Pharmacology I

Protein Synthesis Inhibitors

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Lecture No. : 9

UNIVERSITY OF AL MAARIF
مستقبل له تاريخ

Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics

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

Quinolones

I- Fluoroquinolone

- The discovery of quinolone antimicrobials led to the development of numerous compounds utilized in clinical practice.
- Following the 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**.
- Due to these enhancements, **quinolone antimicrobials** were rapidly integrated into human and agricultural medicine.

Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics

I- Fluoroquinolone

- Unfortunately, **overuse** resulted in

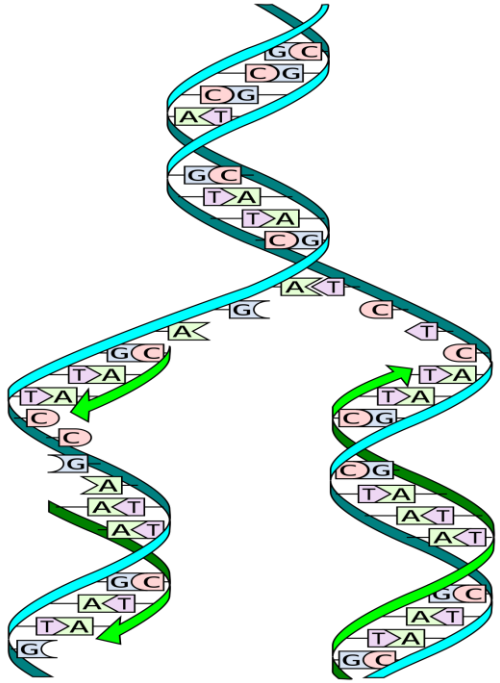
1. **Rising** rates of resistance in **gram-negative and gram positive organisms,**
2. **Increased** frequency of **Clostridium difficile infections**, and
3. **Identification** of **numerous untoward adverse effects**.

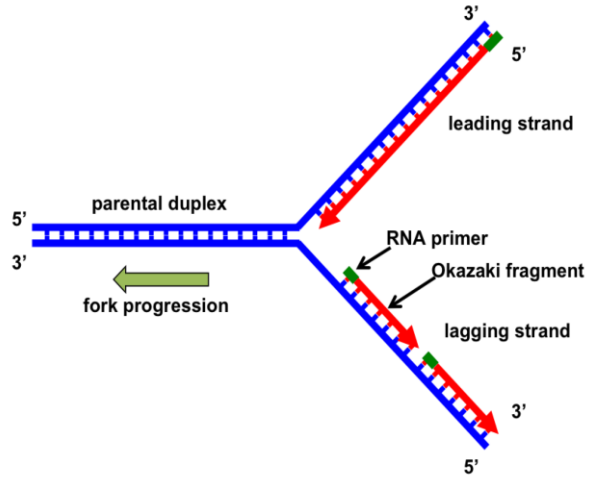
- Consequently, these agents have been **relegated to second-line options for various indications**

I- Fluoroquinolone

- **Mechanism of action**
- Most bacterial species maintain two forms of **Type II topoisomerases** that assist with **deoxyribonucleic acid (DNA) replication**, 1- (DNA gyrase), and 2-topoisomerase IV.

1. **DNA gyrase** is responsible for reducing **torsional stress** ahead of replicating forks by **breaking** double-strand DNA and **introducing** negative supercoils.
2. **Topoisomerase IV** assists in **separating daughter chromosomes** once replication is completed.





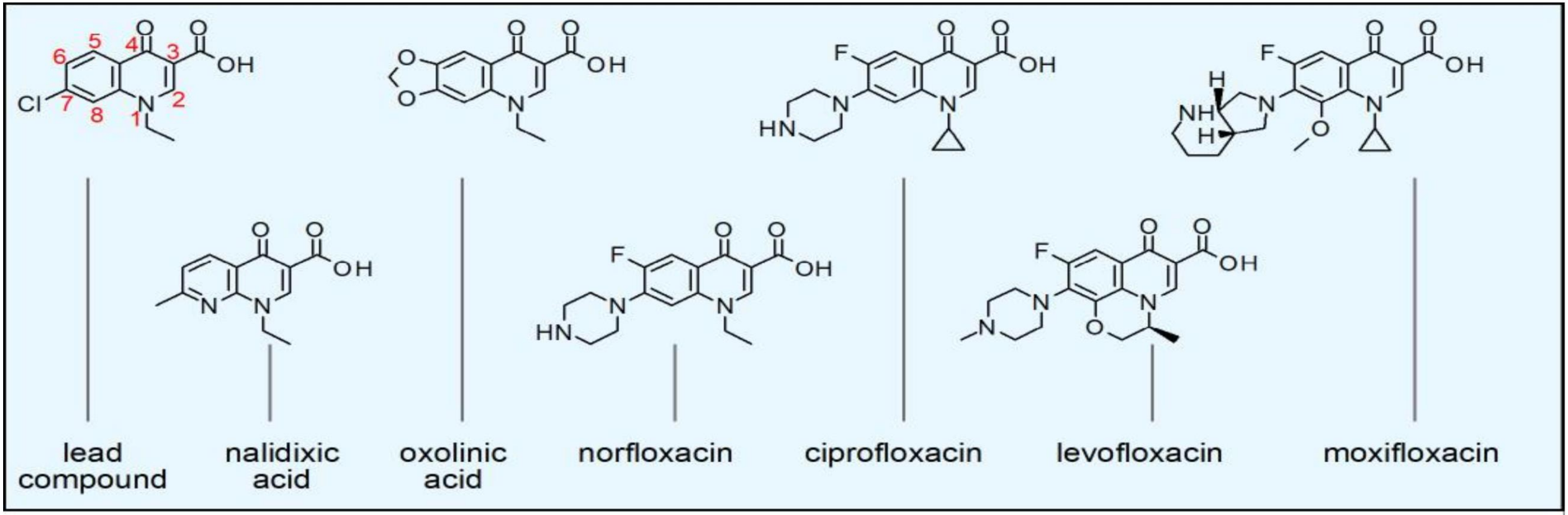
I- Fluoroquinolone

- **Mechanism of action**
- Fluoroquinolones **bind** to these enzymes and interfere with **DNA ligation**.
- 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**.

I- Fluoroquinolone

- **Antimicrobial spectrum**
- Fluoroquinolones are **bactericidal** and exhibit area-under-the-curve/minimum inhibitory concentration (AUC/MIC)-dependent killing.
- A major **facet** of their development cantered on improving microbiologic coverage.
- **Modifications** to the quinolone nucleus steadily **improved topoisomerase inhibitory activity** and **facilitated bacterial cell wall penetration**.

I- Fluoroquinolone



generation 0	1st generation	2nd generation	3rd generation	4th generation
no clinical use	mostly not in use	most of the introduced molecules remain in use		

Gram spectrum

\- | - | - and some + | - and more + | - and many+

potency

I- Fluoroquinolone

- **Antimicrobial spectrum**
- These changes enhanced activity against a variety of pathogens including :

1. **Aerobic gram-negative** and
2. **gram-positive organisms**,
3. **Atypical organisms** (for example, chlamydia, legionella, and mycoplasma spp.), and
4. **Anaerobes**.

II- Fluoroquinolone Classification

- Based on the impact of these structural changes, fluoroquinolones are often **classified according** to the spectrum of activity.

- **First-generation compounds**

- (for example, **Nalidixic acid**) were **narrow spectrum** agents with activity against **aerobic gram-negative bacilli**, mostly **Enterobacteriaceae**.

I- Fluoroquinolone

- **Second-generation compounds**
- (for example, **Ciprofloxacin**)
- It exhibit **improved intracellular penetration** and broadened coverage, which includes

1. **Enterobacteriaceae**,
2. **Pseudomonas aeruginosa**,
3. **Haemophilus influenzae**,
4. **Neisseria spp.**,
5. **Chlamydia spp.**, and
6. **Legionella spp**.

I- Fluoroquinolone

- **Third-generation compounds** (for example, **Levofloxacin**) maintain the **bacterial spectrum of second-generation agents**, with **improved** activity against (**Gm +ve**)

1. **Streptococcus spp.,** including **S. pneumoniae, methicillin-susceptible Staphylococcus aureus, Stenotrophomonas maltophilia, and**
2. **Mycobacterium spp**.

I- Fluoroquinolone

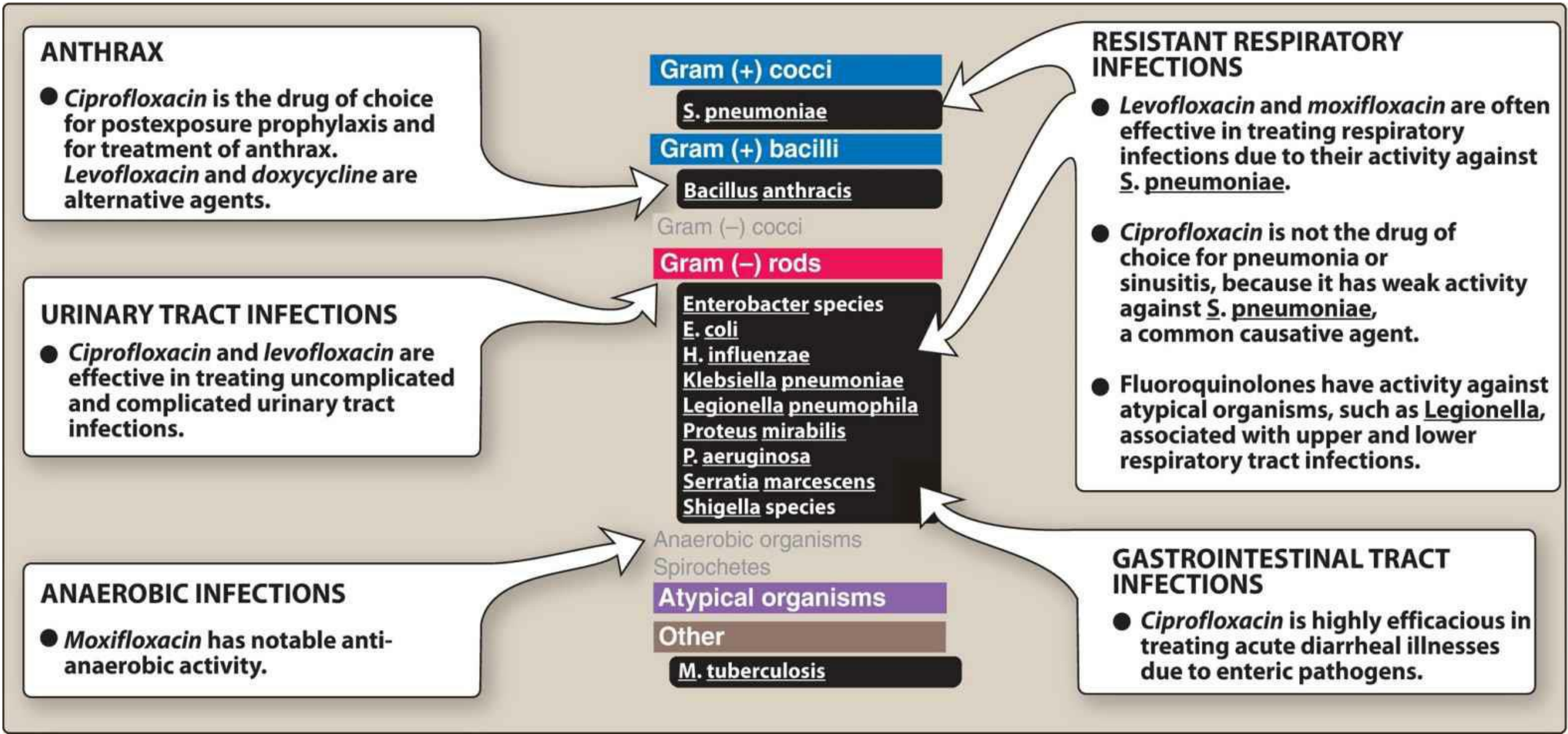
- **Fourth-generation compounds**
- (**Moxifloxacin**, **Gemifloxacin**, **and Delafloxacin**)
- They have enhanced **gram-positive activity**, including **Staphylococcus and Streptococcus spp**.
- **Delafloxacin** has activity against **methicillin-resistant Staphylococcus aureus (MRSA)** and **Enterococcus faecalis**.
- Further, **delafloxacin and moxifloxacin** have activity against **Bacteroides fragilis and Prevotella spp**., while maintaining activity against **Enterobacteriaceae** and **Haemophilus influenzae**.

I- Fluoroquinolone

- From this group, **only** **Delafloxacin** has activity against **Pseudomonas aeruginosa**.
- Lastly, these agents maintain **atypical coverage**, with **moxifloxacin** and **delafloxacin** showing activity against **Mycobacteria spp**.
- Common therapeutic applications of fluoroquinolones are shown in Figure

I- Fluoroquinolone

- **Antimicrobial spectrum**



I- Fluoroquinolone

- **Resistance**
- Numerous mechanisms of fluoroquinolone resistance exist in clinical pathogens.
- High-level fluoroquinolone resistance is primarily driven by:

1. **Chromosomal mutations** within **topoisomerases**,
2. **Decreased entry**,
3. **Efflux systems**, and
4. **Modifying enzymes play a role**.

I- Fluoroquinolone

Mechanisms responsible for resistance include the following:

1. Altered target binding

- Mutations in bacterial genes encoding **DNA gyrase** or **topoisomerase IV** (for example, gyrA or parC) alter target site structure and **reduce the binding** efficiency of fluoroquinolones.

2. Fluoroquinolone degradation

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

I- Fluoroquinolone

Mechanisms responsible for resistance include the following:

2. Decreased accumulation

- Reduced intracellular concentration is linked to

1. A reduction in membrane permeability or
2. Efflux pumps.

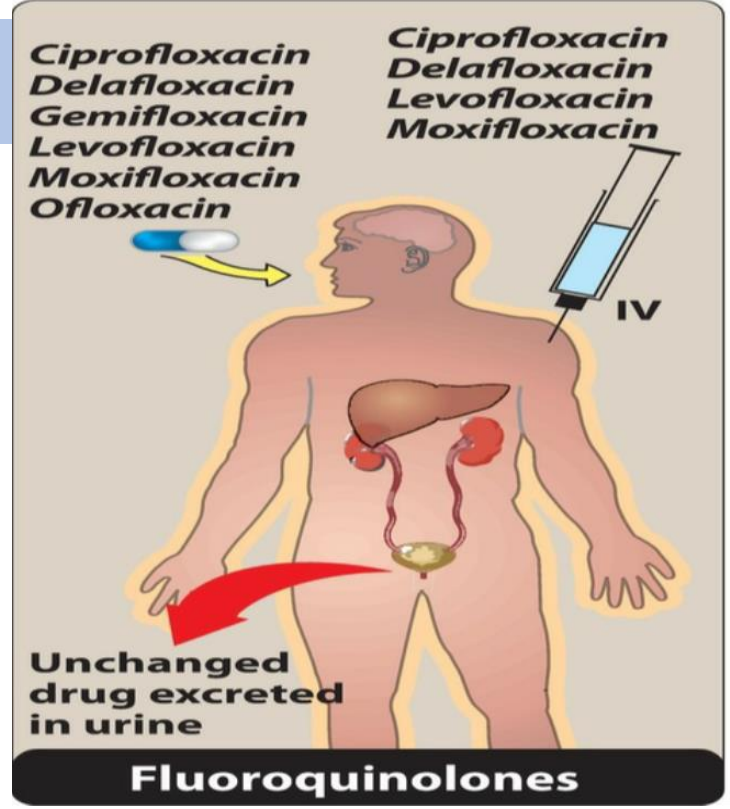
- Alterations in membrane permeability are mediated through a reduction in outer membrane porin proteins, thus limiting drug access to topoisomerases.
- Efflux pumps actively remove fluoroquinolones from the cell.

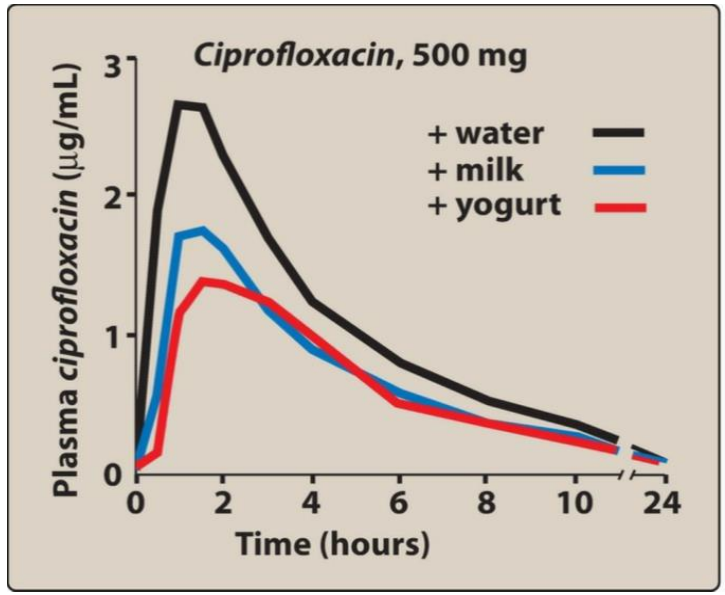
I- Fluoroquinolone

- **Pharmacokinetics**

1. 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 agents.





I- Fluoroquinolone

2. Distribution

- Binding to plasma proteins ranges from **20% to 84%.**
- Fluoroquinolones distribute well into all tissues and body fluids.
- Concentrations are **high** in **bone**, **urine** (except moxifloxacin), **kidney**, **prostatic** tissue (but not prostatic fluid), and **lungs** as compared to serum.

I- Fluoroquinolone

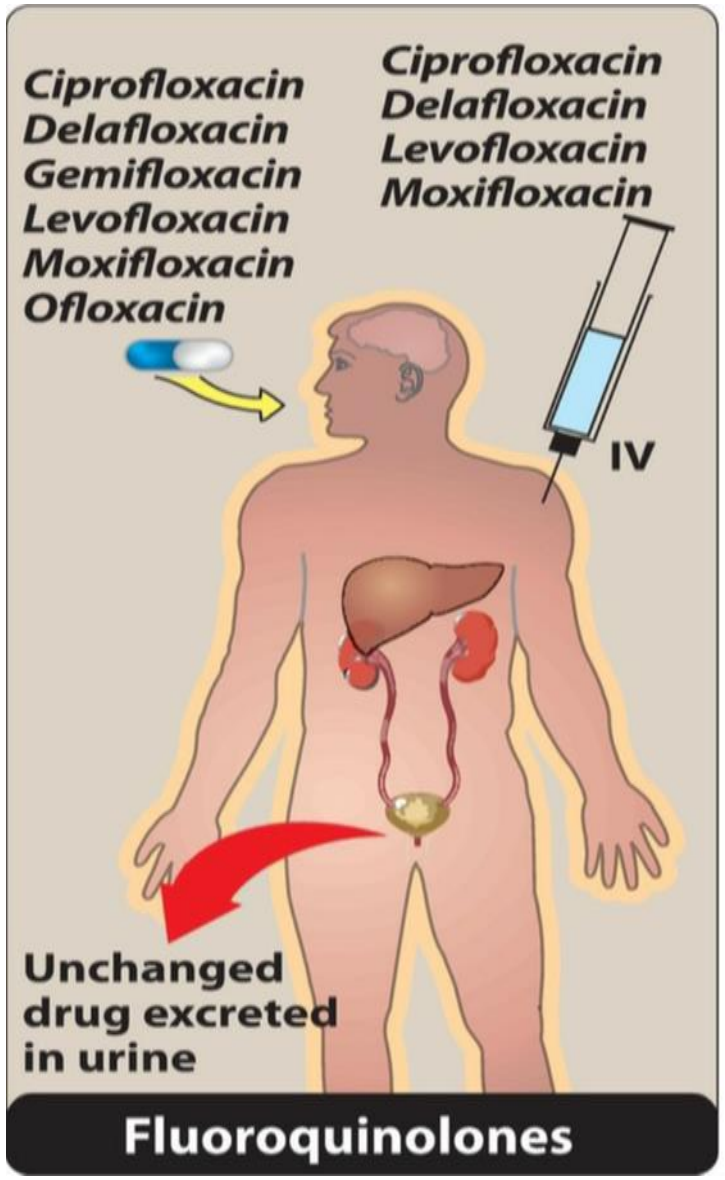
2. Distribution

- Penetration into **CSF** is **good**, and these agents may be considered in certain CNS infections.
- **Accumulation** in **macrophages** and **polymorphonuclear leukocytes** results in activity against intracellular organisms such as **Listeria, Chlamydia, and Mycobacterium**.

I- Fluoroquinolone

3. Elimination

- Most fluoroquinolones are **excreted renally**.
- Therefore, **dosage adjustments** are needed in **renal dysfunction**.
- **Moxifloxacin** is **metabolized** primarily by the **liver**, and while there is some renal excretion, **no dose adjustment is required for renal impairment**.



I- Fluoroquinolone

- **Adverse Reactions**

- In general, fluoroquinolones are **well tolerated** (Figure 31.5).

1. Common adverse effects leading to discontinuation are **nausea, vomiting, headache, and dizziness.**

2. These agents carry boxed warnings for **tendinitis, tendon rupture, peripheral neuropathy, and**

3. **CNS effects** (hallucinations, anxiety, insomnia, confusion, and seizures).

Tendinitis is the inflammation of a tendon

A boxed warning is a serious warning from the FDA

I- Fluoroquinolone

- **Adverse Reactions**

4. 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.

5. **Arthropathy** is uncommon, but **arthralgia and arthritis** are reported with fluoroquinolone use in pediatric patients.

I- Fluoroquinolone

- **Adverse Reactions**
- **Use in the pediatric population should be limited to distinct clinical scenarios** (for example, cystic fibrosis exacerbation).

6. **Hepatotoxicity** or
7. **Blood glucose disturbances** (usually in diabetic patients receiving oral hypoglycemic agents or insulin) have been observed.

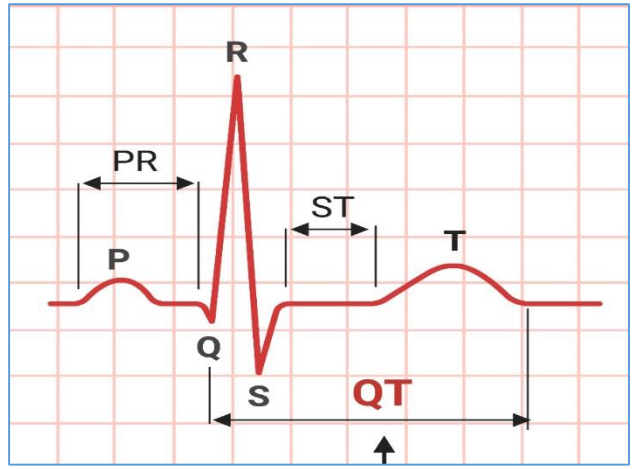
- Identification of any of these events should result in **prompt removal** of the agent.

I- Fluoroquinolone

- **Adverse Reactions**

8. Fluoroquinolones may **prolong the QTc** interval, and these agents should be avoided in patients predisposed to **arrhythmias** or taking medication associated with **QT prolongation**.
9. Ciprofloxacin **inhibits CYP450 1A2- and 3A4-mediated** metabolism.

- Serum concentrations of medications such as Theophylline, Tizanidine, Warfarin, Ropinirole Duloxetine, Caffeine, Sildenafil, and Zolpidem may be increased (Figure 31.6).



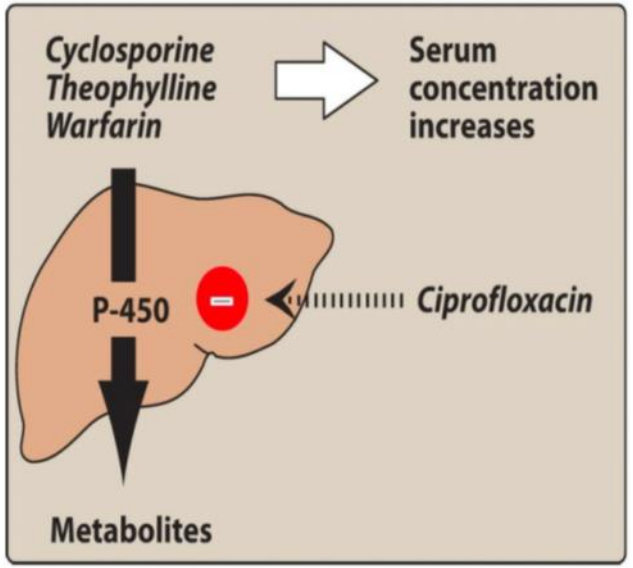


Figure 31.6 Drug interactions with *ciprofloxacin*.

I- Fluoroquinolone

- **Adverse Reactions**

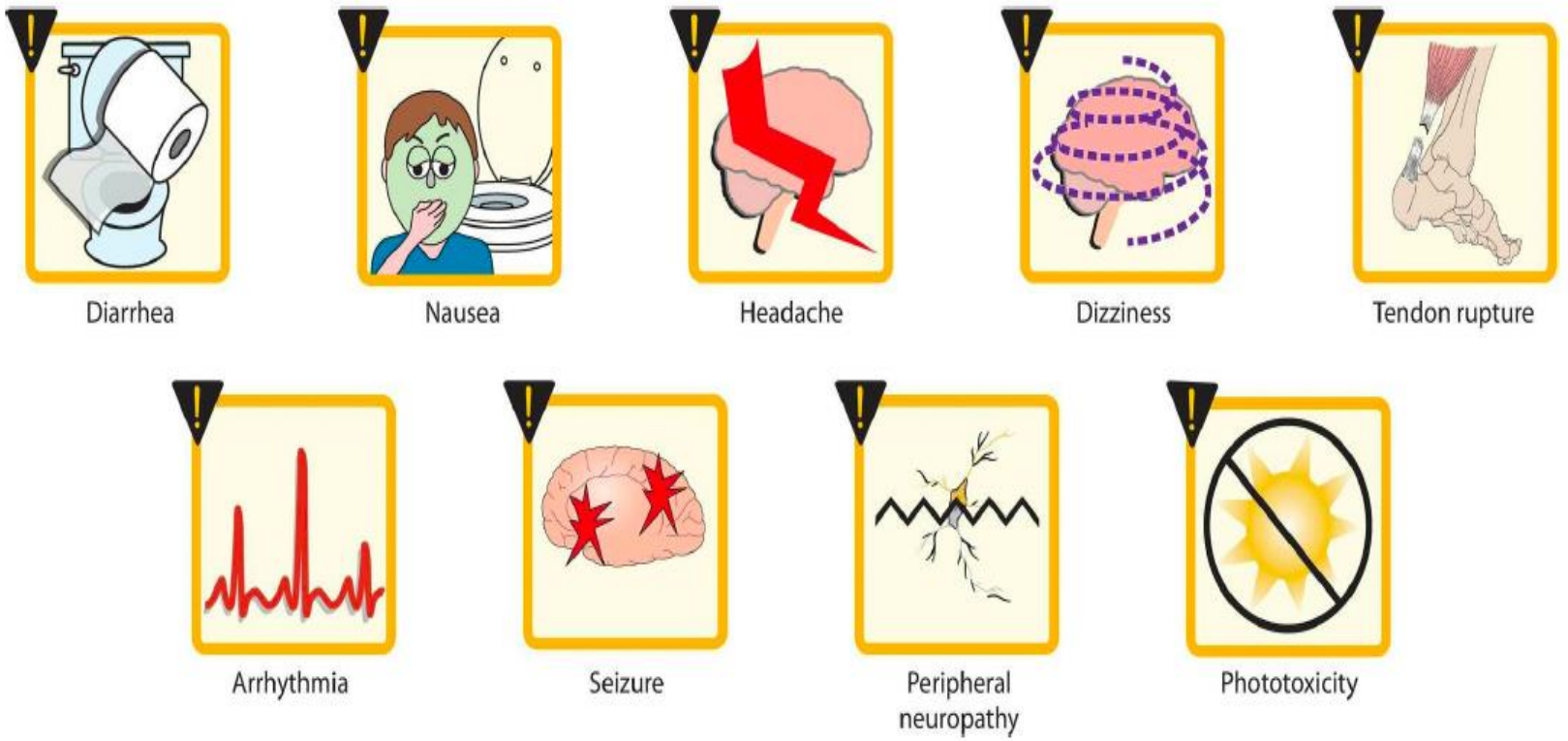


Figure 31.5 Some adverse reactions to fluoroquinolones.

I- Fluoroquinolone

- **Examples of clinically useful fluoroquinolones**
- Due to **increasing resistance** and boxed warnings, **fluoroquinolones should be used with caution in select circumstances.**
- They may be **considered** in:

1. Patients who **do not tolerate other agents** (for example, **severe beta-lactam allergies**) or
2. As **definitive therapy once susceptibilities** are available.

I- Fluoroquinolone

- **Listed below are potential indications for these agents:**

1. Ciprofloxacin (2nd G)

- It has good activity against **gram-negative bacilli**, including ***P. aeruginosa***.
- It is used in the treatment of
  1. **Traveler's diarrhea**,
  2. **Typhoid fever, and**
  3. **Anthrax**.
- It is a **second-line agent** for infections arising from **intra-abdominal, lung, skin, or urine sources**.
- Of note, **high-dose therapy** should be employed when treating ***Pseudomonas infections***.

I- Fluoroquinolone

- **Examples of clinically useful fluoroquinolones**

2. <u>Levofloxacin</u> (3rd G)

- Levofloxacin has **<u>similar activity to ciprofloxacin</u>** and they are often interchanged when managing **gram-negative bacilli**, including ***P. aeruginosa***.
- It has **enhanced** activity against ***S. pneumonia*** and **is first-line therapy for community-acquired pneumonia** (CAP).
- It is a **<u>second-line agent</u>** for the treatment of **Stenotrophomonas.** ***maltophilia***.

I- Fluoroquinolone

3. 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***.

I- Fluoroquinolone

3. Moxifloxacin

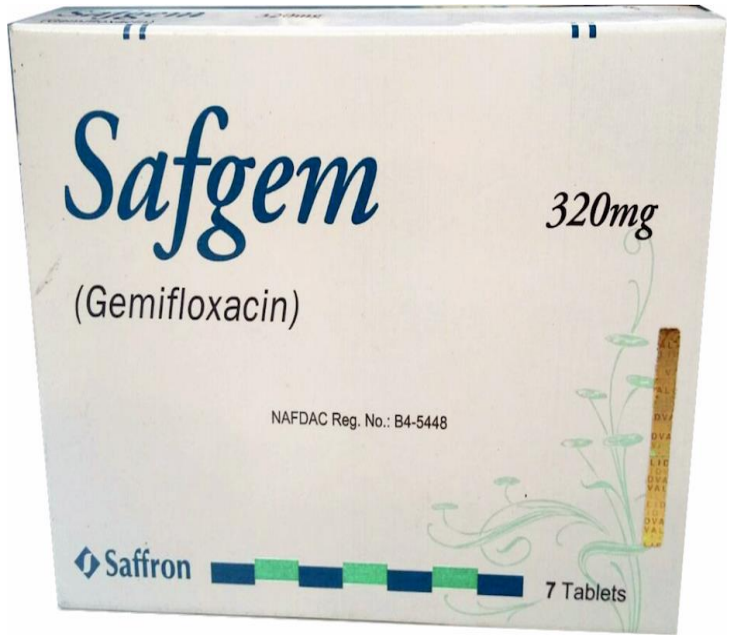
- It may be considered for mild-to-moderate **intra-abdominal infections** **but should be avoided** if patients have fluoroquinolone exposure within the **previous three months**, due to **increasing B. fragilis resistance**.
- It may be considered **a second-line agent** for the management of **drug-susceptible Tuberculosis**.

I- Fluoroquinolone

- **Examples of clinically useful fluoroquinolones**

4. Gemifloxacin

- It is indicated for the management of **community-acquired respiratory infections**.
- Unlike the other compounds, it is **only available as an oral formulation**.



I- Fluoroquinolone

- **Examples of clinically useful fluoroquinolones**

5. Delafloxacin

- It has improved activity against **gram-positive cocci**, including **MRSA** and **Enterococcus spp**.
- Due to its spectrum of activity, it is an option for managing **acute bacterial skin and skin structure infections**.
- It is available as an **intravenous and oral formulation**.

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

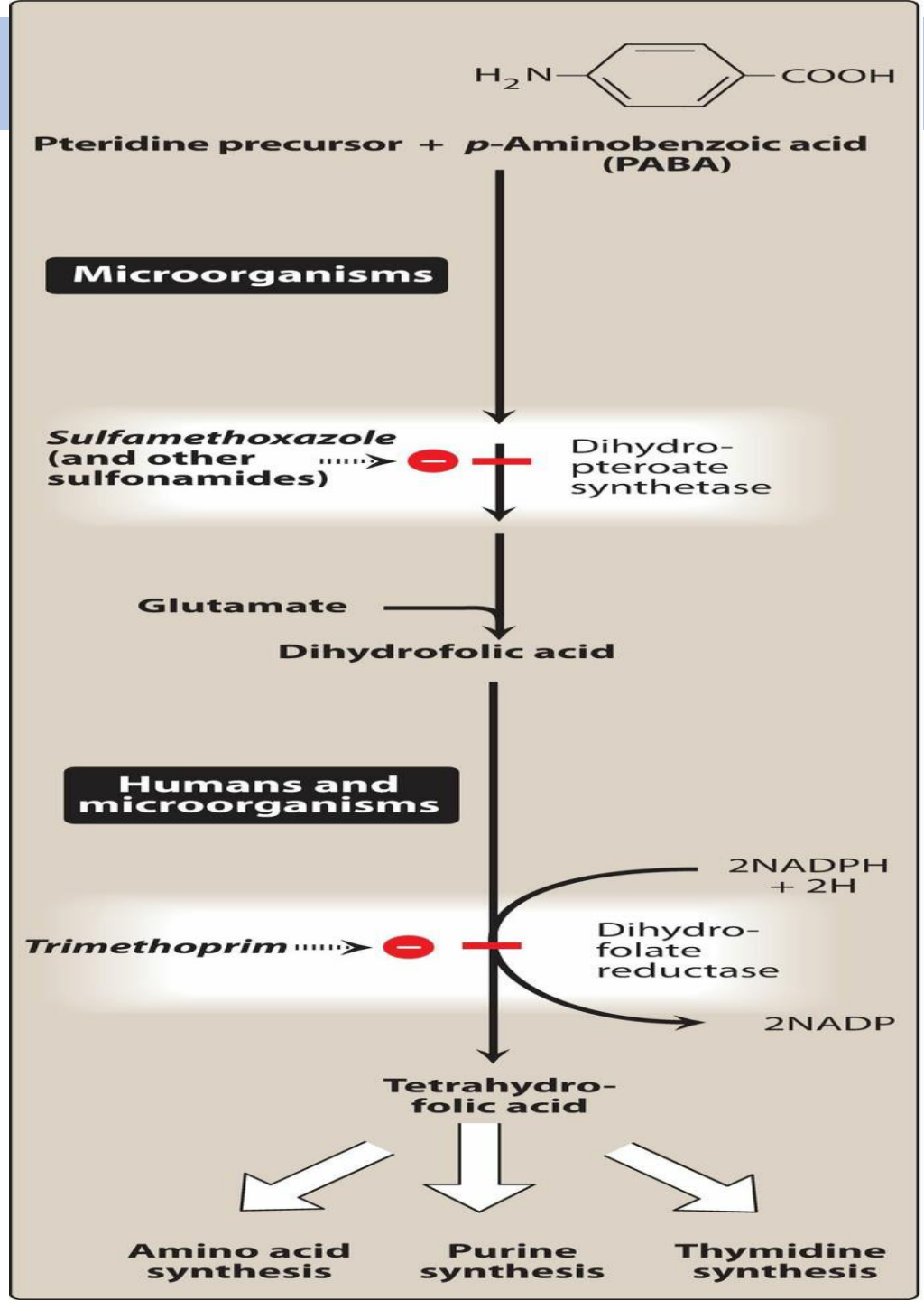
Nitrofurantoin MACROBID, MACRODANTI

II- 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*** (Figure).

II- Folate Antagonists

- **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**.



II- 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.

III. 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**.

III. Sulfonamides

- **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**.
- Because of their structural similarity, sulfonamides **compete** with PABA to **inhibit dihydropteroate synthetase and the genesis of bacterial dihydrofolic acid**.
- These agents, including **cotrimoxazole**, are **bacteriostatic.**

III. Sulfonamides

- **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**., and **Nocardia**.
- Additionally, **sulfadiazine** in combination with the *dihydrofolate reductase inhibitor* **pyrimethamine** is the preferred treatment for **toxoplasmosis**.

III. Sulfonamides

❑ 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**,
3. **Enhanced production of the natural substrate**, PABA.

- [Note: *organisms **resistant** to **one member** of this drug family are **resistant to all**.*]

III. Sulfonamides

❑ Pharmacokinetics

1. Absorption

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

III. Sulfonamides

❑ Pharmacokinetics

1. Absorption

- **Intravenous sulfonamides** are generally **reserved** for patients who are **unable to take oral preparations** or have **severe infections**.
- Because of **the risk of sensitization**, sulfa drugs are **not** usually applied **topically**.

III. Sulfonamides

❑ Pharmacokinetics

1. Absorption

- However, **in burn units**, silver sulfadiazine or mafenide acetate (α-amino-ptoluenesulfonamide) 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** and its **absorption** may contribute to acid–base disturbances.]

III. Sulfonamides

❑ Pharmacokinetics

2. 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.

III. Sulfonamides

❑ Pharmacokinetics

3. Metabolism

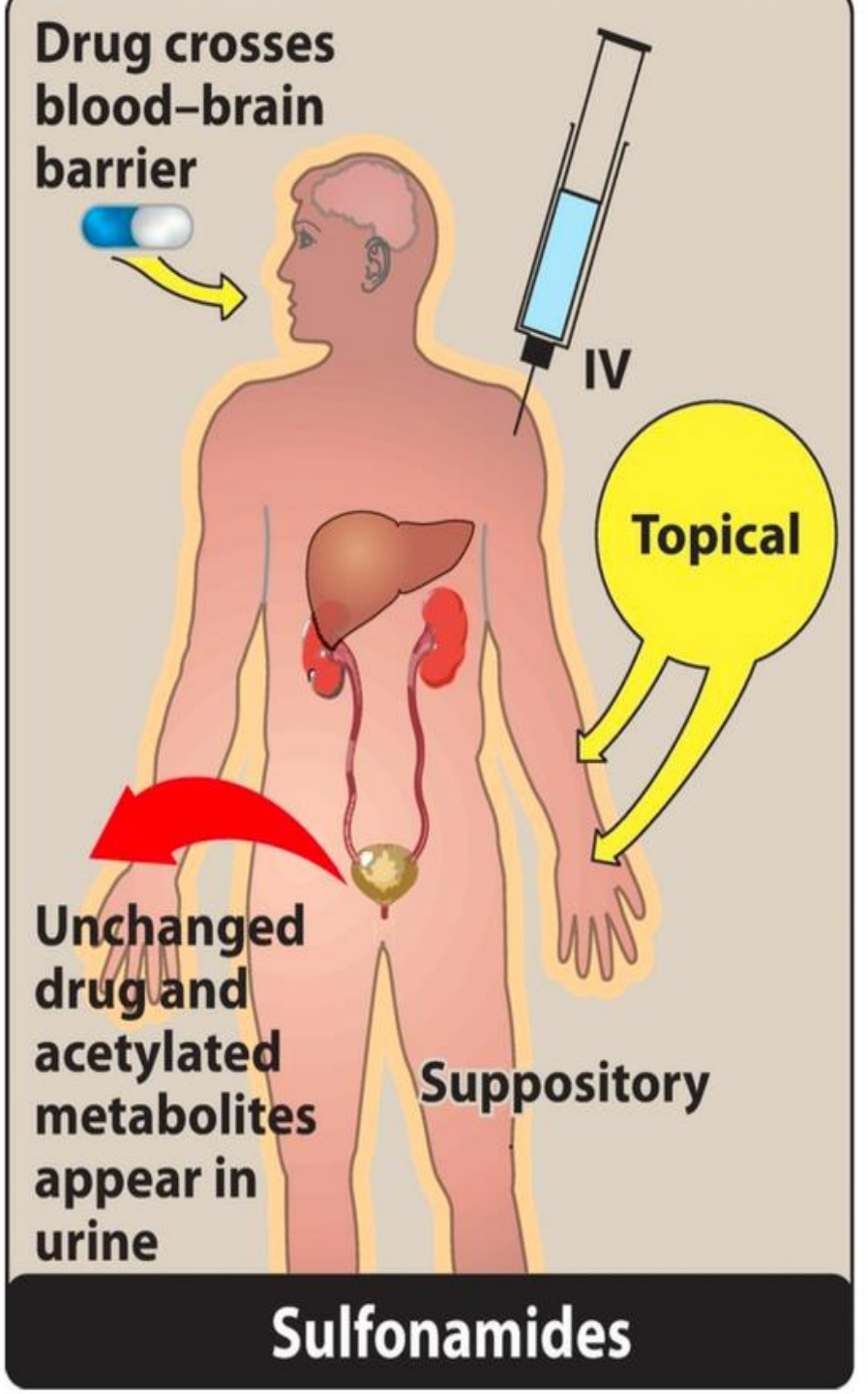
- Sulfa drugs are **acetylated** and **conjugated** primarily in the liver.
- The acetylated product is lacking of antimicrobial activity but retains the **toxic potential** to **precipitate** at **neutral or acidic pH**.
- This causes **crystalluria** (“stone formation”) and potential damage to the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

III. Sulfonamides

❑ Pharmacokinetics

4. Excretion

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



III. Sulfonamides

❑Adverse effects

1. Crystalluria

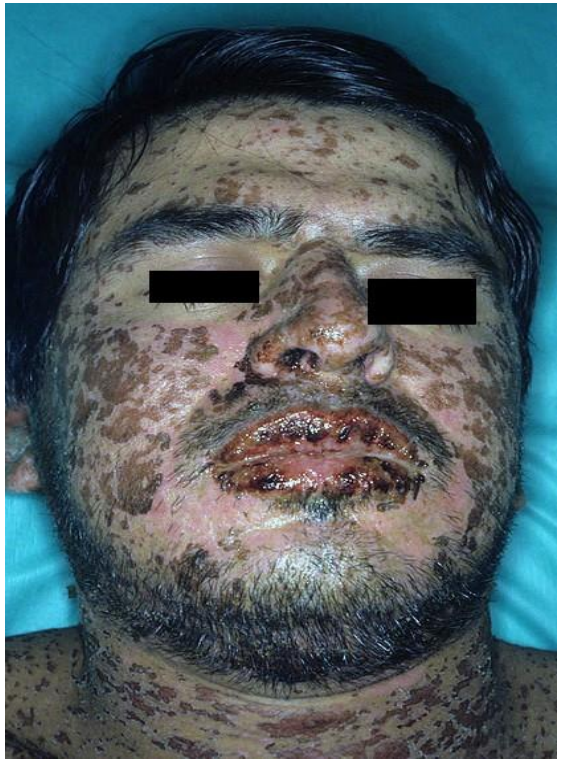
- **Nephrotoxicity** may develop as a result of crystalluria.
- **Adequate hydration and alkalinization** of urine can prevent the problem by reducing the concentration of drug and promoting its ionization.

III. Sulfonamides

❑Adverse effects

2. Hypersensitivity

- Hypersensitivity reactions, such as **rashes**, **angioedema**, or **Stevens-Johnson syndrome**, may occur.
- When patients **report previous sulfa allergies**, it is paramount to acquire a description of the reaction to direct appropriate therapy.



III. Sulfonamides

❑Adverse effects

3. Hematopoietic disturbances

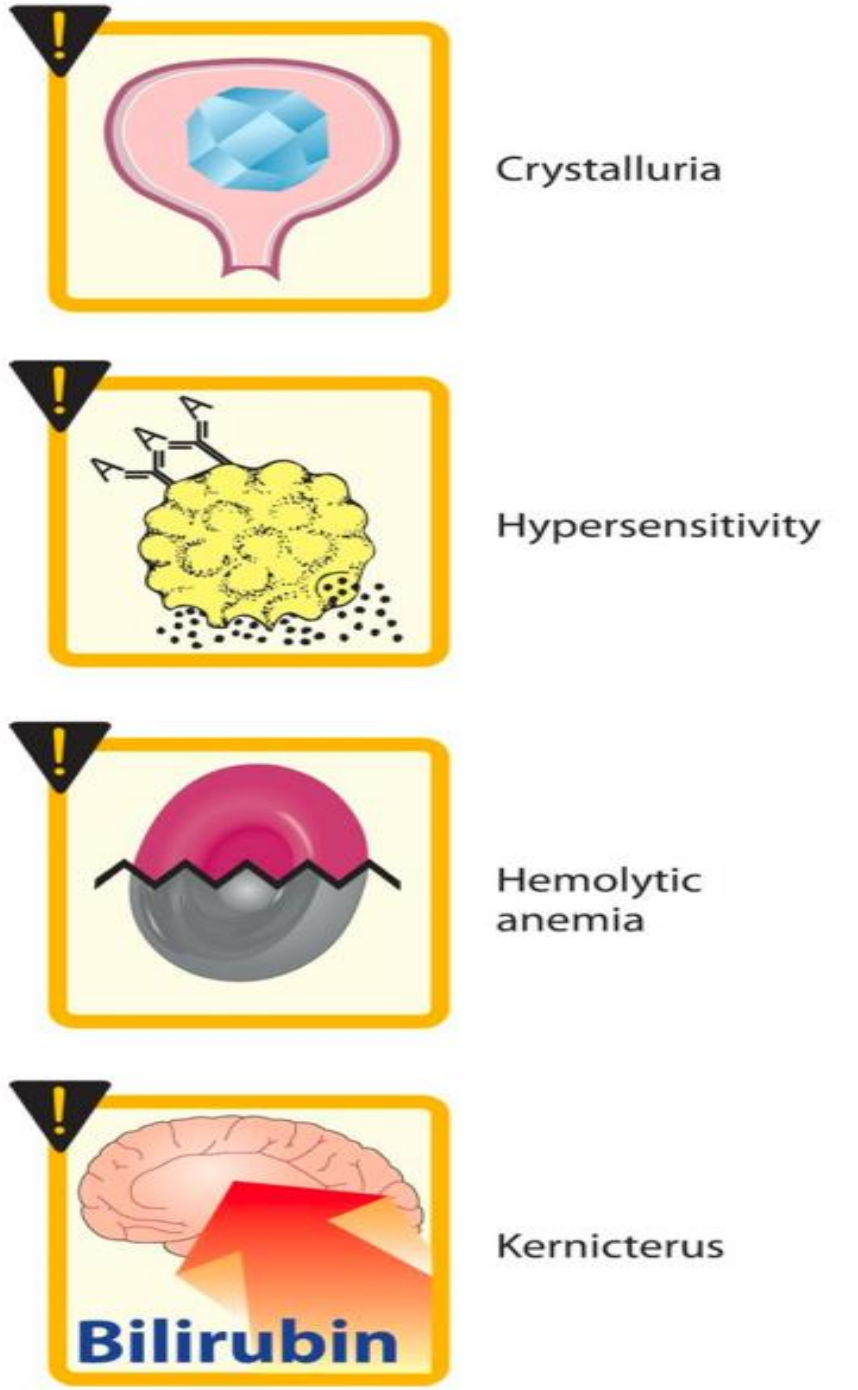
- **Hemolytic anemia** is encountered in patients with **glucose-6-phosphate dehydrogenase (G6PD)** deficiency.
- **Granulocytopenia** and **thrombocytopenia** can also occur.
- Fatal reactions have been reported from associated **agranulocytosis, aplastic anemia, and other blood dyscrasias**.

III. Sulfonamides

❑Adverse effects

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.



ome adverse reactions to sulfonamides.

III. Sulfonamides

❑Adverse effects

5. Drug potentiation

- **Sulfamethoxazole potentiates** the anticoagulant effect of **warfarin** due to **inhibition** of CYP2C9, resulting in reduced clearance of warfarin.
- **Sulfonamides** may also **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.

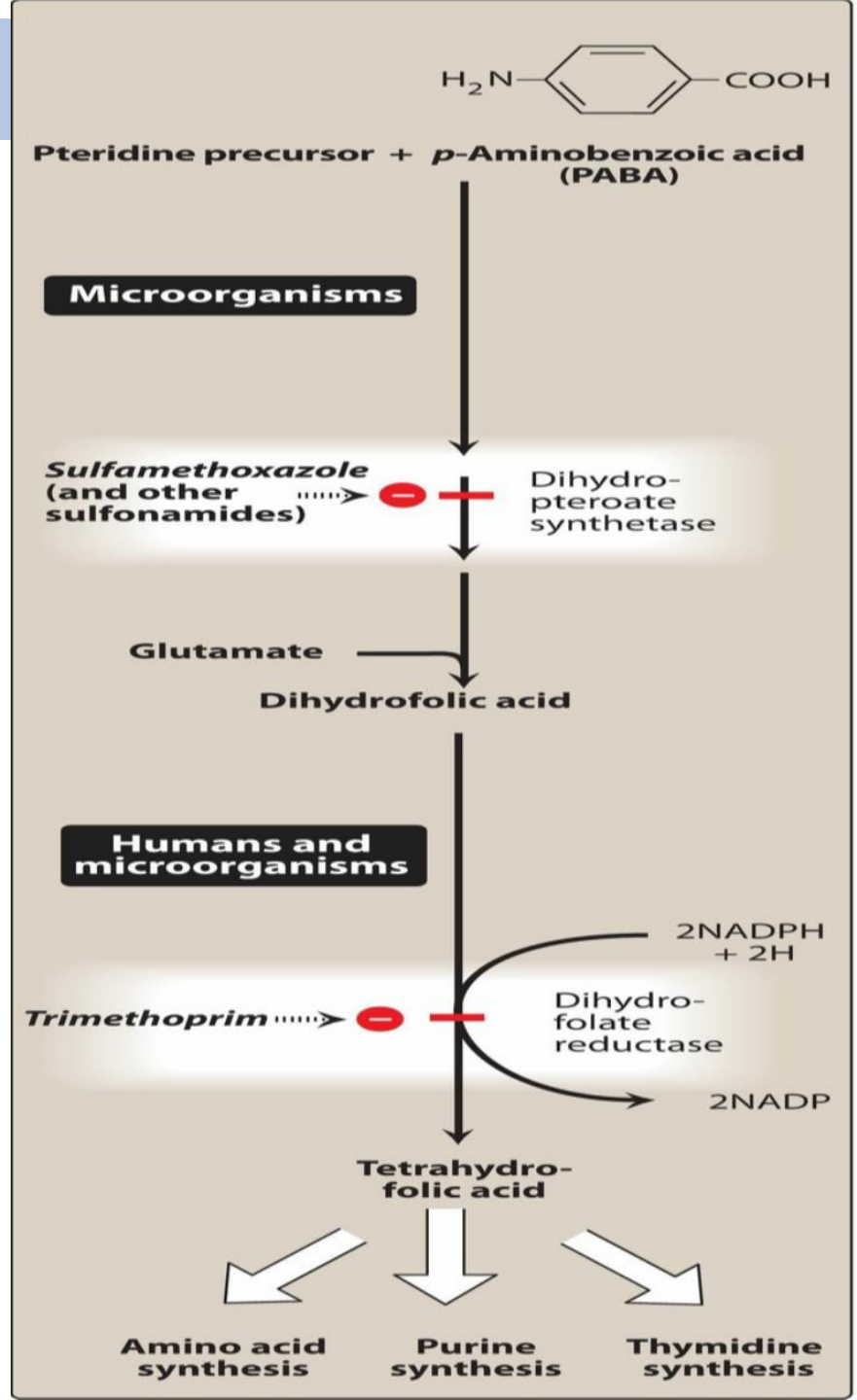
III. Sulfonamides

6. Contraindications

- Due to the danger of **kernicterus**, sulfa drugs should be avoided in **newborns** and **infants less than 2 months of age**, as well as in **pregnant** women at term.
- Sulfonamides should **not be given to patients receiving methenamine**, since they can **crystallize** in the presence of **formaldehyde** produced by this agent.

IV. 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.



IV. Trimethoprim

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

IV. Trimethoprim

- **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 **urinary tract infections** (UTIs) and in the **treatment of bacterial prostatitis** (although fluoroquinolones and cotrimoxazole are preferred).

IV. Trimethoprim

- **Resistance**
- Resistance in **gram-negative bacteria** is due to the presence of an **altered** **dihydrofolate reductase** that has a **lower affinity** for trimethoprim.
- **Efflux pumps** drug may play and **decreased permeability** to the drug may play a role.

IV. Trimethoprim

- **Pharmacokinetics**
- It 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**.
- It undergoes some O-demethylation, but 60% to 80% is renally excreted unchanged.

IV. Trimethoprim

- **Adverse effects**
- It can produce the effects of **folic acid deficiency**.
- These effects include **megaloblastic anemia**, **leukopenia**, and **granulocytopenia**, especially in pregnant 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.
- Trimethoprim has a potassium-sparing effect and may cause **hyperkalemia**, especially at higher doses and when administered with other medication that causes **hyperkalemia** (for example, **angiotensin-converting enzyme inhibitors**).

V. Cotrimoxazole

- The combination of **trimethoprim** with **sulfamethoxazole**, called **cotrimoxazole**, shows greater antimicrobial activity than equivalent quantities of either drug used alone.
- The combination was selected because of the **synergistic activity** and the **similarity** in the half-lives of the two drugs.

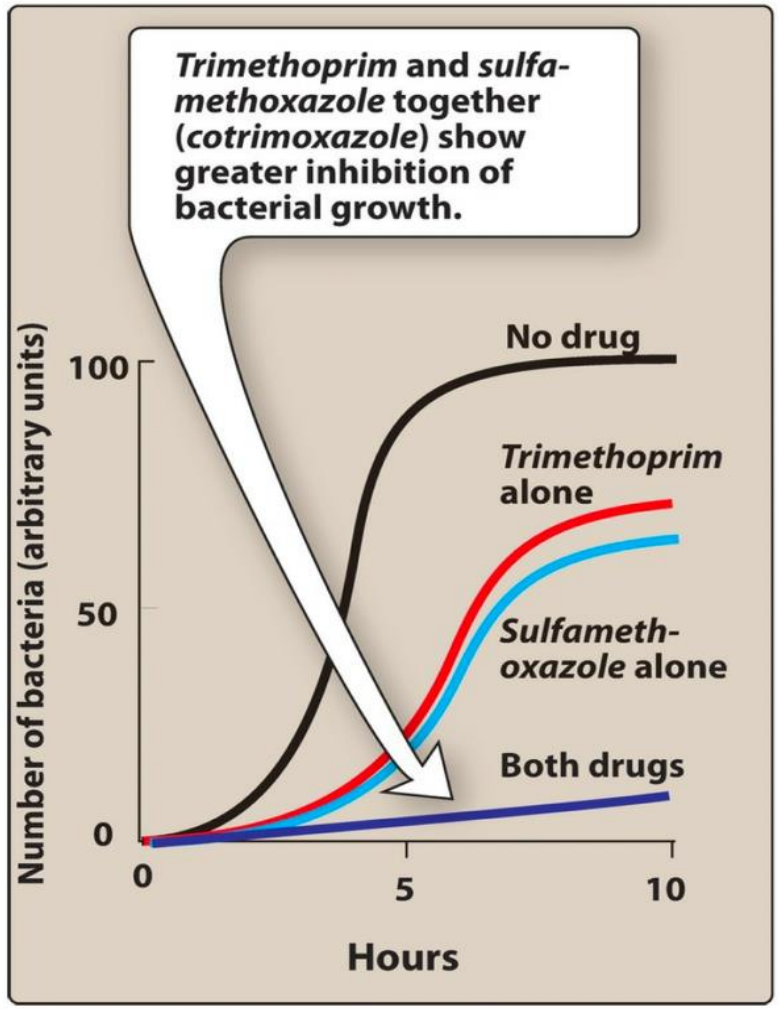


Figure 31.10 Synergism between *trimethoprim* and *sulfamethoxazole* inhibits growth of E. coli.

V. Cotrimoxazole

- **Mechanism of action**
- The **synergistic** antimicrobial activity of cotrimoxazole **results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic acid**.
- Sulfamethoxazole inhibits the **incorporation of PABA into dihydrofolic acid precursors**, and trimethoprim prevents the **reduction of dihydrofolate to tetrahydrofolate** .

V. Cotrimoxazole

- **Antibacterial spectrum**
- Cotrimoxazole has a **broader spectrum of antibacterial** action than the sulfa drugs alone.
- It is effective in **treating UTIs and respiratory tract infections**, as well as **Pneumocystis jirovecii**, **toxoplasmosis**, **Listeria monocytogenes**, and **Salmonella infections**.
- It has activity against **methicillin-resistant S. aureus** and can be particularly useful for **skin and soft tissue infections** caused by this organism.
- It is the drug of choice for infections caused by susceptible **Nocardia spp. And Stenotrophomonas maltophilia**.

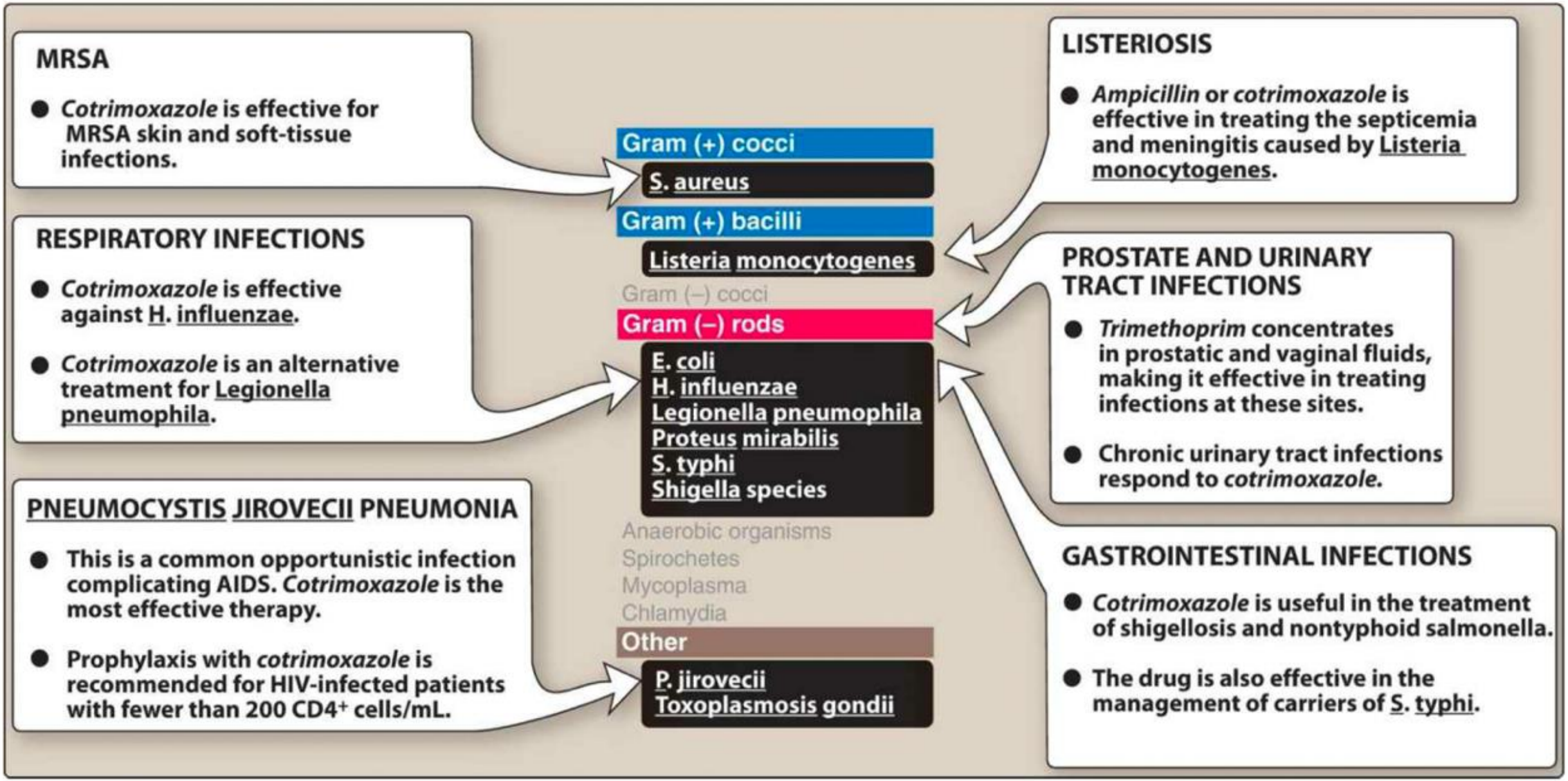


Figure 31.11 Typical therapeutic applications of *cotrimoxazole* (*sulfamethoxazole* plus *trimethoprim*).

V. Cotrimoxazole

- **Resistance**
- Resistance to the trimethoprim–sulfamethoxazole combination is encountered less frequently than resistance to either of the drugs alone, because it requires bacterium to maintain simultaneous resistance to both drugs.
- Significant resistance has been documented in a number of clinically relevant organisms, including E. coli.

V. Cotrimoxazole

- **Pharmacokinetics**
- **Cotrimoxazole** is generally administered orally (Figure 31.12).
- **Intravenous administration** may be utilized in patients with severe pneumonia caused by **Pneumocystis jirovecii**.
- Both agents are distributed throughout the body.
- Trimethoprim concentrates in the relatively **acidic milieu of prostatic fluids**, and this accounts for the use of trimethoprim–sulfamethoxazole in the treatment of **prostatitis**.
- Cotrimoxazole readily crosses the **blood–brain barrier**.
- Both parent drugs and their metabolites are excreted in the **urine**.

V. Cotrimoxazole

- **Adverse effects**
- Adverse reactions and drug interactions related to cotrimoxazole are similar to those expected with each of the individual components, sulfamethoxazole and trimethoprim (Figure 31.13).
- The most common adverse reactions are nausea and vomiting, skin rash, hematologic toxicity, and hyperkalemia.

V. Cotrimoxazole

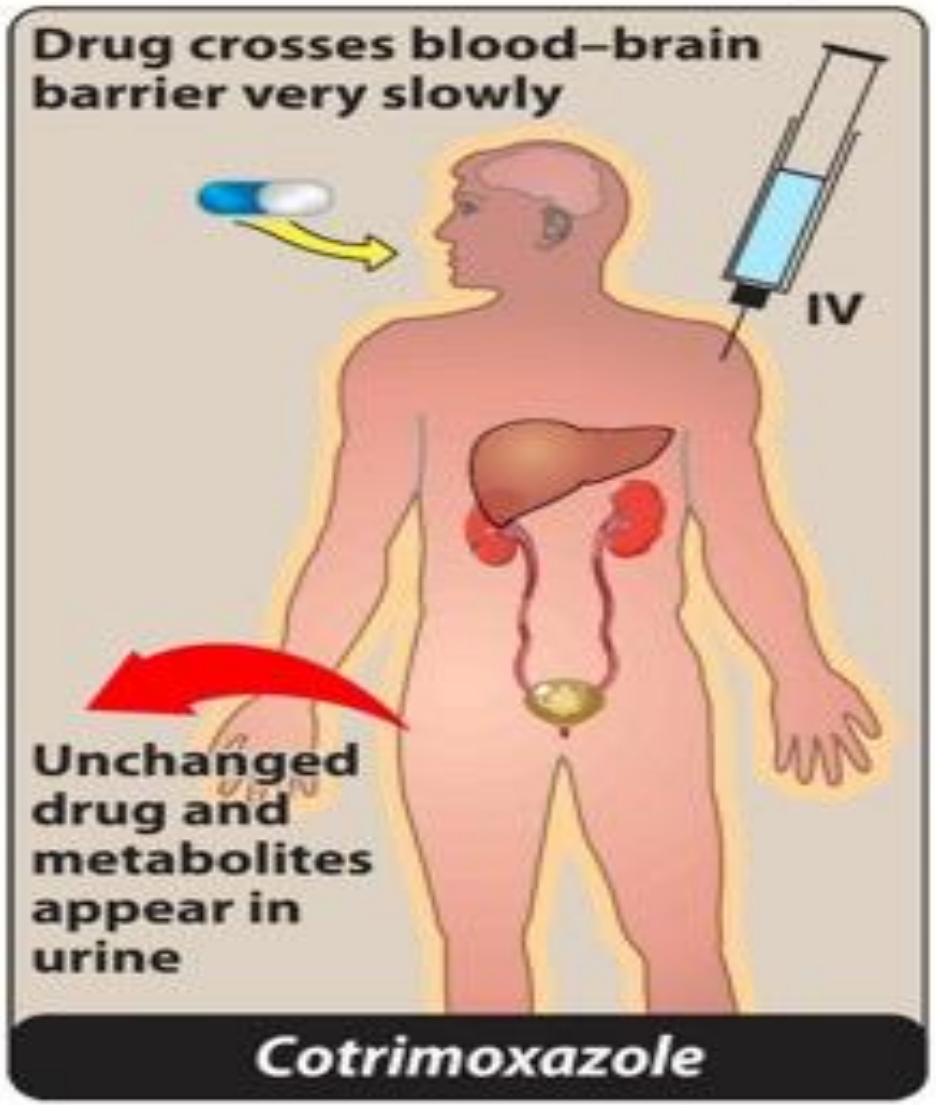


Figure 31.12 Administration and fate of cotrimoxazole

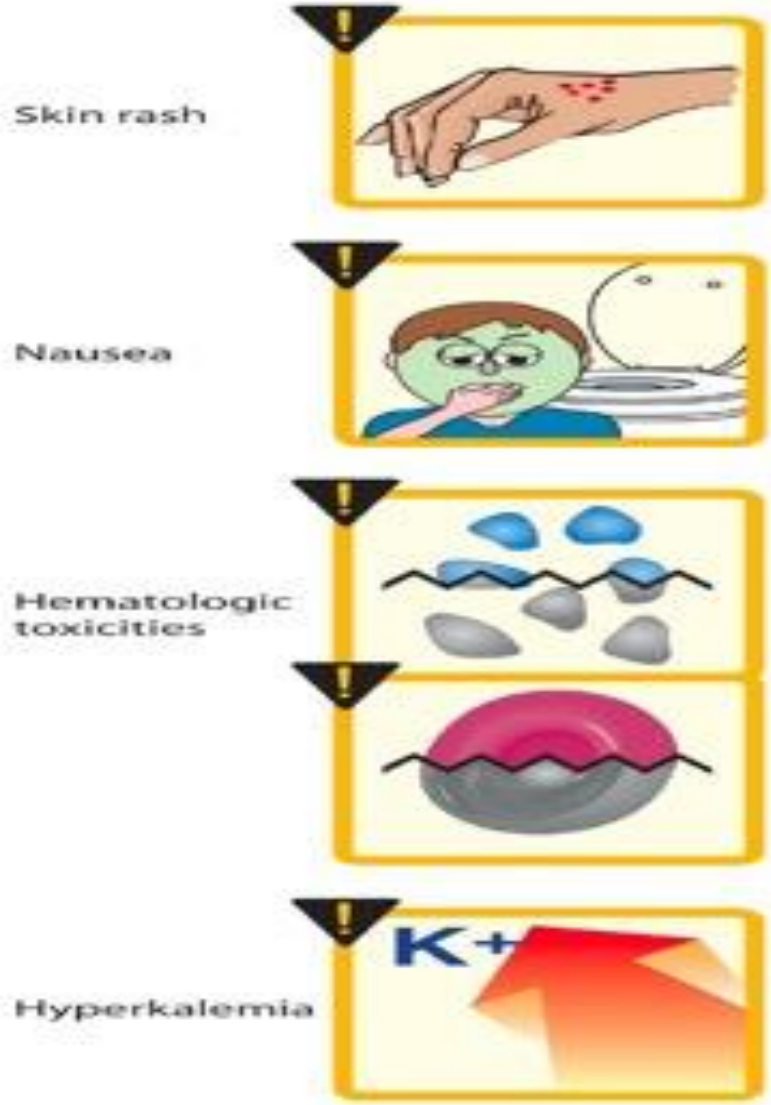


Figure 31.13 Some adverse reactions to cotrimoxazole

VI. Urinary Tract Antiseptics/Antimicrobials

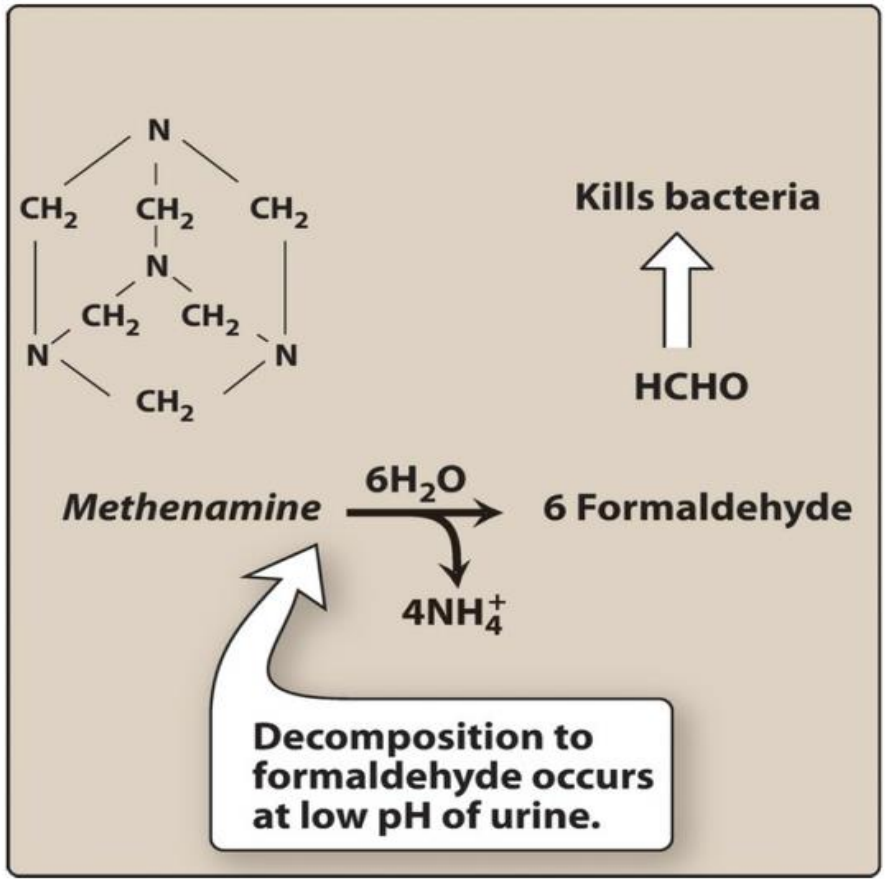
- UTIs are one of the most common bacterial infections in the world, primarily **impacting women and the elderly**.
- Historically, **fluoroquinolones** and **cotrimoxazole** have been the first-line therapy for the treatment of UTIs.
- Unfortunately, **resistance** has increased among common pathogens (for example, **E. coli**).
- As a result, **methenamine**, **nitrofurantoin**, and **fosfomycin** can be considered for **treatment** or **suppression of recurrence**, due to their efficacy against common pathogens and high concentrations in the urine.

VI. Urinary Tract Antiseptics/Antimicrobials

A. Methenamine

- **Mechanism of action**

- Methenamine salts are **hydrolyzed to ammonia** and **formaldehyde** in **acidic urine** (pH ≤ 5.5).
- Formaldehyde **denatures** proteins and nucleic acids, resulting in **bacterial cell death**.
- Methenamine is **combined** with a **weak acid** (for example**, hippuric acid**) to maintain **urine acidity** and promote the production of **formaldehyde**.



VI. Urinary Tract Antiseptics/Antimicrobials

A. Methenamine

- **Antibacterial spectrum**
- Methenamine is primarily used for **chronic suppressive therapy** to reduce the frequency of UTIs.
- Methenamine is active against **E. coli**, **Enterococcus spp., and Staphylococcus spp**.
- It has some activity against **Proteus spp. and Pseudomonas aeruginosa**, but **urine pH must be kept acidic to achieve bactericidal activity**.
- The main benefit of methenamine is the lack of selection for resistant organisms.

VI. Urinary Tract Antiseptics/Antimicrobials

A. Methenamine

- **Pharmacokinetics**
- Methenamine is **orally absorbed**, with up to **30% decomposing** in gastric juices, unless **protected** by **enteric coating**.
- It reaches the **urine** through **tubular secretion** and **glomerular filtration**.
- Concentrations are sufficient to treat susceptible organisms.
- Due to **ammonia formation**, use should be avoided in **hepatic insufficiency**.

VI. Urinary Tract Antiseptics/Antimicrobials

A. Methenamine

- **Adverse effects**
- The major adverse effect of methenamine is **gastrointestinal distress**, although at higher doses, **albuminuria, hematuria, and rashes** may develop.
- Methenamine mandelate is **contraindicated** in patients with **renal insufficiency**, because mandelic acid may precipitate.
- The methenamine hippurate formulation should be used instead.
- [Note: Sulfonamides, such as cotrimoxazole, **react with formaldehyde and must not be used concomitantly with methenamine**. The combination increases the risk of **crystalluria** and mutual **antagonism**.]

VI. Urinary Tract Antiseptics/Antimicrobials

B. Nitrofurantoin

- Nitrofurantoin was introduced into clinical practice for the management of cystitis in the early 1950s.
- For decades, it was rarely used, but was revived due to increasing antibiotic resistance among **Enterobacteriaceae** and is considered **first-line therapy for uncomplicated cystitis**.
- Nitrofurantoin works by **inhibiting DNA and RNA synthesis**.
- Susceptible organisms include **E. coli, Klebsiella spp.**, **Enterococcus spp.**, and **Staphylococcus spp**.
- Following oral administration, it is **rapidly absorbed**, with nearly **40% excreted unchanged in the urine**. Overall, nitrofurantoin is **well tolerated**.

VI. Urinary Tract Antiseptics/Antimicrobials

B. Nitrofurantoin

- **Common adverse events** include **nausea**, **vomiting**, and **diarrhea**.
- The use of the **microcrystalline formulation** decreases the incidence of gastrointestinal toxicity.
- Rare complications of therapy include **pulmonary fibrosis**, **neuropathy**, and **autoimmune hepatitis**.
- These events are observed with prolonged exposure greater than 1 month.
- Additionally, patients with impaired renal function should not receive nitrofurantoin due to an increased risk of adverse events.