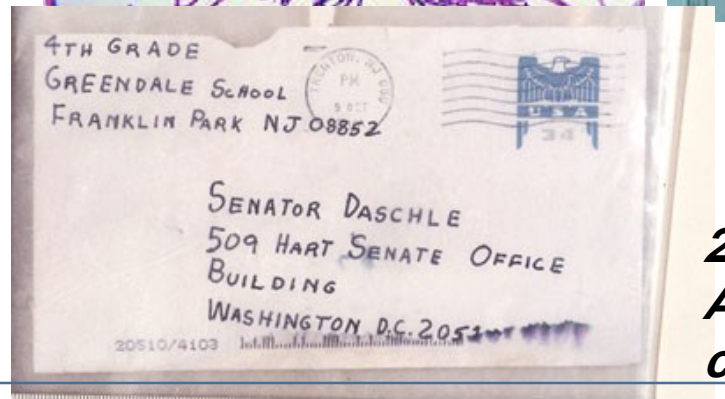
Clinical uses of ciprofloxacin (2nd generation)

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









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

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

Levofloxacin (3rd generation)

- Used in the treatment of prostatitis due to E. coli and sexually transmitted diseases, but not syphilis.
- **UTI**
- **Respiratory infections**
  - Acute sinusitis
  - Acute exacerbation of chronic bronchitis
  - 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.

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)

Pharmacokinetics of FQs

- After oral administration, the fluoroquinolones are well absorbed (bioavailability of 80–95%).
- 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.
- IV of ciprofloxacin & levoflxacin are available.

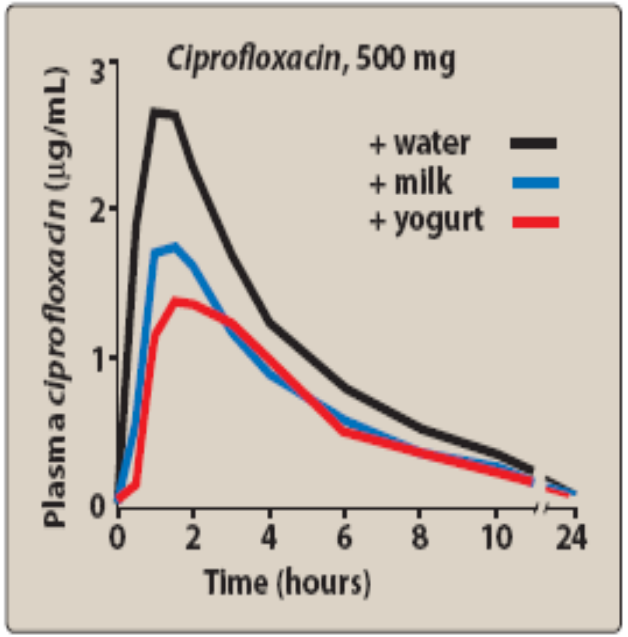


Figure 33.6
Effect of dietary calcium on the absorption of *ciprofloxacin*.

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)

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

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.

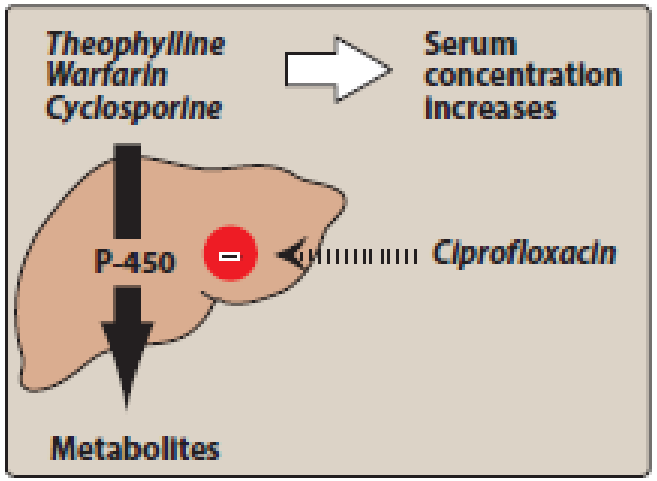
5. Connective tissue problems: may damage growing cartilage and cause an arthropathy (articular cartilage erosion) and tendonitis. Thus, these drugs are not routinely recommended for patients under 18 years of age.

- 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.

- 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

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

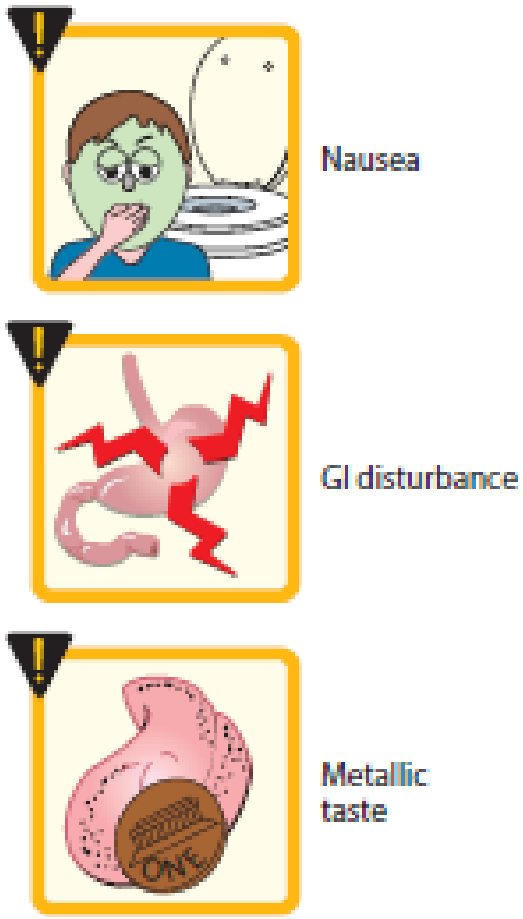


Figure 43.3
Adverse effects of *metronidazole*.

The End