Quinolones and Folic Acid Antagonists

Pharmacology and Toxicology

General Pharmacology

Second Year Medical Students

Tareq Saleh

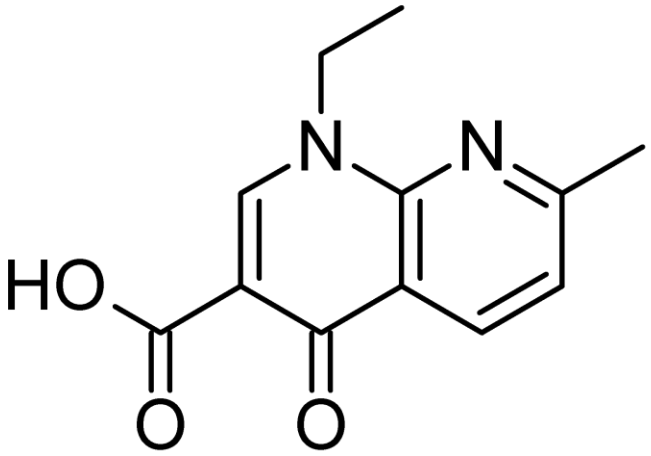
Faculty of Medicine

The Hashemite University

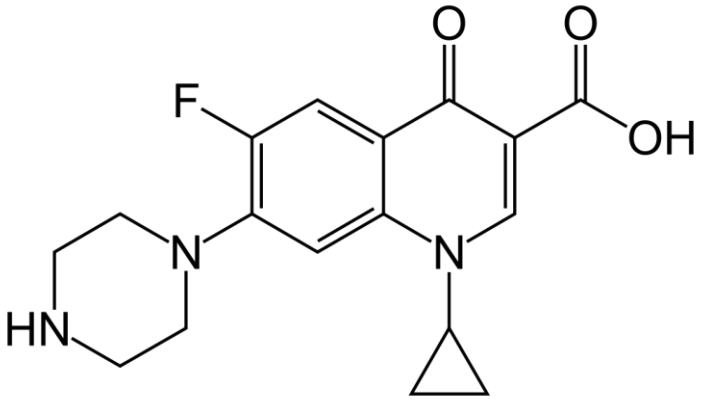
Textbook: Chapter 31 pp 400-412

Fluoroquinolones

Quinolones



Nalidixic acid

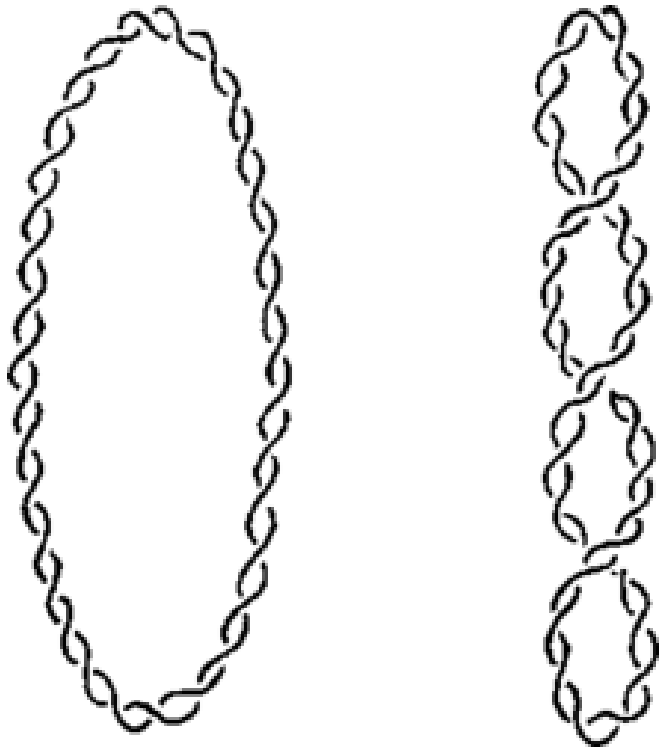


Ciprofloxacin

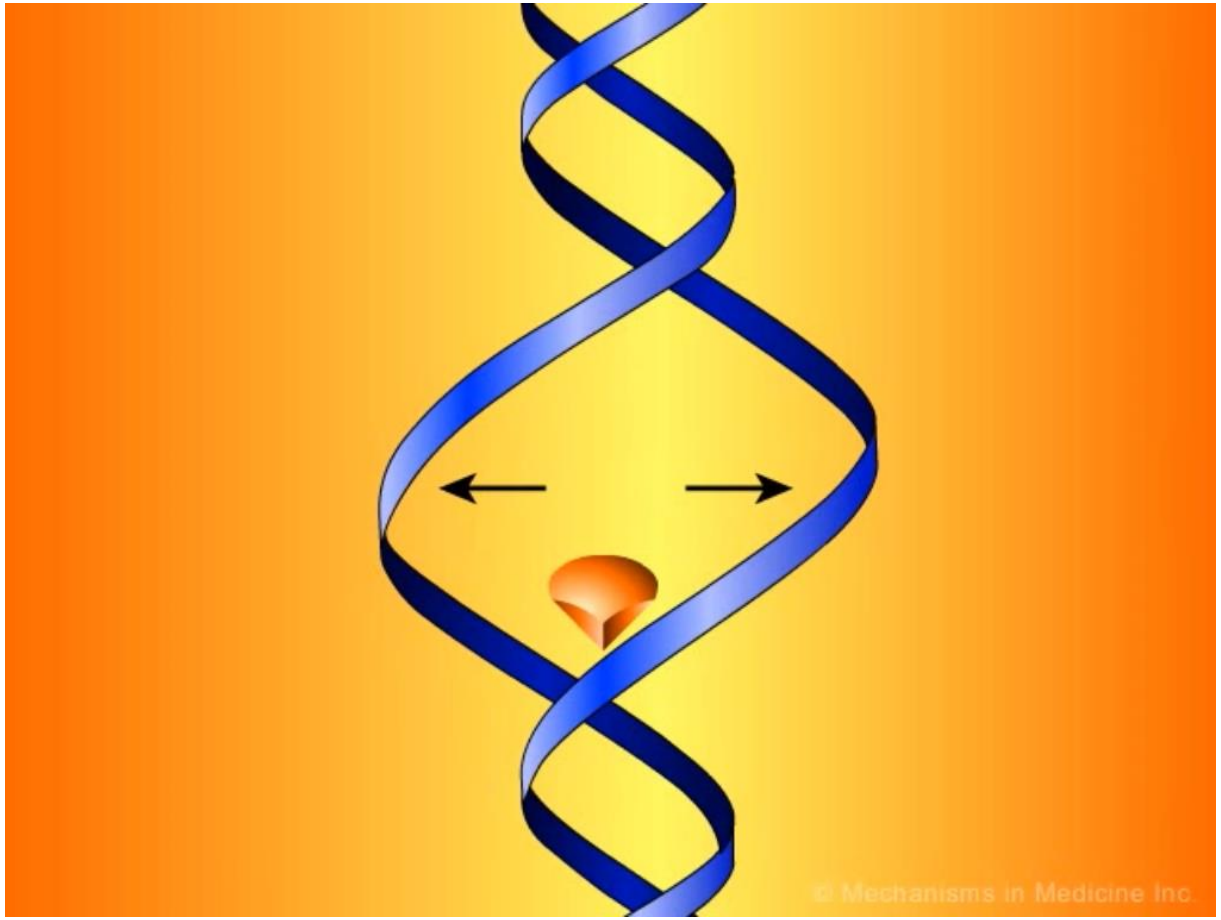
FLUOROQUINOLONES

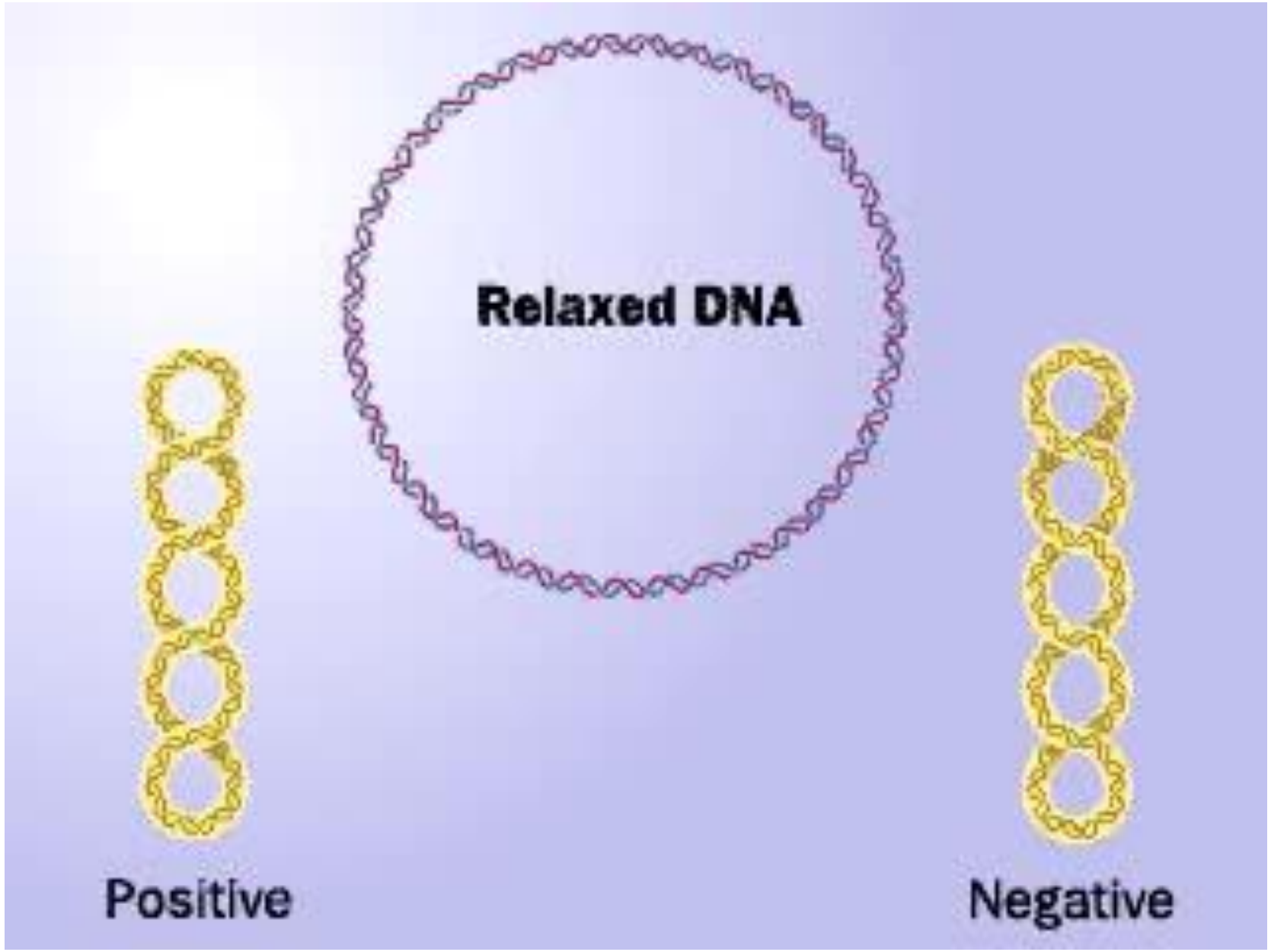
Ciprofloxacin CIPRO
Levofloxacin LEVAQUIN
Moxifloxacin AVELOX
Nalidixic acid
Norfloxacin NOROXIN
Ofloxacin

DNA Supercoiling

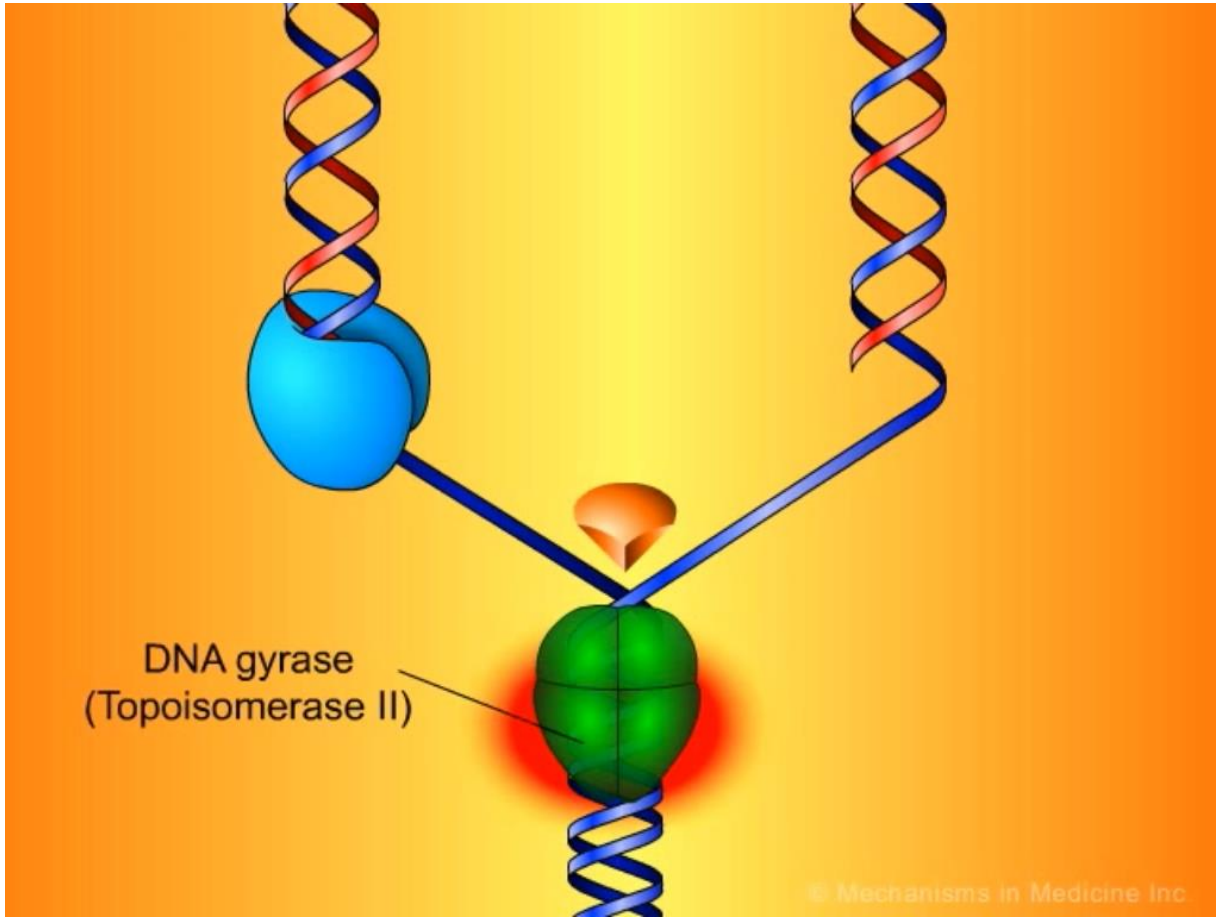


DNA Helicase

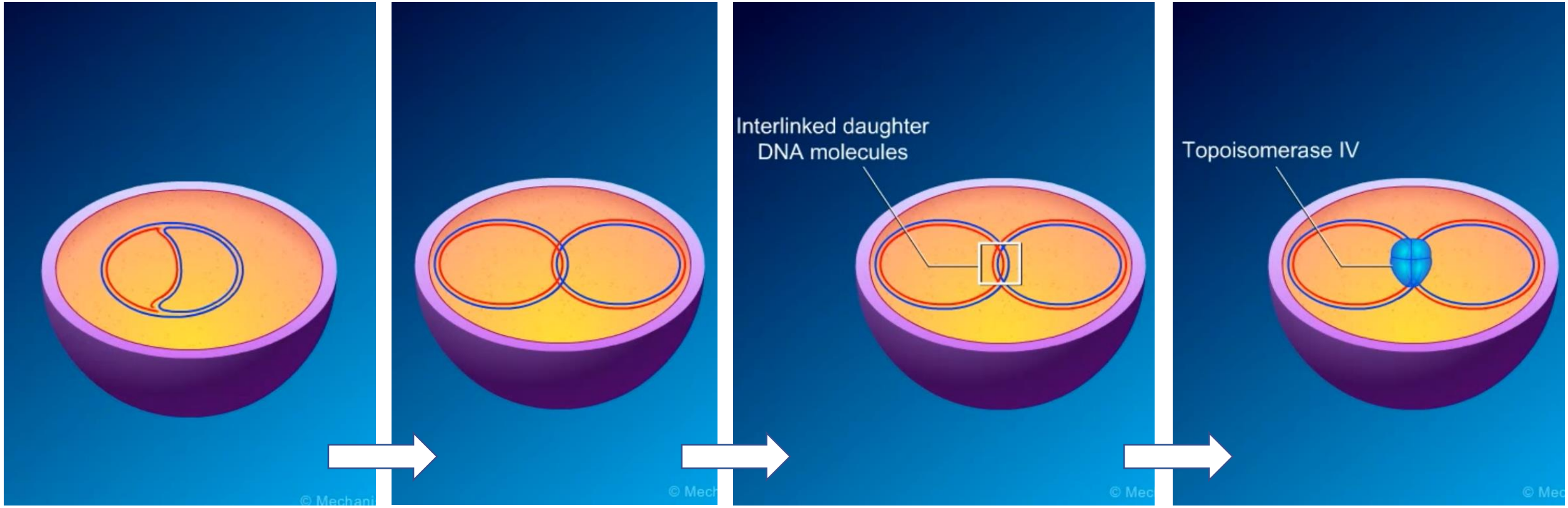




DNA Gyrase



Topoisomerase IV



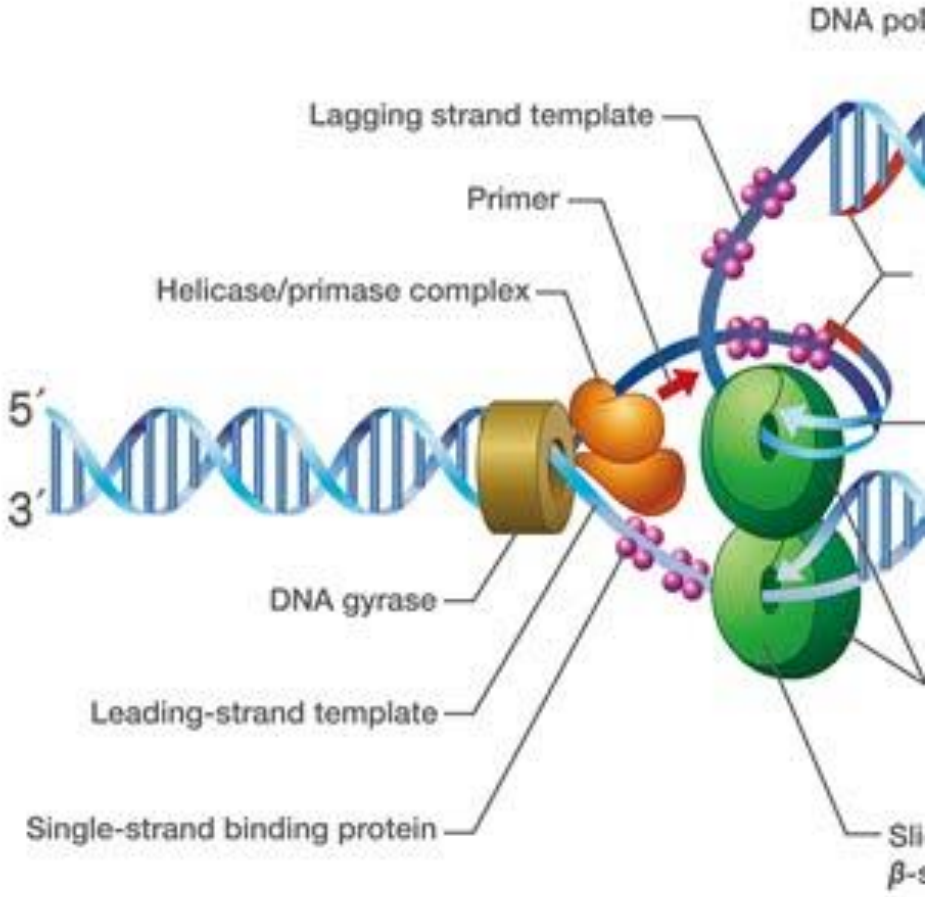
Quinolones

Mechanism of action

- Inhibit ligation step of bacterial DNA gyrase and bacterial topoisomerase IV

-Inhibition of gyrase: increases the number of permanent chromosomal breaks

-Inhibition of topo IV: interferes with the separation of newly replicated DNA



Quinolones

Mechanism of action

In gram-negative: inhibition of gyrase>topo IV

In gram-positive: inhibition of topo IV>gyrase

What does that mean?

Quinolones

Antibacterial spectrum

- Bactericidal
- Time-dependent killing
- Effective against gram-negative (including E.coli and Pseudomonas), atypical, gram-positive (strep), mycobacteria….
- Levofloxacin: excellent activity against *S. pneumoniae*

Quinolones

Antibacterial spectrum

- **First-generation (nonfluorinated): nalidixic acid**

-narrow-spectrum

- **Second-generation: ciprofloxacin and norfloxacin**

-gram-negative (pseudomonas, H.influenzae) and atypical

- **Third-generation: levofloxacin**

-gram-negative, atypical and gram-positive (including S. pneumoniae and MSSA)

- **Fourth-generation: moxifloxacin, Gemifloxacin, delafloxacin**

-enhanced gram-positive effects including staph and strep + coverage of gram-negative Enterobacteriaceae

-Homework: Which fourth-generation fluoroquinolone is effective against MRSA?

Examples of Clinically Useful Fluoroquinolones

Ciprofloxacin

- Effective against gram-negative including P. aeruginosa
- Clinical indications:

1. Gastroenteritis e.g., traveler's diarrhea
2. Typhoid fever
3. Anthrax (drug of choice)
4. Urinary tract infections

(high dose for pseudomonal infections)

Examples of Clinically Useful Fluoroquinolones

Levofloxacin

- Similar to cipro but also effective against gram-positive (strep not staph)
- Clinical indications:

First-line therapy for community acquired-pneumonia

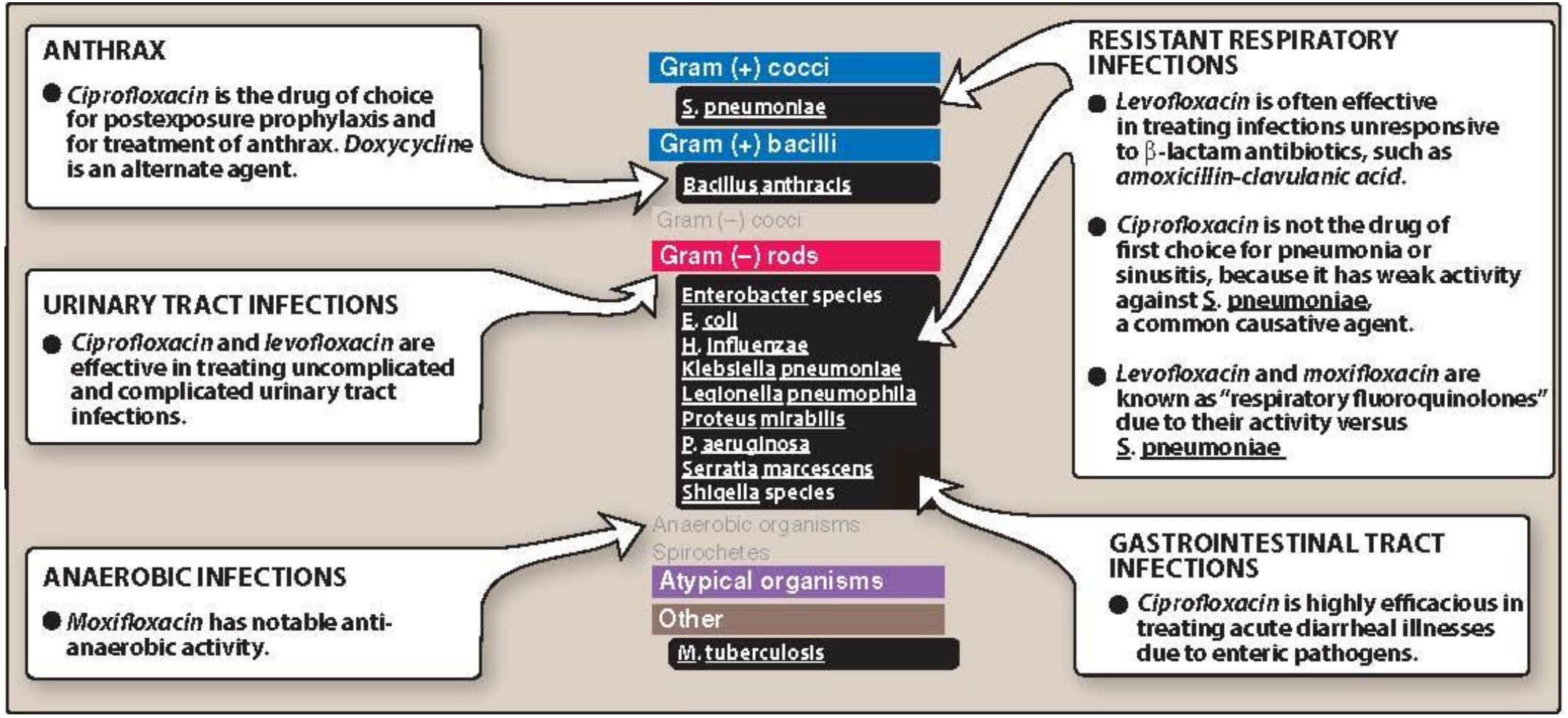
Examples of Clinically Useful Fluoroquinolones

Moxifloxacin

- Effective against gram-negative, S. pneumonia and mycobacterium
- Clinical indications:

1. For community-acquired but not nosocomial pneumonia (weak against pseudomonas)
2. Second-line for TB

Clinical Uses of Fluoroquinolones



Fluoroquinolones and UTIs

"Fluoroquinolones (eg, ofloxacin, ciprofloxacin, levofloxacin) are highly effective in UTIs, but these agents have a propensity for causing collateral damage and should be reserved for important uses other than acute uncomplicated cystitis. IDSA guidelines recommend that fluoroquinolones be used as second-line agents for acute uncomplicated cystitis and as first-line oral therapy for complicated cystitis".

International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

Fluoroquinolones

Mechanisms of resistance

-mainly chromosomal

- **Altered target:**

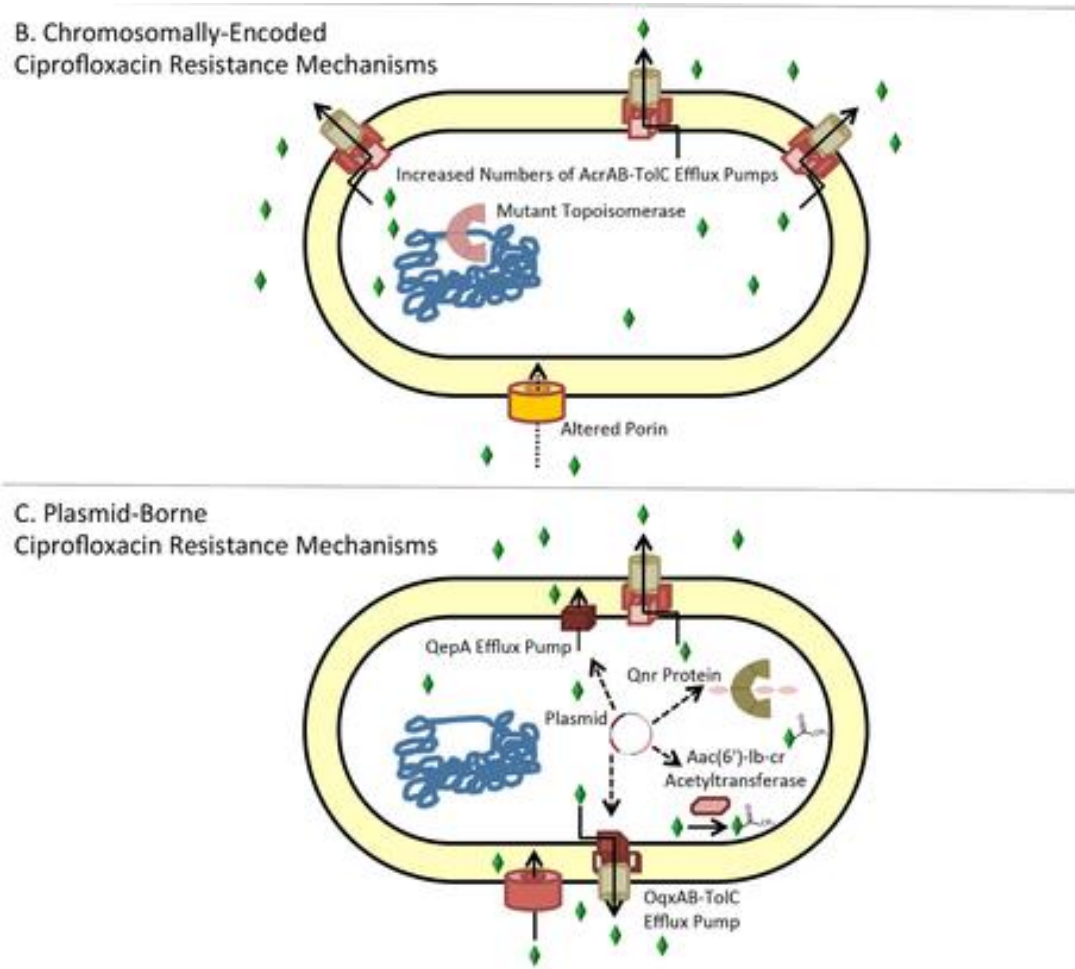
-mutations in *gyrA* or *parC*

- **Decreased accumulation**

-porin channels

-efflux pumps

- **Fluoroquinolone degradation**
- Cross-resistance



Fluoroquinolones

Pharmacokinetics

- **Absorption**

-mainly oral – IV/ophthalmic preps of cipro and levo

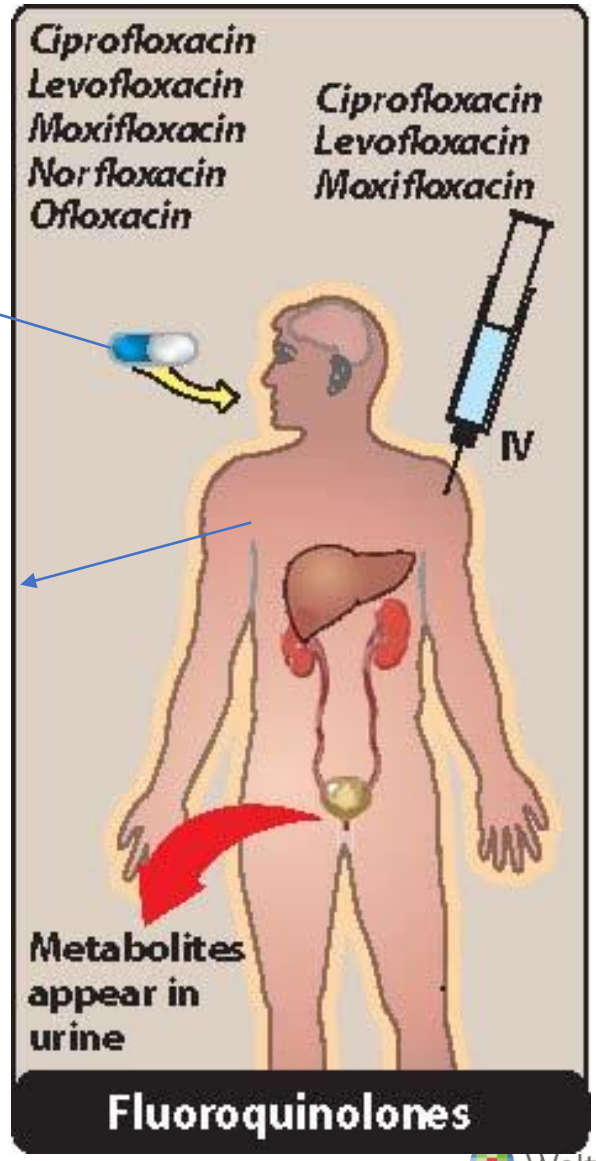
-food, Ca^{++}, Al^{+3} and Mg^{++} interfere with absorption

- **Distribution**

-very well distributed (high conc in bone, urine and lung)

-good CSF distribution

-concentrate in macrophages and neutrophils



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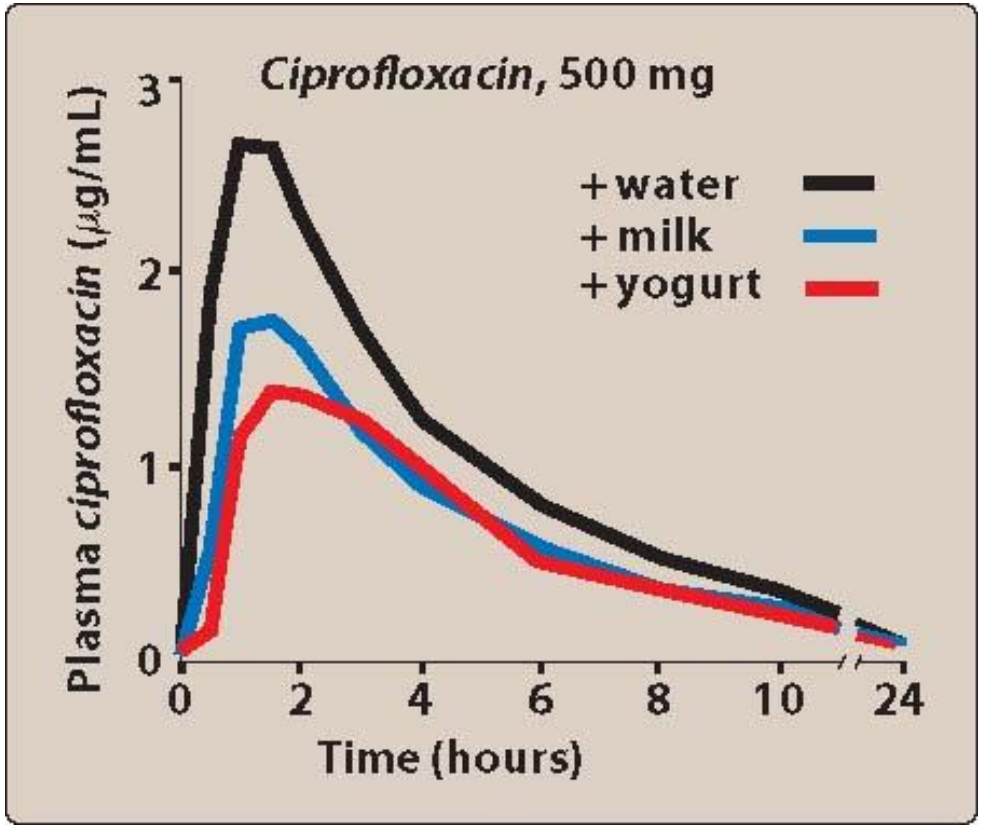


Fluoroquinolones

Pharmacokinetics

- **Elimination**

-most fluoroquinolones are excreted renally

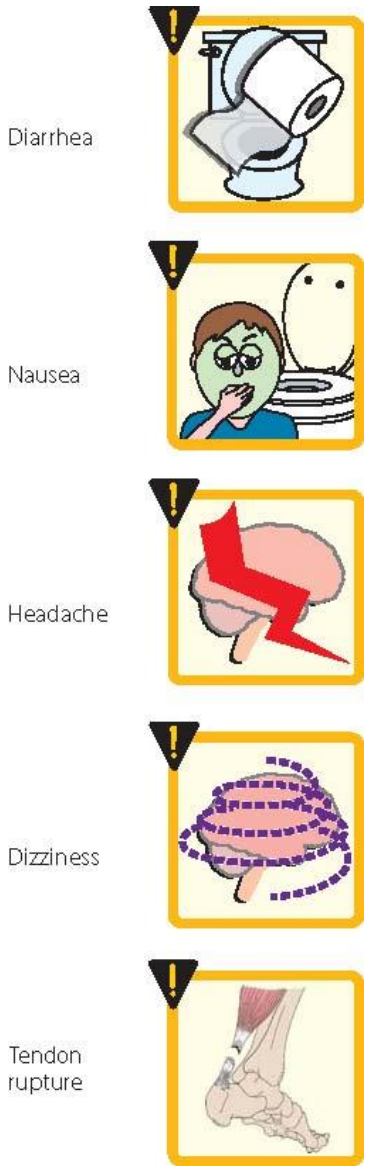
-Moxifloxacin is excreted by liver (can be used in patients with renal impairment)

Quinolones

Adverse effects

-generally well-tolerated

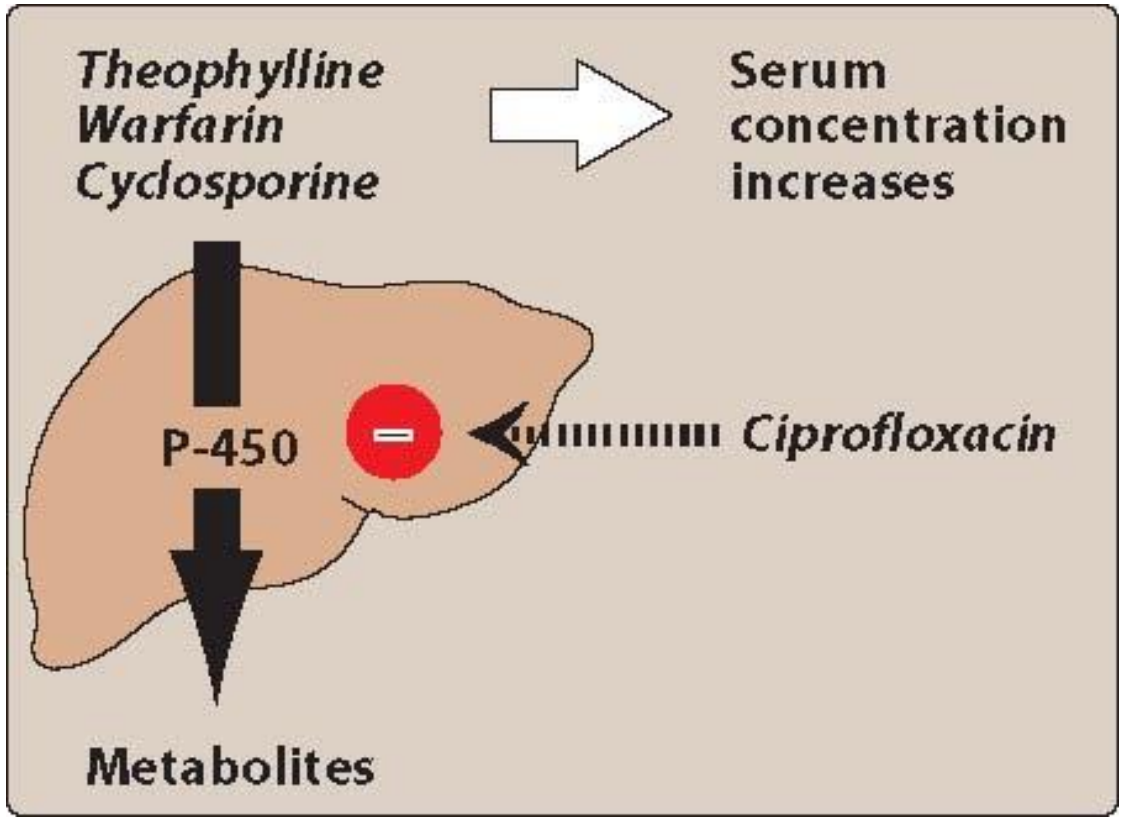
- **N/V/D**
- **Headache and dizziness**
- **Peripheral neuropathy and glucose dysregulation**
- **Phototoxicity**
- **(boxed warning) Articular cartilage erosion, tendinitis, tendon rupture**
- **QT prolongation**



Quinolones

Drug-drug interaction

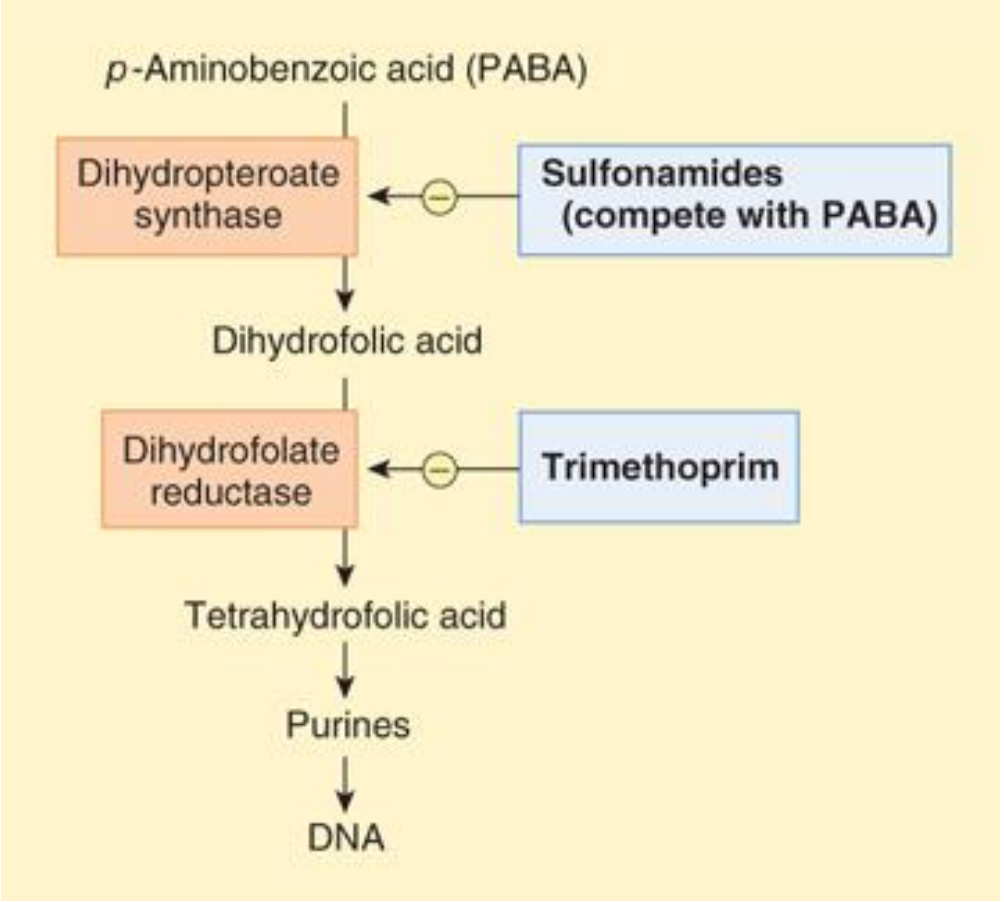
- Cipro can inhibit metabolism of theophylline, others
- Quinolones can raise serum warfarin



Folate Antagonists

Folic Acid Antagonists

- Purine and pyrimidine synthesis requires folate-derived cofactors
- Folic acid is necessary for DNA replication and cellular growth
- Many bacteria are impermeable to folate →rely on de novo synthesis
- Folic acid must be converted into tetrahydrofolate

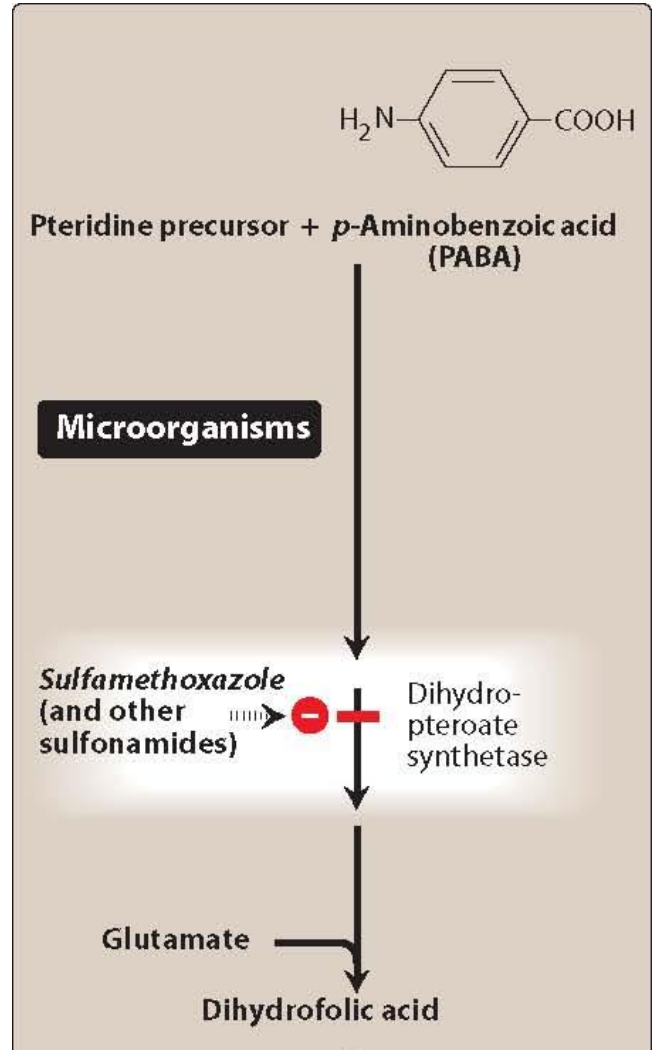


Sulfonamides

Sulfonamides

Mechanism of action:

- Sulfonamides are synthetic analogues of PABA
- PABA is used to synthesize dihydrofolate
- Sulfonamides inhibit *dihydropteroate synthetase*
- Bacteriostatic



Sulfonamides

Antibacterial spectrum

- Effective against Enterobacteriaceae causing UTIs
- Effective against H. influenza, streptococcus, staphylococcus spp.

Mechanisms of resistance

- Altered dihydropteroate synthetase
- Decreased cellular permeability
- Enhanced production of PABA

INHIBITORS OF FOLATE SYNTHESIS	
Mafenide	SULFAMYLON
Silver sulfadiazine	SILVADENE
Sulfasalazine	AZULFIDINE

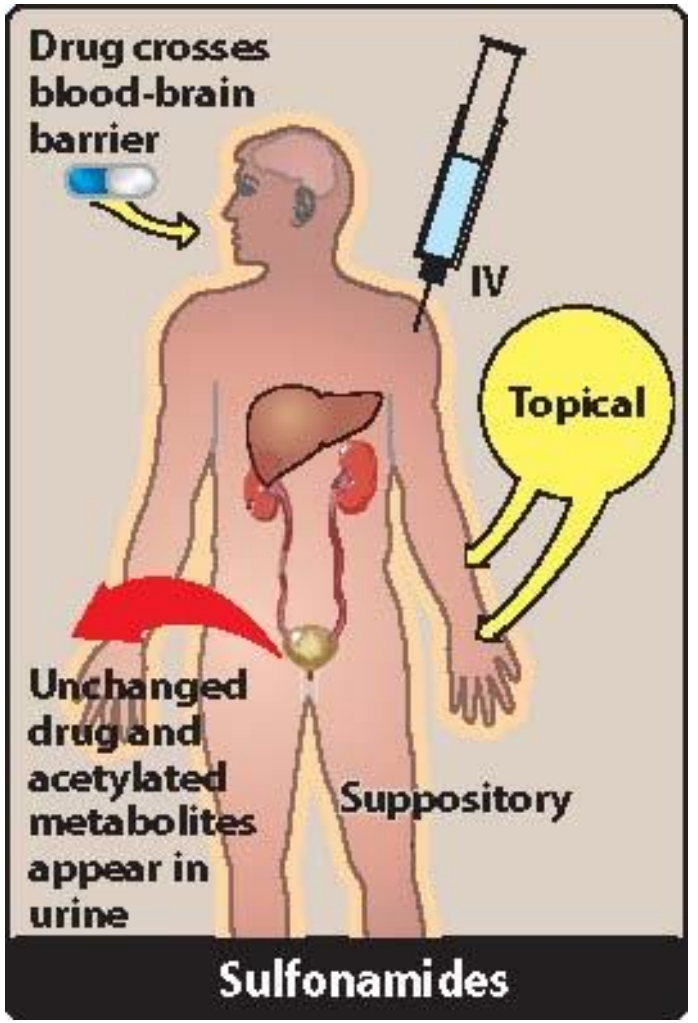
Sulfonamides

Pharmacokinetics

- **Absorption**

-oral: well-absorbed (except sulfasalazine)

-how can you use sulfasalazine?

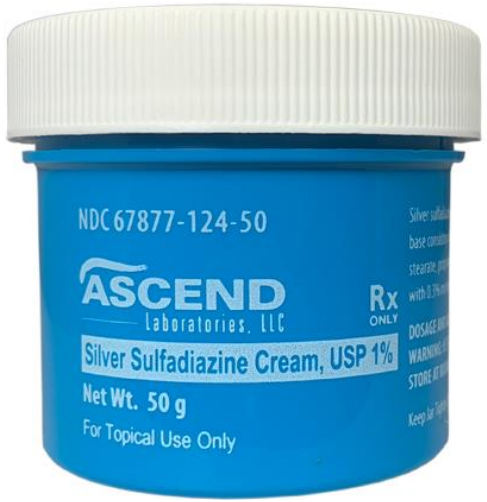


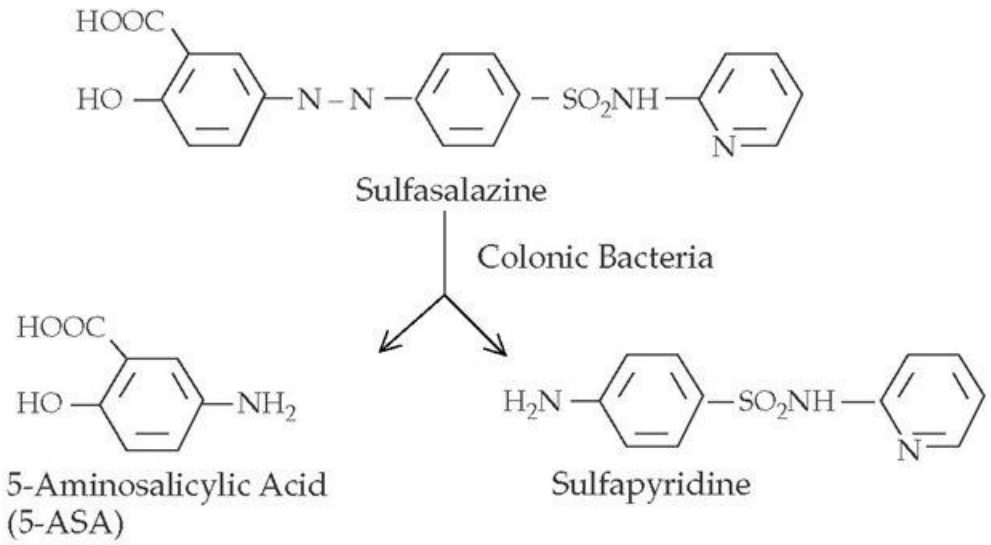
Special Uses

TOXOPLASMOSIS RX

First Line

- Pyrimethamine (200mg-L/75C) + Sulfadiazine(6-8g/d -4d/d) till improve CD4 count
- Pyrimethamine + Clindamycine





Sulfonamides

Pharmacokinetics

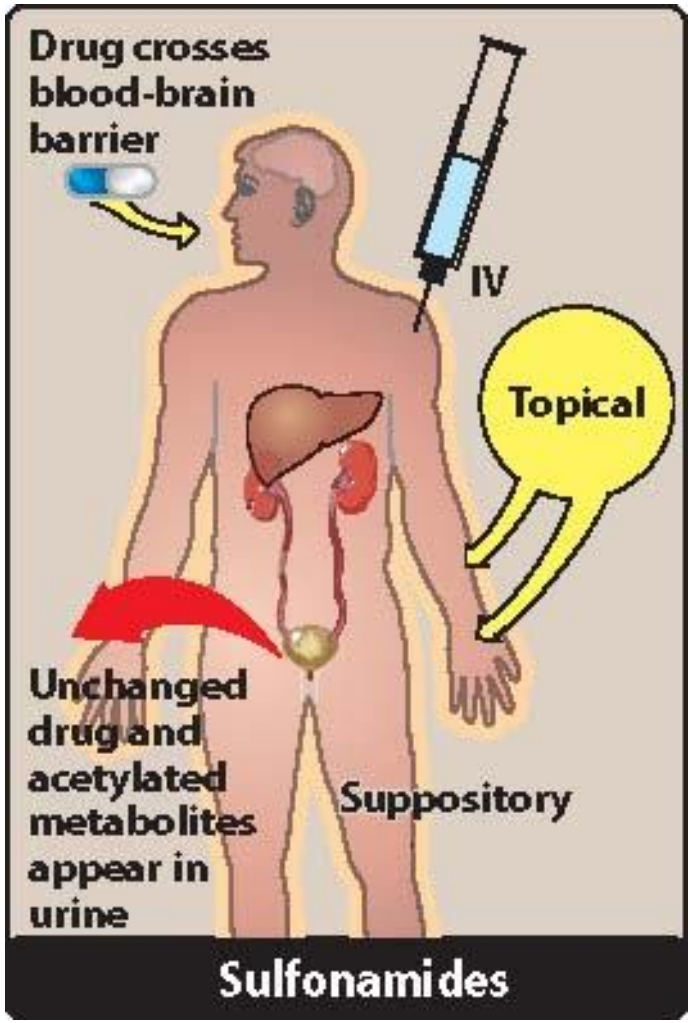
- **Distribution**

-highly-bound to serum albumin

-distribute well through body fluids including CSF

-cross placenta

-eliminated in breast milk



Sulfonamides

Pharmacokinetics

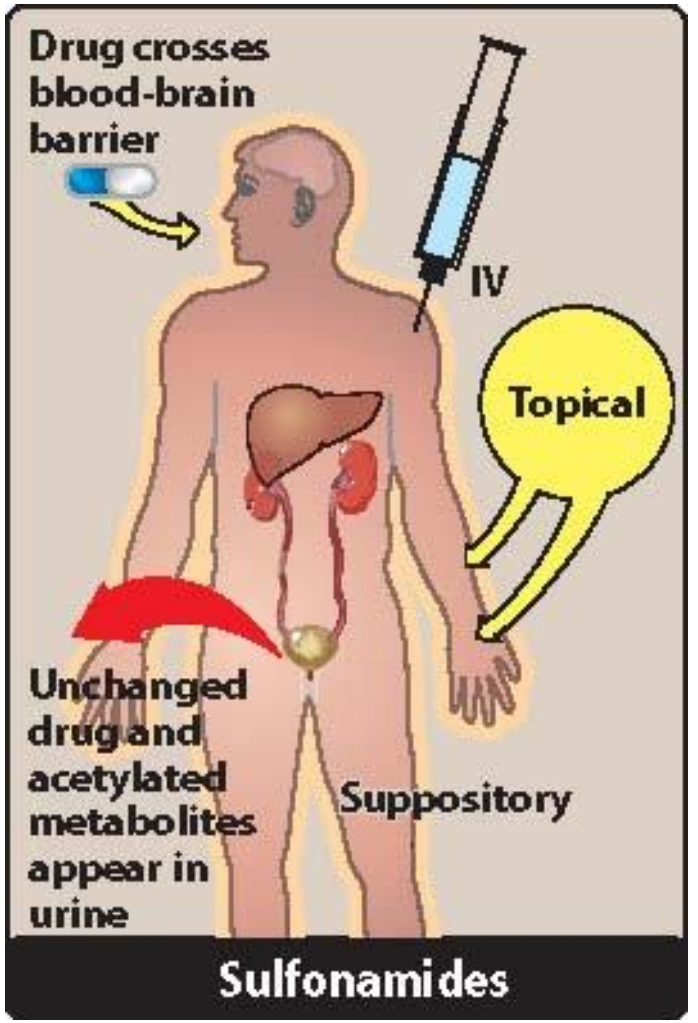
- **Metabolism**

-metabolized in the liver (acetylation and conjugation)

-acetylated metabolites can crystalize in urine causing renal stones

- **Elimination**

-eliminated by glomerular filtration and secretion



Sulfonamides

Adverse effects

- **Crystalluria**

-nephrotoxicity

-requires adequate hydration and urine alkalinization

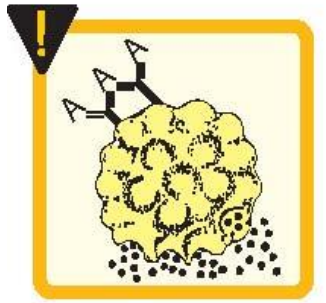
- **Hypersensitivity**

-sulfa allergies

- **Hematopoietic disturbances:**

-hemolytic anemia in patients with G6PD deficiency

Crystalluria



Hypersensitivity

Hemolytic anemia

Sulfonamides

Adverse effects

- **Kernicterus**

-in newborns

-sulfa displace protein-bound bilirubin in plasma

- **Drug-drug interaction**

-increase anticoagulant effect of warfarin

- **Contraindications**

-newborn, infants, breastfeeding women

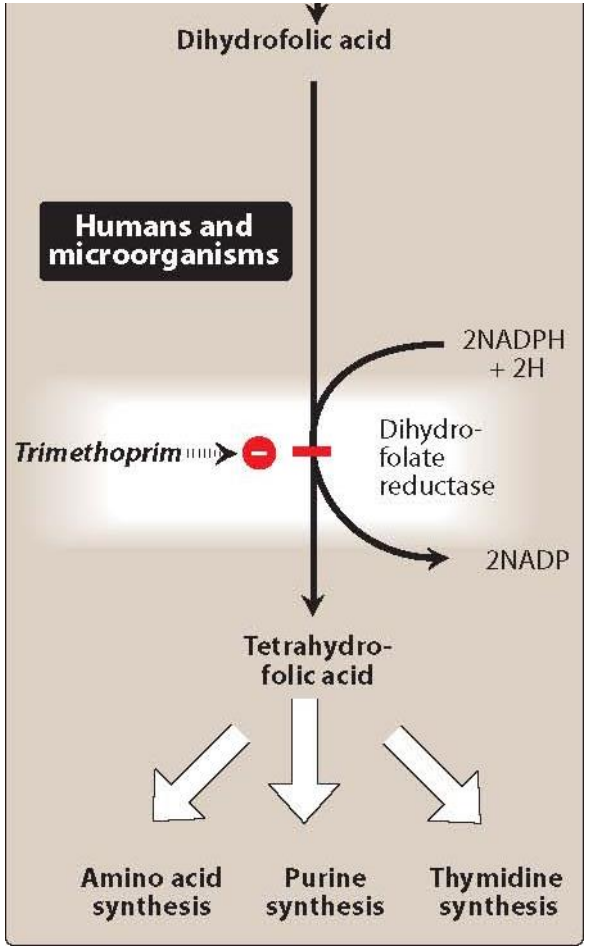
-with methenamine

Trimethoprim

Trimethoprim

Mechanism of action

- Dihydrofolate is reduced to tetrahydrofolate (active form of folate) by dihydrofolate reductase
- Trimethoprim inhibits dihydrofolate reductase
- Decreases purine and pyrimidine synthesis
- Bacterial vs mammalian selectivity
- Mostly combined with sulfa drugs



Trimethoprim

Antibacterial spectrum

- Similar to sulfa drugs e.g., sulfamethoxazole
- More potent as a single agent
- Can be used alone. For what? … but not very often…

Mechanisms of resistance

- Altered dihydrofolate reductase
- Efflux pumps

Trimethoprim

Adverse effects

- can produce the effects of folic acid deficiency.

-megaloblastic anemia

-leukopenia

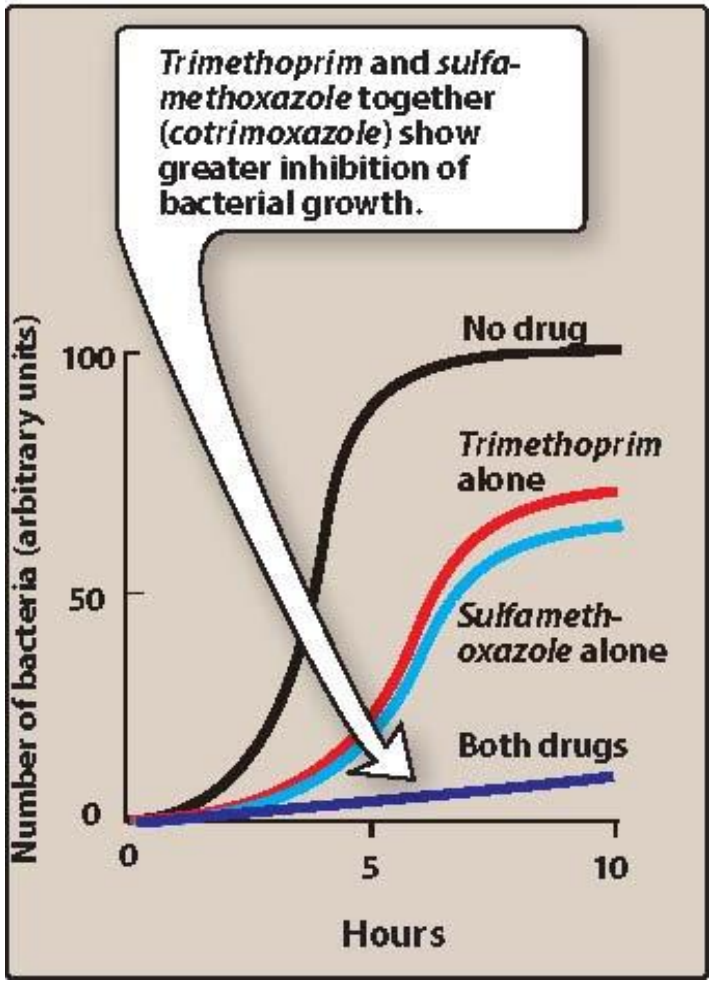
-granulocytopenia,

***Reversed by administration of folinic acid, which does not enter bacteria.

- Hyperkalemia

Trimethoprim/Sulfamethoxazole (Cotrimoxazole)

- The combination has a synergistic effect
- inhibition of two sequential steps in the synthesis of tetrahydrofolic acid.

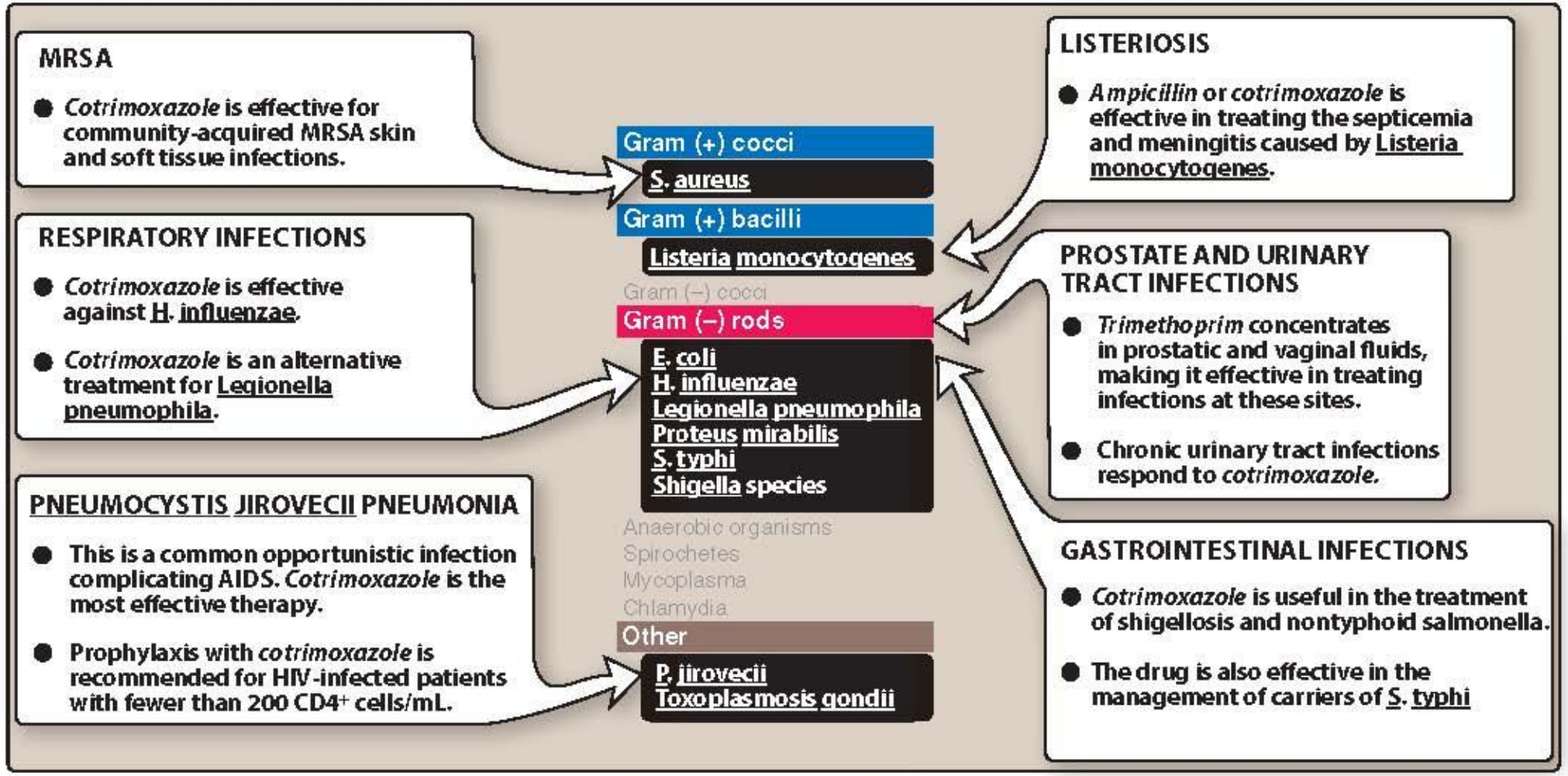


Trimethoprim/Sulfamethoxazole (Cotrimoxazole)

Antibacterial spectrum

- Effective in treating UTIs and RTIs
- Effective against *Pneumocystis jirovecii* pneumonia
- Skin and soft tissue MRSA infections
- Drug of choice for infections caused by Nocardia spp.

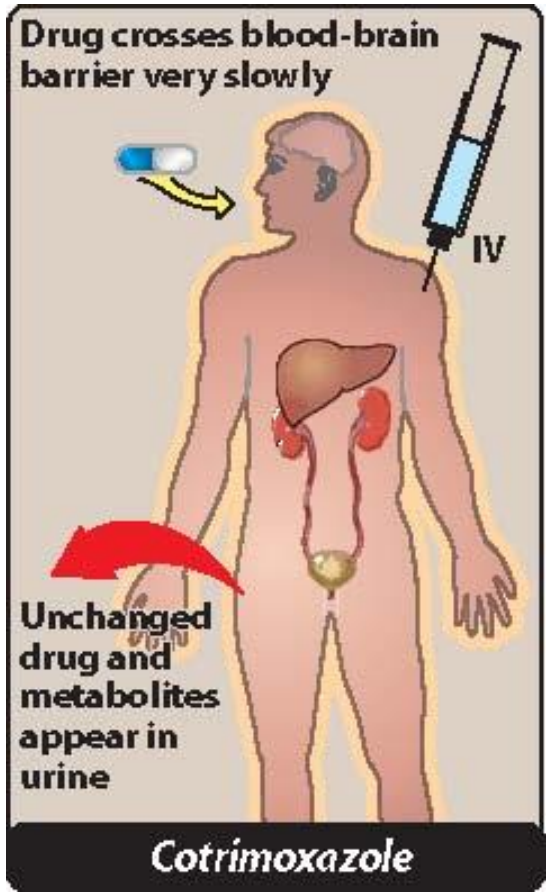
Trimethoprim/Sulfamethoxazole (Cotrimoxazole)



Trimethoprim/Sulfamethoxazole (Cotrimoxazole)

Pharmacokinetics

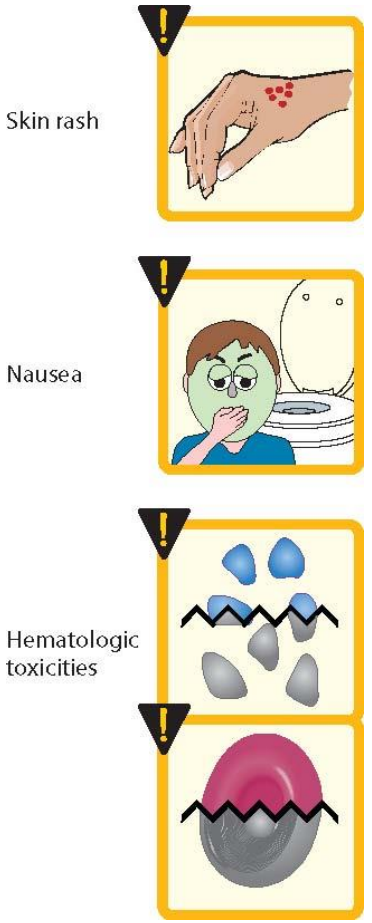
- Administered orally (IV reserved for severe cases of PCP)
- Crosses BBB
- Excreted in the urine



Trimethoprim/Sulfamethoxazole (Cotrimoxazole)

Adverse effects

- N/V/D
- Skin reactions
- Glossitis/stomatitis
- Hyperkalemia
- Megaloblastic anemia
- Hemolytic anemia in patients with G6PD def
- Drug-drug interaction with warfarin



Urinary Tract Antiseptics/Antimicrobials

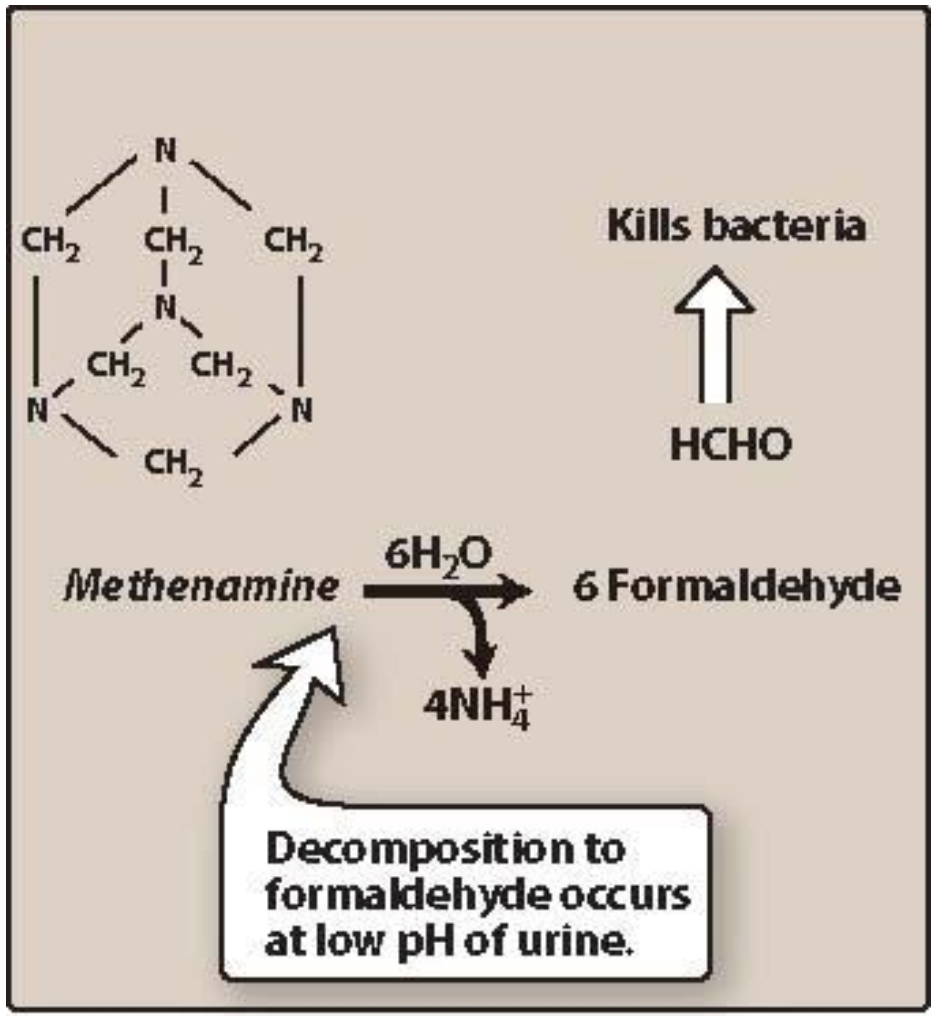
- UTIs are more prevalent in women and elderly
- Most common cause: *E. coli* (80% of uncomplicated UTIs)
- Second most common cause: *Staphylococcus saprophyticus*

Most frequently used agents:

1. **Cotrimoxazole**
2. **Nitrofurantoin**
3. **Fluoroquinolones**
4. **Methenamine**

Methenamine

- **MOA**: decomposes at an acidic pH of 5.5 or less in the urine → produces formaldehyde → toxic to most bacteria
- **Antibacterial spectrum**: used for chronic suppressive therapy to reduce UTIs
- Some activity against Pseudomonas or Proteus spp



Nitrofurantoin

- Nitrofurantoin is now first-line for uncomplicated cystitis
- **MOA**: Major inhibitor of DNA and RNA synthesis
- Useful against *E.coli*
- Can also cause hemolytic anemia in patients with G6PD
- Should not be used in patients with renal impairment or term pregnant women