PHARMACOLOGY - 2

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Quinolones, Sulfonamides & Trimethoprim

PHARMACOLOGY-2

Quinolones, trimethoprim & sulfonamides

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LEARNING OUTCOMES

After completing studying this chapter, the student should be able to:

- Classify the drugs into subgroups such as quinolones and sulfonamides.
- Recognize the bacterial spectrum of all these antibiotic and antibacterial groups.
- Summarize the most remarkable pharmacokinetic features of these drugs.
- Numerate the most important side effects associated with these agents.
- Select the antibiotic of choice to be used in certain infections, as associated with the patient status including comorbidity, the species of bacteria causing the infection and concurrently prescribed drugs.
- Reason some remarkable clinical considerations related to the use or contraindication or precaution of a certain drug.
- Illustrate the mechanism of action of each of these drugs.

FLUOROQUINOLONES:

FLUOROQUINOLONES:

- Following synthesis of **nalidixic acid** in the early 1960s, continued modification of the quinolone nucleus expanded the spectrum of activity, improved pharmacokinetics, and stabilized compounds against common mechanisms of resistance.

- **Overuse** resulted in rising rates of **resistance** in gram-negative and gram-positive organisms, increased frequency of *Clostridium difficile* infections, and identification of numerous tough adverse effects.

- Consequently, these agents have been relegated to **second-line options** for various indications.

FLUOROQUINOLONES:

FLUOROQUINOLONES

Ciprofloxacin CIPRO
Delafloxacin BAXDELA
Gemifloxacin FACTIVE
Levofloxacin LEVAQUIN
Moxifloxacin AVELOX, MOXEZA, VIGAMOX
Ofloxacin GENERIC ONLY

INHIBITORS OF FOLATE SYNTHESIS

Mafenide SULFAMYLON
Silver sulfadiazine SILVADENE, SSD, THERMAZENE
Sulfadiazine GENERIC ONLY
Sulfasalazine AZULFIDINE

INHIBITORS OF FOLATE REDUCTION

Pyrimethamine DARAPRIM
Trimethoprim PRIMSOL, TRIMPEX

COMBINATION OF INHIBITORS OF FOLATE SYNTHESIS AND REDUCTION

Cotrimoxazole (trimethoprim + sulfamethoxazole) BACTRIM, SEPTRA

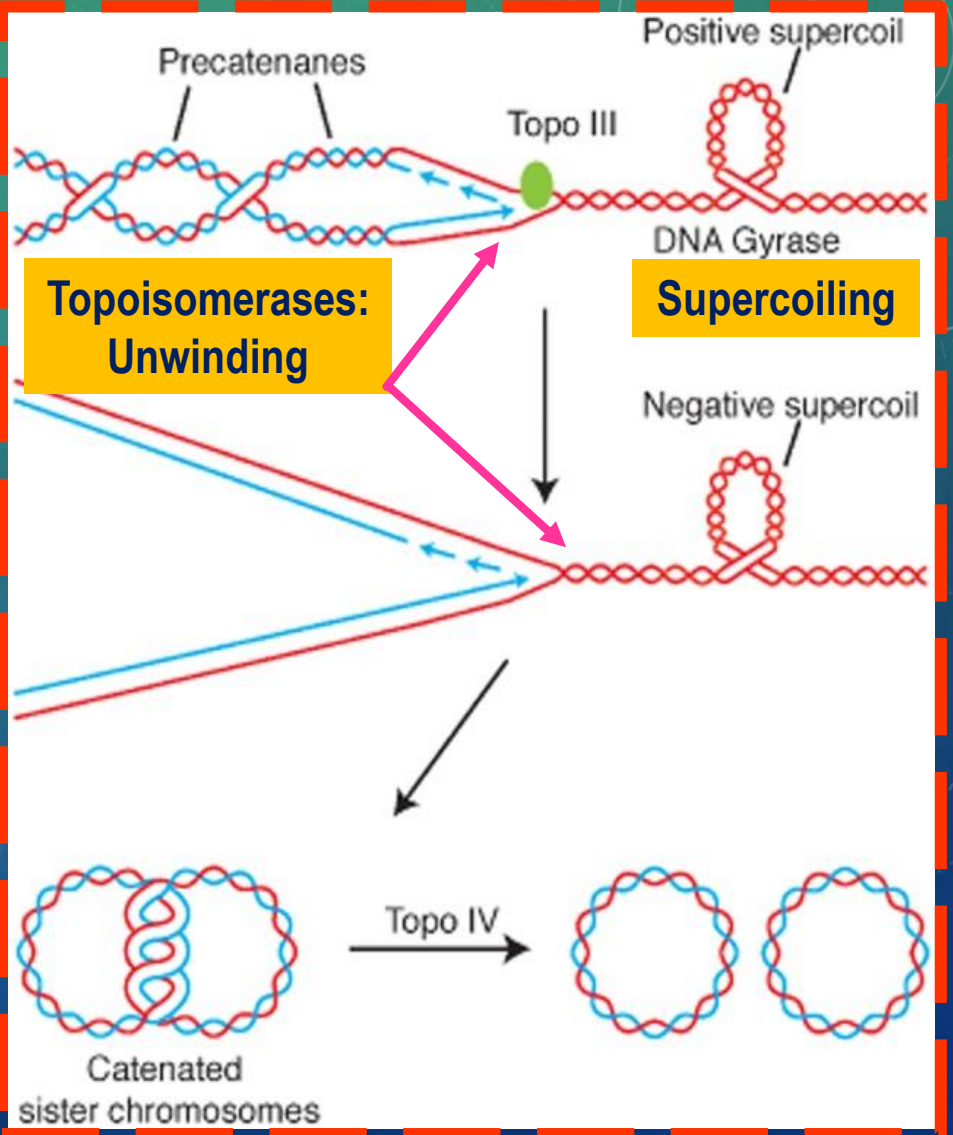
URINARY TRACT ANTISEPTICS

Methenamine HIPREX, UREX
Nitrofurantoin MACROBID, MACRODANTIN

Only will be mentioned here

FLUOROQUINOLONES:

- Most bacterial species maintain two distinct type II topoisomerases that assist with deoxyribonucleic acid (DNA) replication:
  - **DNA gyrase** {supercoiling} and
  - **Topoisomerase IV** {Unwinding}.
- Following cell wall entry through porin channels, fluoroquinolones bind to these enzymes and interfere with DNA ligation.



FLUOROQUINOLONES:

- This interference increases the number of permanent chromosomal breaks, triggering cell lysis.
- In general, fluoroquinolones have different targets for gram-negative (DNA gyrase) and gram-positive organisms (topoisomerase IV), resulting in rapid cell death.

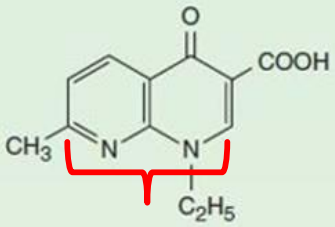
Antimicrobial spectrum:

- Fluoroquinolones are bactericidal.
- Modifications to the quinolone nucleus steadily improved topoisomerase inhibitory activity and facilitated bacterial cell wall penetration → increasing activity against G (+) and (-) and atypical organisms such as, *Chlamydia*, *Legionella*, and *Mycoplasma* spp., and anaerobes.
- Accordingly, their classification is based on the spectrum of activity.

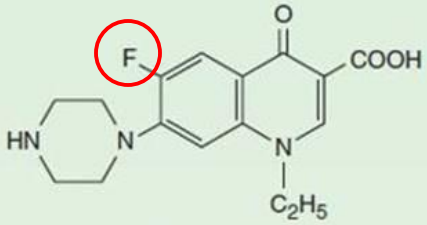
FLUOROQUINOLONES:

- Fluoroquinolones were originally developed because of their excellent activity against **GRAM-NEGATIVE AEROBIC** bacteria;
- The earliest agents had limited activity against **Gram-positive** organisms.
- Subsequent members of the group have improved activity against **Gram-positive cocci**.

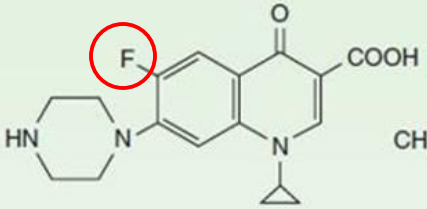
1. **FIRST-GENERATION** compounds (for example, **nalidixic acid**) were **narrow** spectrum agents with activity against **aerobic gram-negative bacilli**, mostly Enterobacteriaceae.
2. **SECOND-GENERATION** compounds {**norfloxacin**, **ciprofloxacin**, **enoxacin**, **lomefloxacin**, **levofloxacin**, **ofloxacin,** and **pefloxacin**} possess excellent **Gram-negative** activity and moderate to good activity against **Gram-positive** bacteria.



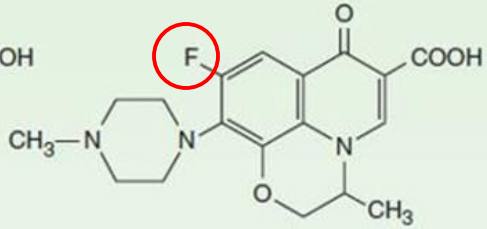
Nalidixic acid



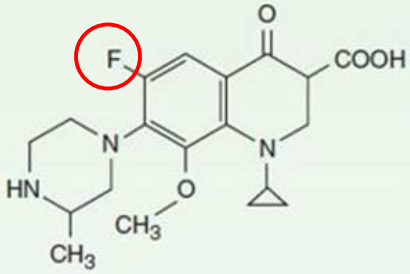
Norfloxacin



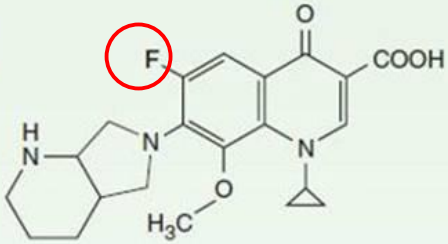
Ciprofloxacin



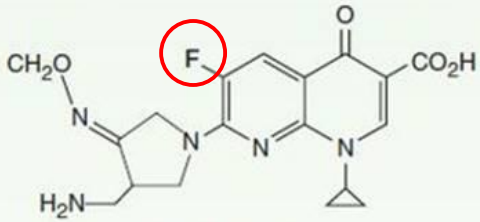
Levofloxacin



Gatifloxacin



Moxifloxacin



Gemifloxacin

FLUOROQUINOLONES:

- **Norfloxacin**, which is no longer available in the USA, is the least active of the fluoroquinolones against **both** Gram-negative and Gram-positive organisms.

- Second-generation compounds exhibit improved intracellular penetration and broadened coverage, which includes Enterobacteriaceae, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Neisseria* spp., *Chlamydia* spp., and *Legionella* spp.
- **MRSA** strains are often resistant.

- **Ciprofloxacin** is the most active agent of this group against Gram-negative organisms, particularly *P aeruginosa*.

FLUOROQUINOLONES:

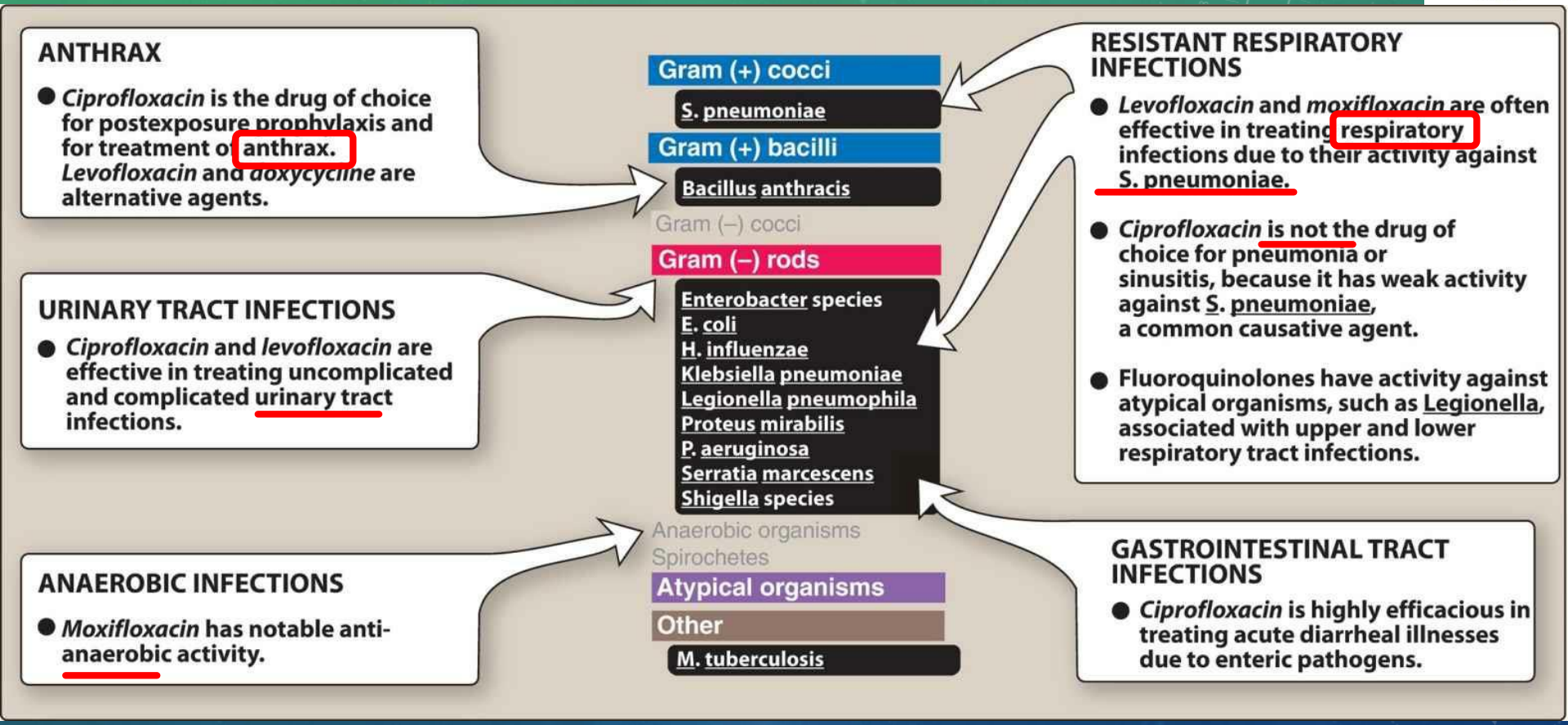
3. Third-generation drugs: (conflict in classification);

- **Levofloxacin**, the l-isomer of ofloxacin, has **superior** activity against Gram-positive organisms, especially *Streptococcus pneumoniae*.

4. Fourth-generation compounds:

- Comprise **moxifloxacin**, **gemifloxacin**, and **delafloxacin**.
- They have enhanced gram-positive activity, including *Staphylococcus* and *Streptococcus* spp.
- **Delafloxacin** has activity against methicillin-resistant *Staphylococcus aureus* (**MRSA**) and *Enterococcus faecalis*.
- **Delafloxacin** is the only drug from this group that has activity against *Pseudomonas aeruginosa*.

FLUOROQUINOLONES:



JNJ-Q2 avarofloxacin; is a novel, fifth-generation fluoroquinolone with excellent extended activity against resistant Gram-positive and Gram-negative organisms including **MRSA**, and **fluoroquinolone-resistant *S. pneumoniae***.

FLUOROQUINOLONES:

Drug	Half-Life (h)	Oral Bioavailability (%)	Peak Serum Concentration (mcg/mL)	Oral Dose (mg)	Primary Route of Excretion
Ciprofloxacin	3–5	70	2.4	500 twice daily	Renal
Gemifloxacin	8	70	1.6	320 once daily	Renal and nonrenal
Levofloxacin	5–7	95	5.7	500 once daily	Renal
Moxifloxacin	9–10	>85	3.1	400 once daily	Nonrenal
Norfloxacin	3.5–5	80	1.5	400 twice daily	Renal
Ofloxacin	5–7	95	2.9	400 twice daily	Renal

Resistance:

- Numerous mechanisms of fluoroquinolone resistance exist in clinical pathogens.
- High-level fluoroquinolone resistance is primarily driven by chromosomal [1] MUTATIONS WITHIN TOPOISOMERASES, although [2] DECREASED ENTRY, [3] EFFLUX systems, and [4] MODIFYING ENZYMES play a role.
- Mechanisms responsible for resistance include the following:

FLUOROQUINOLONES:

1. Altered target binding:

- Mutations in bacterial genes encoding DNA gyrase or topoisomerase IV alter target site structure and reduce binding efficiency of fluoroquinolones.

2. Decreased accumulation:

- Reduced intracellular concentration is linked to:

  A. Reduction in membrane permeability or

  B. Efflux pumps.

- Alterations in membrane permeability are mediated through a reduction in outer membrane **porin proteins**.
- Efflux pumps actively remove fluoroquinolones from the cell.

3. Fluoroquinolone degradation:

- An aminoglycoside acetyltransferase variant can **acetylate** fluoroquinolones, rendering them inactive.

FLUOROQUINOLONES:

PHARMACOKINETICS:

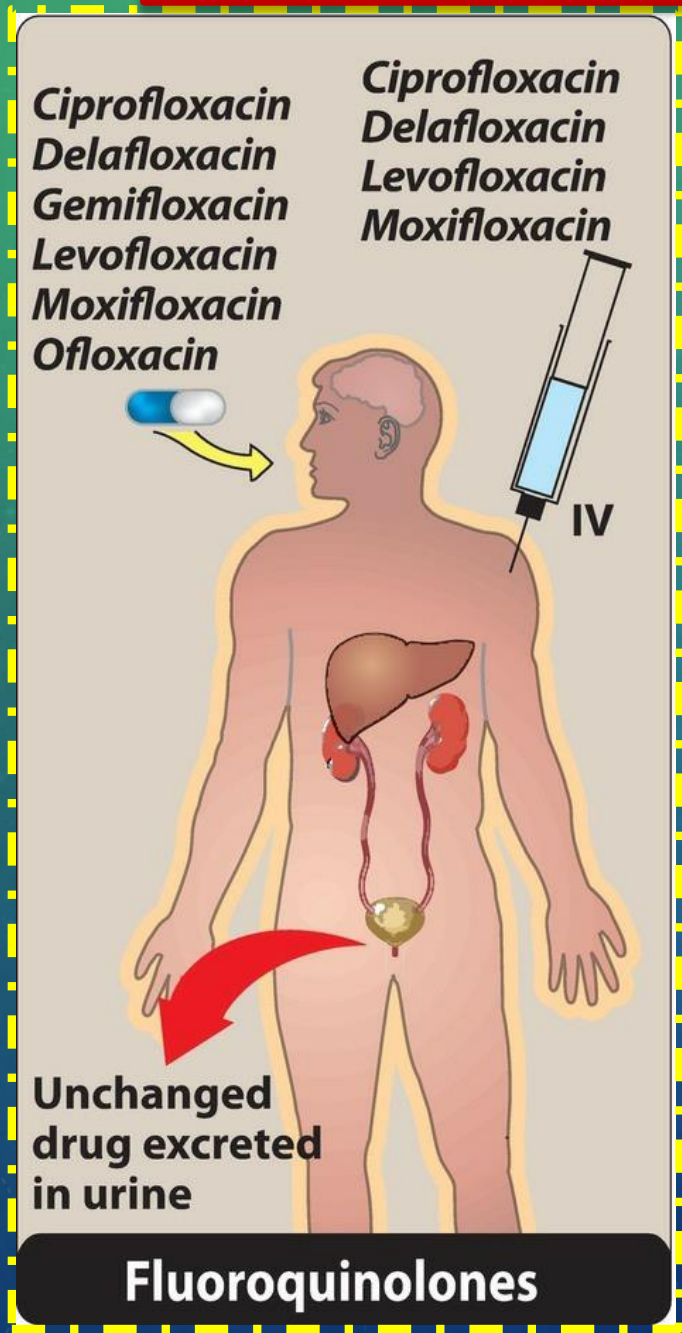
Absorption:

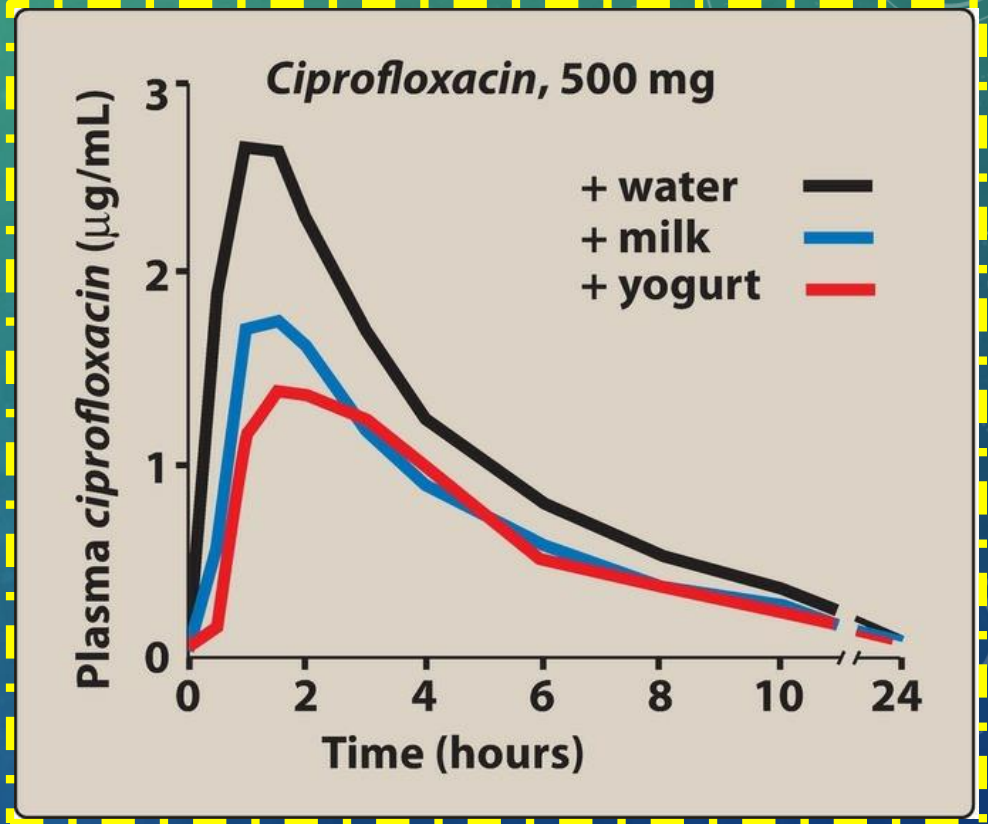
- Fluoroquinolones are well absorbed after oral administration, with levofloxacin and moxifloxacin having a bioavailability that exceeds 90%.
- Ingestion of fluoroquinolones with **sucralfate**, **aluminum-** or **magnesium-containing antacids**, or dietary supplements containing **iron** or **zinc** can reduce the absorption.
- **Calcium** and other **divalent cations** also interfere with the absorption of these agent.

Distribution:

- Fluoroquinolones distribute *well* into *all* tissues and body fluids.

FLUOROQUINOLONES:





FLUOROQUINOLONES:

- Concentrations are **high** in bone, urine (except moxifloxacin), kidney, prostatic tissue (but not prostatic fluid), and lungs as compared to serum.
- Penetration into cerebrospinal fluid is **good**, and these agents may be considered in certain central nervous system (CNS) infections.
- Accumulation in macrophages and polymorphonuclear leukocytes results in activity against **intracellular** organisms such as ***Listeria***, ***Chlamydia*** {STD-causing pathogen} and ***Mycobacterium***.

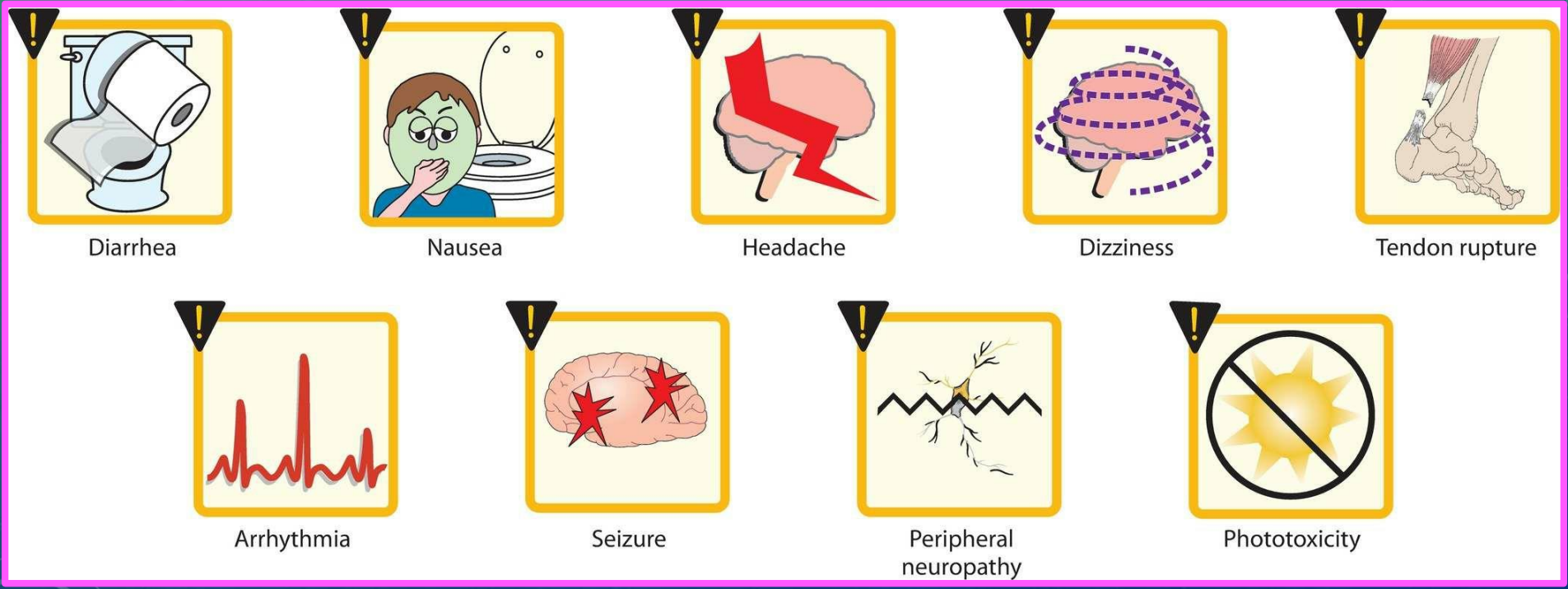
Elimination:

- Most fluoroquinolones are excreted **RENALLY**. Therefore, dosage adjustments are needed in renal dysfunction.

FLUOROQUINOLONES:

- **Moxifloxacin** is metabolized primarily by the **liver**, and while there is some renal excretion, **NO** dose adjustment is required for renal impairment.

ADVERSE REACTIONS:

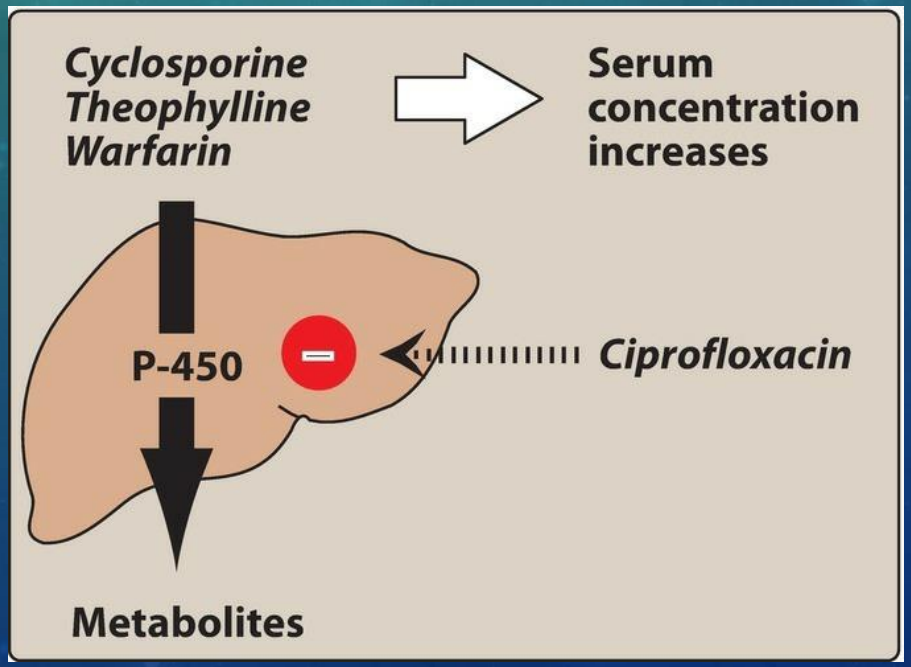


FLUOROQUINOLONES:

- In general they are well tolerated.
- **Common** adverse effects leading to discontinuation are nausea, vomiting, headache, and dizziness.
- These agents carry boxed warnings for **tendinitis**, **tendon rupture** [Achilles tendon] **peripheral neuropathy**, and **CNS effects** (hallucinations, anxiety, insomnia, confusion, and seizures).
- Patients taking fluoroquinolones are at risk for **phototoxicity** resulting in exaggerated sunburn reactions.
- **PATIENTS SHOULD USE SUNSCREEN AND AVOID EXCESSIVE EXPOSURE TO ULTRAVIOLET (UV) LIGHT.**
- **Arthralgia** and **arthritis** can occur yet they are not common.
- Use in the **pediatric** population should be limited to distinct clinical scenarios.

FLUOROQUINOLONES:

- **Hepatotoxicity** or **blood glucose disturbances**.
- Fluoroquinolones may **prolong the QTc interval**, and these agents **should be avoided** in patients predisposed to arrhythmias or taking medication associated with QT prolongation.
- **CIPROFLOXACIN** inhibits P450 1A2- and 3A4-mediated metabolism.



FLUOROQUINOLONES:

Ciprofloxacin:

- It has a good activity against **gram-negative bacilli,** including *P. aeruginosa.*
- Ciprofloxacin is used in the treatment of **traveler's diarrhea**, **typhoid fever**, and **anthrax**.
- It is a second-line agent for infections arising from intra-abdominal, lung, skin, or urine sources.

Levofloxacin:

- Levofloxacin has similar activity to ciprofloxacin and they are often interchanged when managing **gram-negative bacilli**, including *P. aeruginosa*.
- Levofloxacin has enhanced activity against *S. pneumoniae*.
- It is **first-line** therapy for community-acquired pneumonia (CAP).

FLUOROQUINOLONES:

Moxifloxacin:

- It has enhanced activity against gram-positive organisms (for example, *S. pneumoniae*), gram-negative anaerobes, and *Mycobacterium* spp.
- The drug may be used for CAP, but not hospital-acquired pneumonia due to poor coverage of *P. aeruginosa*.
- Moxifloxacin may be considered as a **second-line** agent for management of drug-susceptible tuberculosis.

Delafloxacin:

- IT has improved activity against gram-positive cocci, including **MRSA**.
- Therefore, it is an option for managing acute bacterial **skin** and skin structure infections.

FLUOROQUINOLONES:

AVAROFLOXACIN: [JNJ-Q2]

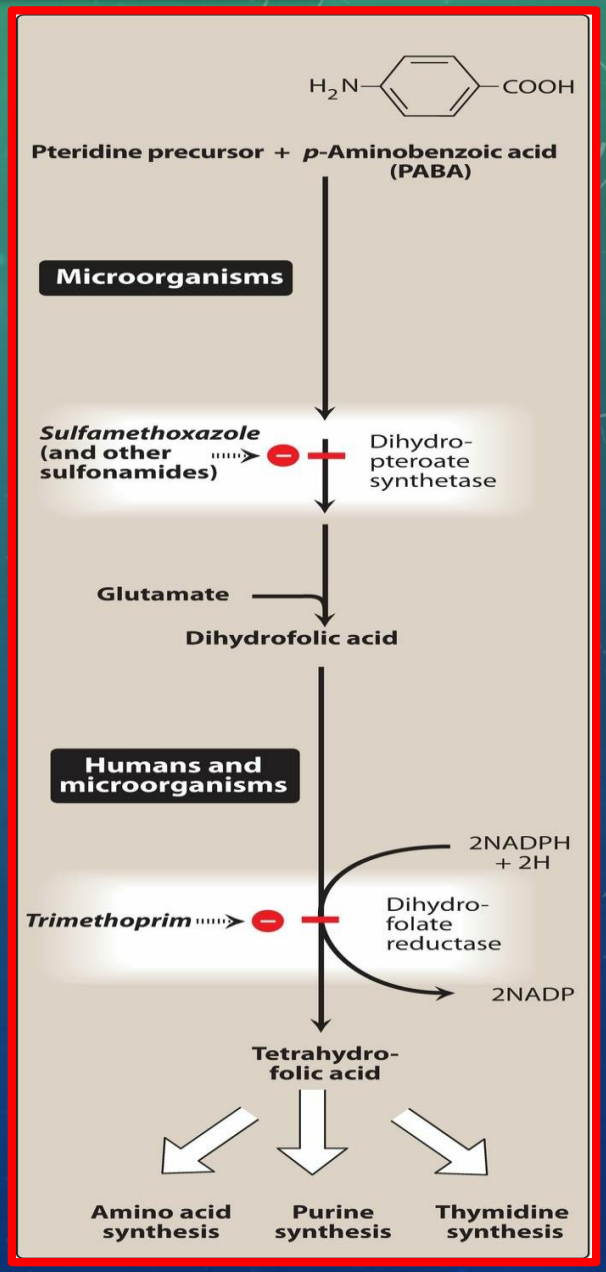
- Avarofloxacin (JNJ-Q2) is a novel broad-spectrum fluoroquinolone antibacterial drug developed for the treatment of:
  - ✓ Acute bacterial skin, skin-structure infections.
  - ✓ Community-acquired pneumonia.

FOLATE ANTAGONISTS:

- Folic acid is a coenzyme essential in the synthesis of ribonucleic acid (RNA), DNA, and certain amino acids.
- In the absence of folate, cells cannot grow or divide.
- Humans use **dietary** folate to synthesize the critical folate derivative, tetrahydrofolic acid.
- By contrast, many bacteria are impermeable to folate derivatives, and rely on their ability to synthesize folate **de novo** {from the beginning}.
- **Sulfonamides** (sulfa drugs) are a family of antibiotics that inhibit de novo synthesis of folate.
- A second type of folate antagonist, **trimethoprim**, prevents microorganisms from converting dihydrofolic acid to tetrahydrofolic acid.

FOLATE ANTAGONISTS

- Thus, both **SULFONAMIDES** and **TRIMETHOPRIM** interfere with the ability of an infecting bacterium to perform DNA synthesis and other essential cellular functions
- The combination of the sulfonamide sulfamethoxazole with trimethoprim (the generic name for the combination is cotrimoxazole) provides a **synergistic** effect.



SULFONAMIDES

- Sulfa drugs were among the first antibiotics used in clinical practice.
- Today, they are seldom prescribed alone except in developing countries, where they are employed because of low cost and efficacy.

MECHANISM OF ACTION:

- Microorganisms use the enzyme dihydropteroate synthetase to create dihydrofolic acid from the precursor molecule **p-aminobenzoic acid** (PABA).
- Sulfonamides are synthetic analogs of PABA. {BACTERIOSTATIC}
- Because of their structural similarity, sulfonamides compete with PABA to inhibit dihydropteroate synthetase and the genesis of bacterial dihydrofolic acid.

FOLATE ANTAGONISTS

ANTIBACTERIAL SPECTRUM:

- Sulfa drugs have *in vitro* activity against gram-**negative** and gram-**positive** organisms.
- Common organisms include Enterobacteriaceae, *Haemophilus influenzae*, *Streptococcus* spp., *Staphylococcus* spp.
- Additionally, **sulfadiazine** in combination with the dihydrofolate reductase inhibitor **pyrimethamine** is the **preferred** treatment for **toxoplasmosis**.

✓ **Toxoplasmosis:** a disease that results from infection with the *Toxoplasma gondii* parasite, one of the world's most common parasites. Infection usually occurs by eating undercooked contaminated meat, exposure from infected cat feces, or mother-to-child transmission during pregnancy.

FOLATE ANTAGONISTS

Resistance:

- Bacteria that obtain *folate from their environment* are naturally resistant to sulfa drugs.
- Acquired bacterial resistance to the sulfa drugs can arise from plasmid transfers or random mutations.
- **Resistance may be due to:**

1. Altered *dihydropteroate synthetase*,
2. Decreased cellular *permeability* to sulfa drugs, or
3. Enhanced production of the natural substrate, *PABA.*

❖ **Organisms resistant to one member of this drug family are resistant to all.**

FOLATE ANTAGONISTS

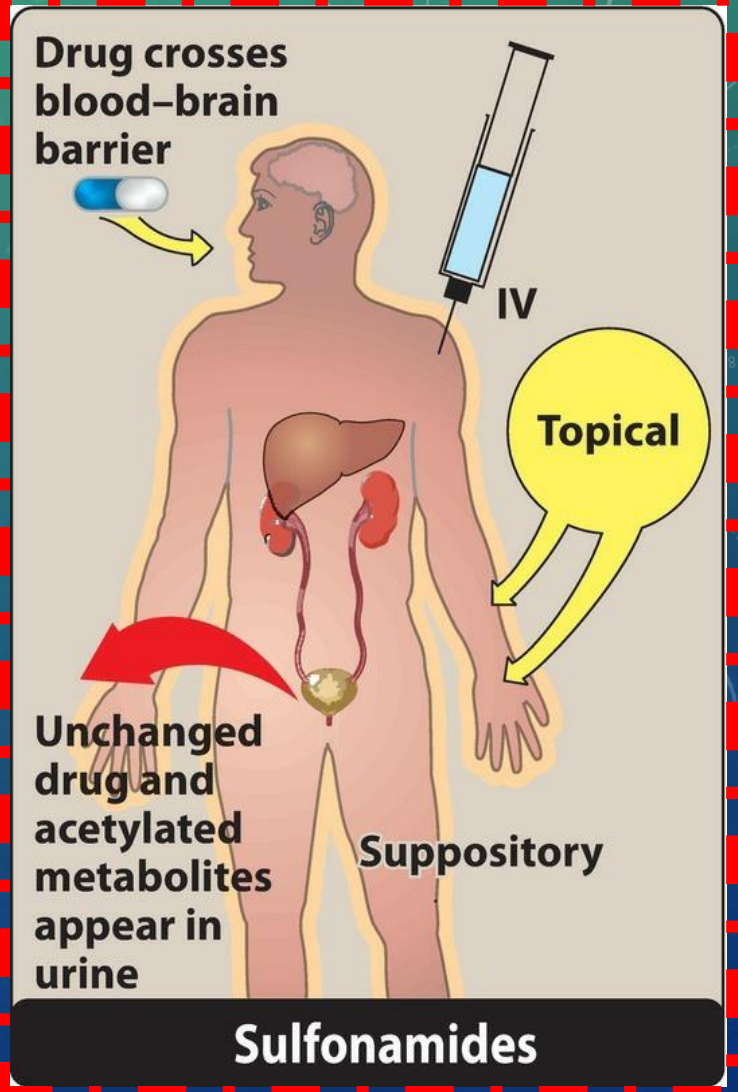
Pharmacokinetics:

ABSORPTION:

- Most sulfa drugs are well absorbed following **oral** administration.
- An exception is **sulfasalazine**; that it is not absorbed when administered orally or as a suppository and, therefore, is reserved for treatment of **chronic inflammatory bowel diseases**.
- Intestinal flora split **sulfasalazine** into **sulfapyridine** and **5-aminosalicylate (5-ASA)**.
- **5- aminosalicylate** is responsalbe for with the anti-inflammatory effect.
- Absorption of sulfapyridine can lead to toxicity in patients who are slow acetylators.

FOLATE ANTAGONISTS

- Because of the risk of **sensitization**, sulfa drugs are not usually applied topically.
- However, **silver sulfadiazine** or **mafenide acetate** (α-amino-p-toluenesulfonamide) ***creams*** have been effective in reducing burn-associated sepsis because they prevent colonization of bacteria.
- NOTE: Silver sulfadiazine is preferred because mafenide produces pain on application.



FOLATE ANTAGONISTS

DISTRIBUTION:

- Sulfa drugs are bound to serum albumin in circulation and widely distribute throughout body tissues.
- Sulfa drugs penetrate well into cerebrospinal fluid (even in the absence of inflammation) and cross the placental barrier to enter fetal tissues.

METABOLISM:

- Sulfa drugs are **acetylated** and conjugated primarily in the liver.
- The acetylated product is *devoid* of antimicrobial activity but retains the *toxic* potential to **precipitate** at neutral or acidic pH.
- This causes **crystalluria** (**stone formation**) and potential damage to the kidney.

FOLATE ANTAGONISTS

EXCRETION:

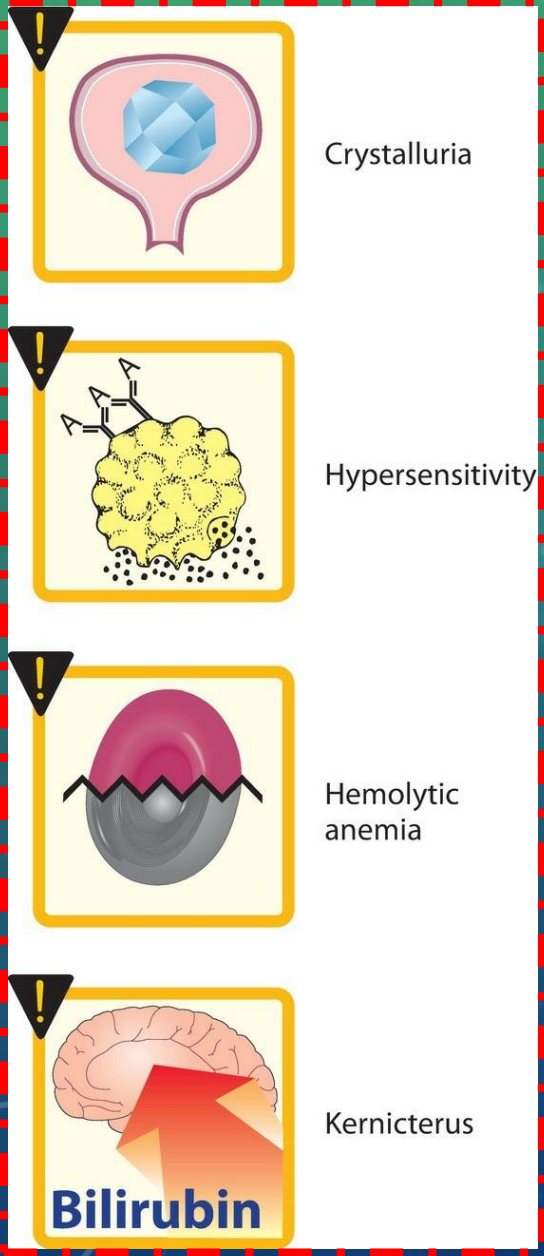
- Unchanged sulfa drug and metabolites are eliminated via glomerular filtration and secretion.
- Thus, they requiring dose adjustments with renal impairment.
- Sulfonamides may be eliminated in breast milk.

ADVERSE EFFECTS:

1. Crystalluria:

- Nephrotoxicity may develop as a result of **crystalluria**.
- Adequate **hydration** and **alkalinization** of urine can prevent the problem by reducing the concentration of drug and promoting its ionization.

FOLATE ANTAGONISTS



2. Hypersensitivity:

- Hypersensitivity reactions, such as rashes, angioedema, or Stevens-Johnson syndrome [skin blisters and peels off], may occur.

3. Hematopoietic disturbances:

- **Hemolytic** anemia is encountered in patients with **GLUCOSE-6-PHOSPHATE DEHYDROGENASE** (**G6PD**) deficiency. **Granulocytopenia** and **thrombocytopenia** can also occur.
- **Fatal** reactions have been reported from associated **agranulocytosis** and **aplastic anemia**.

4. Kernicterus:

- **BILIRUBIN**-associated brain damage (**kernicterus**) may occur in newborns, because sulfa drugs displace bilirubin from binding sites on serum albumin. The bilirubin is then free to pass into the CNS, because the blood–brain barrier is not fully developed.

Drug potentiation:

- Sulfamethoxazole potentiates the anticoagulant effect of **WARFARIN** due to **{1}** inhibition of CYP2C9, resulting in reduced clearance of warfarin.
- Sulfonamides may also **{2}** displace **WARFARIN** from binding sites on serum albumin.
- Serum **METHOTREXATE** levels may rise through protein binding displacement.
- Other CYP2C9 substrates, such as **PHENYTOIN**, may have increased concentrations when given with sulfonamides.

FOLATE ANTAGONISTS

CONTRAINDICATIONS:

- Due to the danger of kernicterus, sulfa drugs should be avoided in:
  - **Newborns** and **infants** less than **2 months** of age.
  - In **pregnant** women at term {**37 weeks of gestation**}.
- Sulfonamides should **not** be given to patients receiving **methenamine**, since they can ***CRYSTALLIZE*** in the presence of formaldehyde produced by this agent.
- **Methenamine (urotropin):** is used to prevent or control returning urinary tract infections caused by certain bacteria.
- Other antibiotics must be used first to treat and cure the infection.
- Methenamine is an antibiotic that stops the growth of bacteria in urine.

FOLATE ANTAGONISTS

TRIMETHOPRIM:

- Trimethoprim, a potent inhibitor of bacterial dihydrofolate reductase, was initially available in combination with the sulfonamide **SULFAMETHOXAZOLE** and later approved for use as a single agent.
- Today, **trimethoprim** is most commonly used in combination with **sulfamethoxazole**.

Mechanism of action:

- Trimethoprim is a potent inhibitor of bacterial **dihydrofolate reductase.**
- Inhibition of this enzyme prevents the formation of the metabolically active form of folic acid, **tetrahydrofolic acid**, and thus, interferes with normal bacterial cell functions.

FOLATE ANTAGONISTS

- Trimethoprim binds to bacterial dihydrofolate reductase **more readily** than it does to human dihydrofolate reductase, which accounts for the **selective toxicity** of the drug.

Antibacterial spectrum:

- The antibacterial spectrum of trimethoprim is similar to that of sulfamethoxazole.
- However, trimethoprim is **20- to 50-fold more potent** than the sulfonamides.
- Trimethoprim may be used alone in the treatment of **[1] urinary tract infections (UTIs)** and **[2]** in the treatment of **bacterial prostatitis.**
- However, fluoroquinolones and cotrimoxazole are preferred.

FOLATE ANTAGONISTS

RESISTANCE:

- Resistance in gram-negative bacteria is due to the presence of an [1] altered dihydrofolate reductase that has a lower affinity for trimethoprim {enzyme with lower affinity}.
- [2] Efflux pumps and [3] decreased permeability to the drug may play a role.

PHARMACOKINETICS:

- Trimethoprim is rapidly absorbed following **oral** administration.
- Because the drug is a **weak base**, higher concentrations of trimethoprim are achieved in the relatively **acidic** prostatic and vaginal fluids.
- The drug is widely distributed into body tissues and fluids, including penetration into the cerebrospinal fluid.

FOLATE ANTAGONISTS

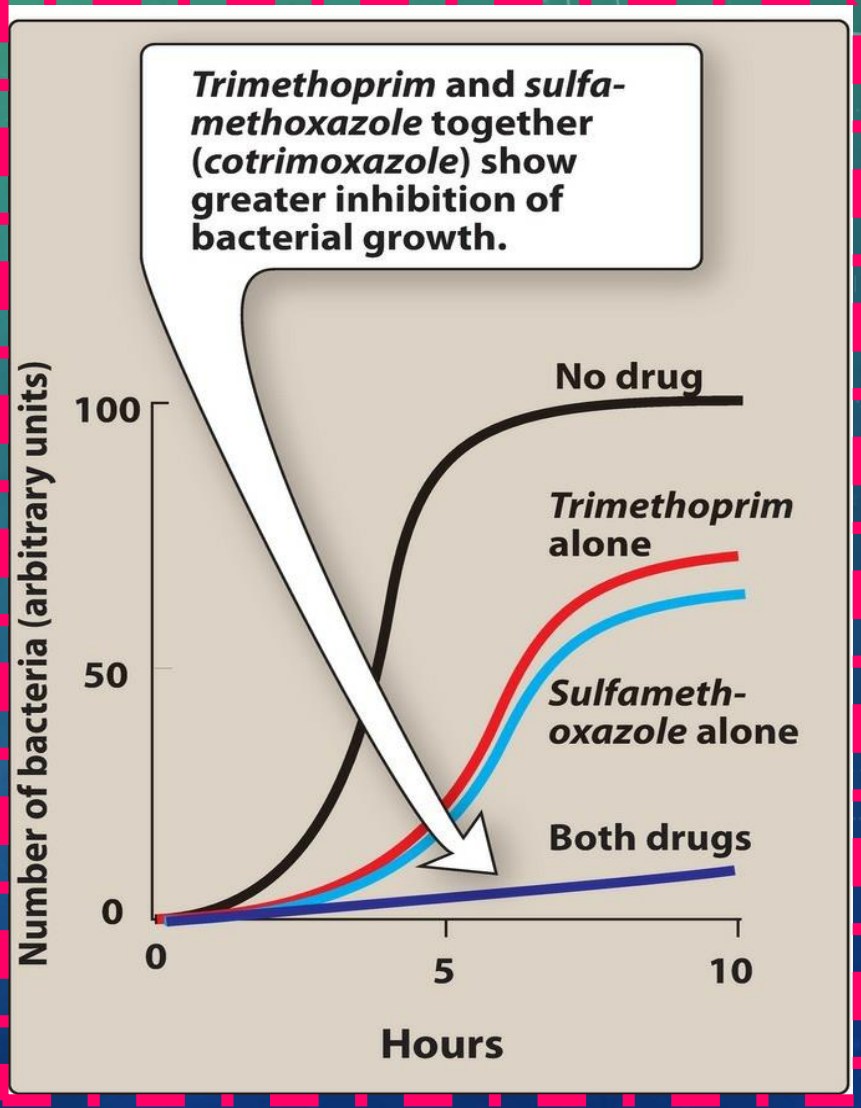
ADVERSE EFFECTS:

- Trimethoprim can produce the effects of **folic acid deficiency** that include: **megaloblastic anemia**, **leukopenia**, and **granulocytopenia**, especially in pregnant patients and those with nutrient-poor diets.
- These blood disorders may be reversed by simultaneous administration of **folinic acid** (also known as **leucovorin**), which does not enter bacteria.
- **Folinic acid** is a medication used to decrease the toxic effects of methotrexate and pyrimethamine.
- It is also used in combination with 5-fluorouracil to treat colorectal cancer, may be used to treat folate deficiency that results in anemia, and methanol poisoning.[folate compounds decrease **formate** accumulation after methanol by stimulating formate oxidation or utilization, decreasing **metabolic acidosis**].

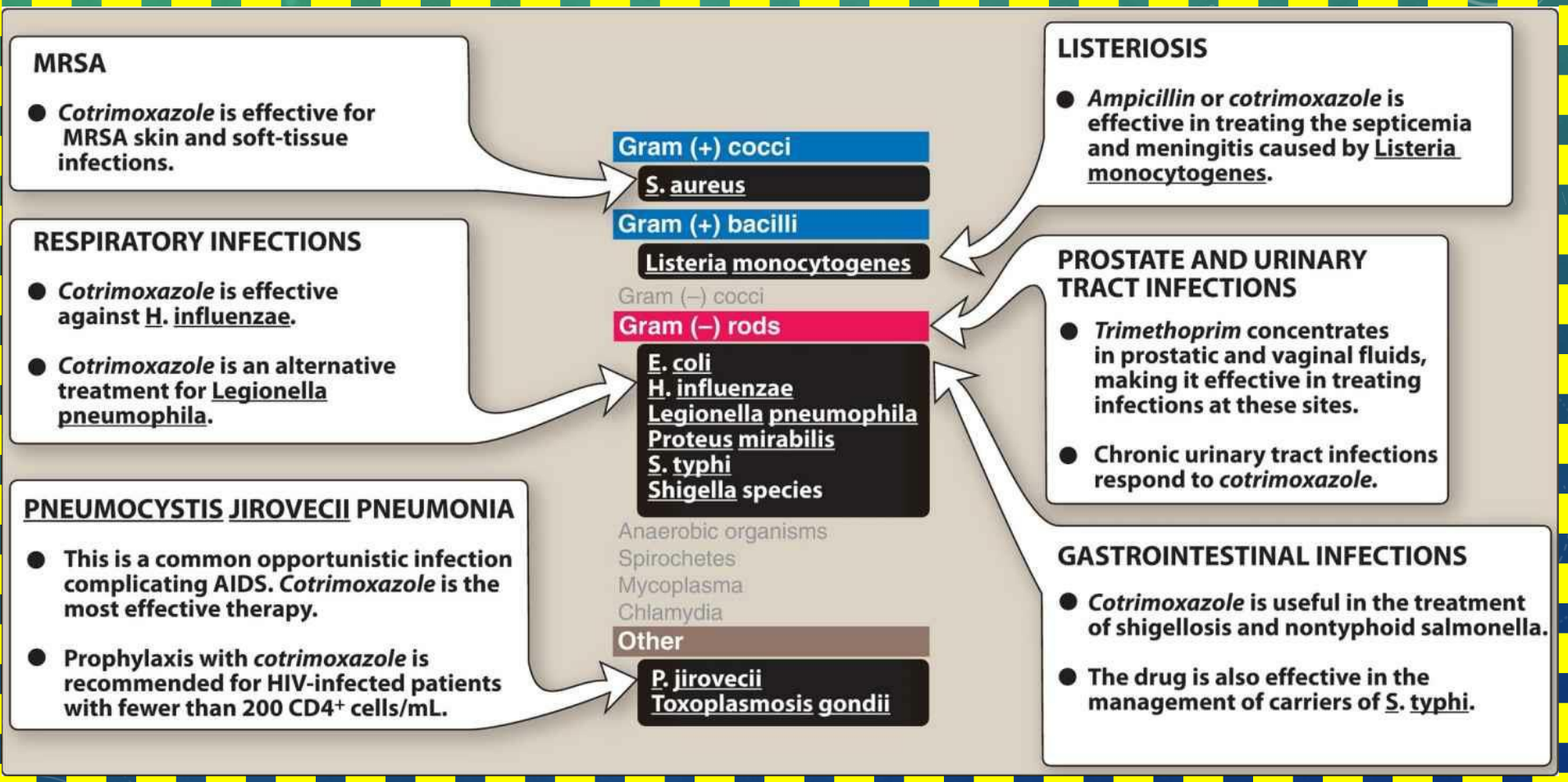
FOLATE ANTAGONISTS

COTRIMOXAZOLE

- Trimethoprim has a **potassium-sparing** effect and may cause **hyperkalemia**, especially at:
  - **[1]** higher doses and
  - **[2]** when administered with other medication that causes hyperkalemia (for example, angiotensin converting enzyme inhibitors).



FOLATE ANTAGONISTS



THE END

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