

Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics

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Illustrated Reviews: Pharmacology

I. FLUOROQUINOLONES

- *Nalidixic acid is the predecessor to all fluoroquinolones.*
- Unfortunately, fluoroquinolone use has been closely tied to
 - Clostridium difficile infection and the
 - spread of antimicrobial resistance in many organisms (for example, methicillin resistance in staphylococci).

The unfavorable effects of fluoroquinolones on the induction and spread of antimicrobial resistance are sometimes referred to as “collateral damage,” a term which is also associated with third-generation cephalosporins (for example, ceftazidime).

A. Mechanism of action

- Fluoroquinolones enter bacteria through **porin channels** and exhibit antimicrobial effects on
 - **DNA gyrase** (bacterial **topoisomerase II**) and
 - bacterial **topoisomerase IV**.
- Inhibition of DNA gyrase results in relaxation of supercoiled DNA, promoting DNA strand breakage.
- Inhibition of topoisomerase IV impacts chromosomal stabilization during cell division, thus interfering with the separation of newly replicated DNA.
- In gram-negative organisms (for example, **Pseudomonas aeruginosa**), the inhibition of **DNA gyrase** is more significant than that of **topoisomerase IV**, whereas in gram-positive organisms (for example, **Streptococcus pneumoniae**), the opposite is true.

H.W: clarify the following:

- Agents with higher affinity for topoisomerase IV (for example, *ciprofloxacin*) *should not* be used for *S. pneumoniae* infections, while those with more topoisomerase II activity (for example, *moxifloxacin*) *should not be used* for *P. aeruginosa* infections.

B. Antimicrobial spectrum

- Fluoroquinolones are **bactericidal** and exhibit area under the curve/minimum inhibitory concentration (AUC/MIC)–dependent killing.
- Bactericidal activity is more pronounced as serum drug concentrations increase to approximately 30-fold the MIC of the bacteria.
- In general, fluoroquinolones are effective against
 - **gram-negative organisms** (Escherichia coli, P. aeruginosa, Haemophilus influenzae),
 - **atypical organisms** (Legionellaceae, Chlamydiaceae),
 - **gram-positive organisms** (streptococci), and some
 - **mycobacteria** (Mycobacterium tuberculosis).

- Fluoroquinolones are typically not used for the treatment of *Staphylococcus aureus* or enterococcal infections.
- They are **not effective against syphilis** and have limited utility against *Neisseria gonorrhoeae* due to disseminated resistance worldwide.
- *Levofloxacin* and *moxifloxacin* are sometimes referred to as “**respiratory fluoroquinolones**,” because they have excellent activity against *S. pneumoniae*, which is a common cause of community-acquired pneumonia (CAP).
- *Moxifloxacin* also has activity against many anaerobes.
- Fluoroquinolones are commonly considered alternatives for patients with a documented severe β -lactam allergy.

- Fluoroquinolones may be classified into “generations” based on their antimicrobial targets.
- The non fluorinated quinolone *nalidixic acid* is considered to be **first generation**, with a narrow spectrum of susceptible organisms.
- *Ciprofloxacin and norfloxacin* are **second generation** because of their activity against aerobic gram-negative and atypical bacteria.
- In addition, these fluoroquinolones exhibit significant intracellular penetration, allowing therapy for infections in which a bacterium spends part or all of its life cycle inside a host cell (for example, chlamydia, mycoplasma, and mycobacteria).
- *Levofloxacin* is classified as **third generation** because of its increased activity against gram-positive bacteria.
- Lastly, the **fourth generation** includes only *moxifloxacin* because of its activity against anaerobic and gram- positive organisms.

C. Examples of clinically useful fluoroquinolones

- **1. Norfloxacin:** *Norfloxacin [nor-FLOX-a-sin]* is infrequently prescribed due to
 - poor oral bioavailability and a short half-life.
 - It is effective in treating nonsystemic infections, such as urinary tract infections (UTIs), prostatitis, and infectious diarrhea (unlabeled use).
- **2. Ciprofloxacin:** *Ciprofloxacin [sip-row-FLOX-a-sin]*
 - is effective in the treatment of many systemic infections caused by gram-negative bacilli .
 - Of the fluoroquinolones, it has the best activity against *P. aeruginosa* and is commonly used in cystic fibrosis patients for this indication.
 - With 80% bioavailability, the intravenous and oral formulations are frequently interchanged.
 - Traveler's diarrhea caused by *E. coli* as well as typhoid fever caused by *Salmonella typhi* can be effectively treated with *ciprofloxacin*.
 - *Ciprofloxacin* is also used as a second-line agent in the treatment of tuberculosis.
 - Although typically dosed twice daily, an extended-release formulation is available for once-daily dosing, which may improve patient adherence to treatment.

- **3. Levofloxacin: *Levofloxacin [leave-oh-FLOX-a-sin]***
 - is the l-isomer of *ofloxacin [oh-FLOX-a-sin]* and has largely replaced it clinically.
 - Due to its broad spectrum of activity, *levofloxacin is utilized in a wide range of infections, including prostatitis, skin infections, CAP, and nosocomial pneumonia.*
 - Unlike *ciprofloxacin*, *levofloxacin has excellent activity against S. pneumoniae respiratory infections.*
 - *Levofloxacin has 100% bioavailability and is dosed once daily.*
- **4. Moxifloxacin: *Moxifloxacin [mox-ee-FLOX-a-sin]***
 - enhanced activity against gram-positive organisms (for example, *S. pneumoniae*) but also has
 - excellent activity against many anaerobes,
 - although resistance to *Bacteroides fragilis* has been reported.
 - It has poor activity against *P. aeruginosa*.
 - *Moxifloxacin* does not concentrate in urine and is not indicated for the treatment of UTIs.

D. Resistance

The mechanisms responsible for this resistance include the following:

- **1. Altered target:**
 - Chromosomal mutations in bacterial genes (for example, gyrA or parC) have been associated with a **decreased affinity for fluoroquinolones** at their site of action.
 - Both topoisomerase IV and DNA gyrase may undergo mutations.
- **2. Decreased accumulation:**
 - Reduced intracellular concentration is linked to
 - 1) **porin channels** (decreased number of porin proteins in the outer membrane of the resistant cell)
 - 2) **efflux pumps** (pumps drug out of the cell)

ANTHRAX

- *Ciprofloxacin* is the drug of choice for postexposure prophylaxis and for treatment of anthrax. *Doxycycline* is an alternate agent.

URINARY TRACT INFECTIONS

- *Ciprofloxacin* and *levofloxacin* are effective in treating uncomplicated and complicated urinary tract infections.

ANAEROBIC INFECTIONS

- *Moxifloxacin* has notable anti-anaerobic activity.

Gram (+) cocci

S. pneumoniae

Gram (+) bacilli

Bacillus anthracis

Gram (-) cocci

Gram (-) rods

Enterobacter species

E. coli

H. influenzae

Klebsiella pneumoniae

Legionella pneumophila

Proteus mirabilis

P. aeruginosa

Serratia marcescens

Shigella species

Anaerobic organisms

Spirochetes

Atypical organisms

Other

M. tuberculosis

RESISTANT RESPIRATORY INFECTIONS

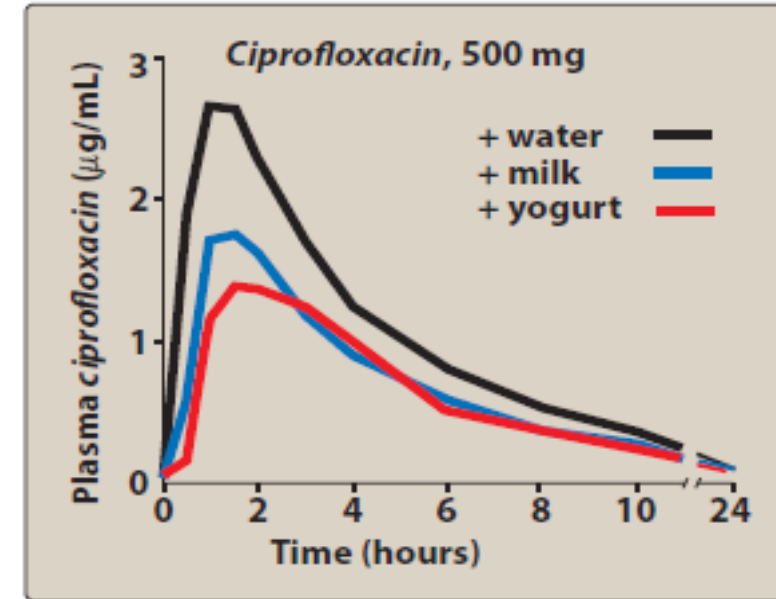
- *Levofloxacin* is often effective in treating infections unresponsive to β -lactam antibiotics, such as *amoxicillin-clavulanic acid*.
- *Ciprofloxacin* is not the drug of first choice for pneumonia or sinusitis, because it has weak activity against *S. pneumoniae*, a common causative agent.
- *Levofloxacin* and *moxifloxacin* are known as "respiratory fluoroquinolones" due to their activity versus *S. pneumoniae*.

GASTROINTESTINAL TRACT INFECTIONS

- *Ciprofloxacin* is highly efficacious in treating acute diarrheal illnesses due to enteric pathogens.

E. Pharmacokinetics

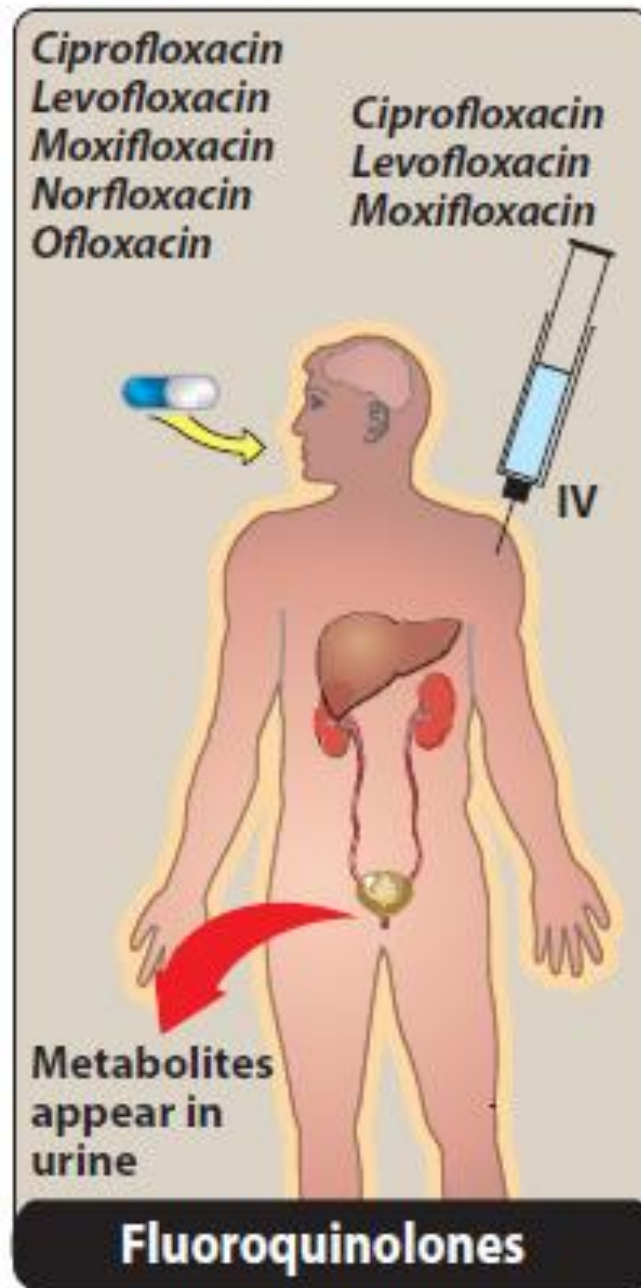
- **1. Absorption:**



- Only 35% to 70% of orally administered *norfloxacin* is absorbed, compared with 80% to 99% of the other fluoroquinolones.
- **Intravenous** and **ophthalmic** preparations of *ciprofloxacin*, *levofloxacin*, and *moxifloxacin* are available.
- 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.

- **2. Distribution:**

- Binding to plasma proteins ranges from 10% to 40%.
- The fluoroquinolones **distribute well into all tissues** and body fluids, which is one of their major clinical advantages.
- Penetration into cerebrospinal fluid is relatively low except for *ofloxacin*.
- Fluoroquinolones also accumulate in macrophages and polymorphonuclear leukocytes, thus having activity against intracellular organisms.



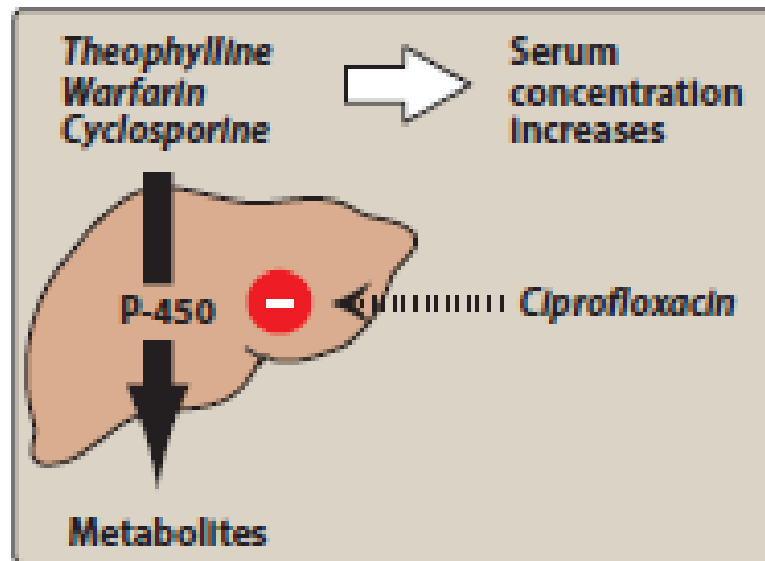
- **3. Elimination:**

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

- **F. Adverse reactions**

- In general, these agents are well tolerated.
- the most common adverse effects of fluoroquinolones are **nausea, vomiting, and diarrhea**.
- Headache and dizziness or lightheadedness may occur. Thus, patients with **central nervous system (CNS) disorders**, such as epilepsy, should be treated cautiously with these drugs.
- **Peripheral neuropathy** and **glucose dysregulation** (hypoglycemia and hypoglycemia) have also been noted.
- Fluoroquinolones can cause **phototoxicity**, and patients taking these agents should be advised to use sunscreen and avoid excess exposure to sunlight.

- Articular cartilage erosion (**arthropathy**) has been observed in immature animals exposed to fluoroquinolones.
- Therefore, these agents should be avoided in pregnancy and lactation and in children under 18 years of age. [Note: Careful monitoring is indicated in children with cystic fibrosis who receive fluoroquinolones for acute pulmonary exacerbations.]
- An increased risk of **tendinitis** or **tendon rupture** may also occur with systemic fluoroquinolone use.
- *Moxifloxacin* and other fluoroquinolones may prolong the QTc interval and, thus, should not be used in patients who are predisposed to arrhythmias or those who are taking other medications that cause QT prolongation.
- *Ciprofloxacin* can increase serum levels of **theophylline** by inhibiting its metabolism. Quinolones may also raise the serum levels of **warfarin**, **caffeine**, and **cyclosporine**.



Diarrhea



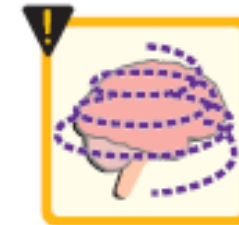
Nausea



Headache



Dizziness



Tendon rupture



FOLATE ANTAGONISTS

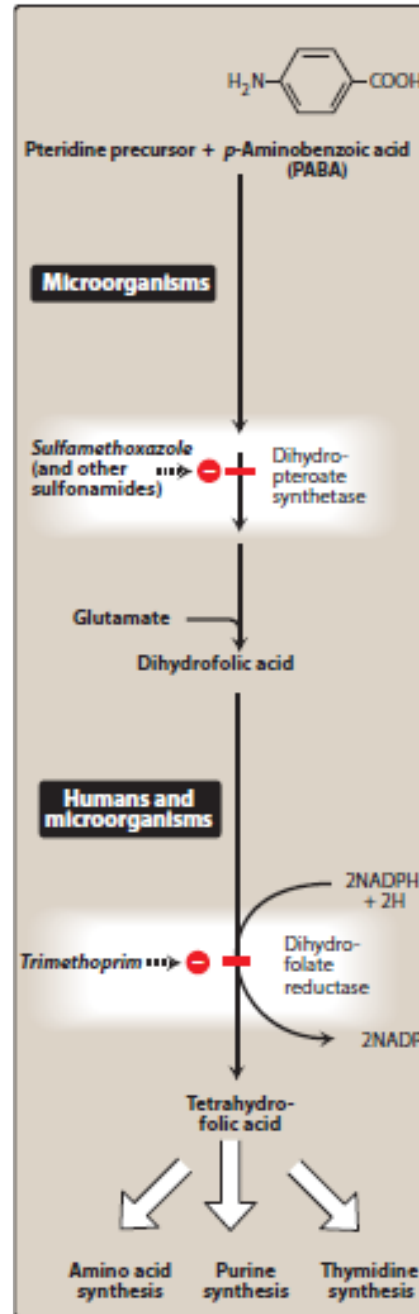
- Enzymes requiring folate-derived cofactors are essential for the synthesis of **purines and pyrimidines** (precursors of RNA and DNA) and other compounds necessary for cellular growth and replication.
- Therefore, **in the absence of folate, cells cannot grow or divide.**
- To synthesize the critical folate derivative, **tetrahydrofolic acid**, humans must first obtain preformed folate in the form of **folic acid from the diet.**
- In contrast, **many bacteria** are impermeable to folic acid and other folates and, therefore, must rely on their ability to **synthesize folate de novo.**

- The **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**, with minimal effect on the ability of human cells to make this conversion.
- Thus, both sulfonamides and *trimethoprim* interfere with the ability of an infecting bacterium to perform DNA synthesis.
- Combining the sulfonamide *sulfamethoxazole* with *trimethoprim* (the generic name for the combination is **cotrimoxazole**) provides a synergistic combination.

III. SULFONAMIDES

- **A. Mechanism of action**

- In many microorganisms, dihydrofolic acid is synthesized from *p*-aminobenzoic acid (PABA), pteridine, and glutamate.
- All the sulfonamides currently in clinical use are **synthetic analogs of PABA**.
- Because of their structural similarity to PABA, the sulfonamides compete with this substrate for the bacterial enzyme, **dihydropteroate synthetase**.
- They thus **inhibit the synthesis of bacterial dihydrofolic acid** and, thereby, the formation of its essential cofactor forms.
- The sulfa drugs, including *cotrimoxazole*, are bacteriostatic.



- **B. Antibacterial spectrum**

- Sulfa drugs are active against select *Enterobacteriaceae* in the urinary tract and *Nocardia* infections.
- In addition, *sulfadiazine* [sul-fa- DYE-a-zeen] in combination with the dihydrofolate reductase inhibitor *pyrimethamine* [py-ri-METH-a-meen] is the preferred treatment for toxoplasmosis.
- *Sulfadoxine* in combination with *pyrimethamine* is used as an antimalarial drug.

- **C. Resistance**

- Bacteria that can obtain folate from their environment are naturally resistant to these drugs.
- Acquired bacterial resistance to the sulfa drugs can arise from **plasmid transfers** or **random mutations**.
 - [Note: Organisms resistant to one member of this drug family are resistant to all.]
- Resistance is generally irreversible and may be due to
 - 1) an altered dihydropteroate synthetase,
 - 2) decreased cellular permeability to sulfa drugs, or
 - 3) enhanced production of the natural substrate, PABA.

D. Pharmacokinetics

- **1. Absorption:**
- After oral administration, most sulfa drugs are **well absorbed**
- An exception is *sulfasalazine* [sul-fa- SAL-a-zeen].
- It is not absorbed when administered orally or as a suppository and, therefore, is reserved for treatment of **chronic inflammatory bowel** disease (for example, ulcerative colitis).
- [Note: Local 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.]
- Intravenous sulfonamides are generally reserved for patients who are unable to take oral preparations.

- Because of the risk of sensitization, sulfa drugs are not usually applied topically.
- However, in **burn** units, creams of **silver sulfadiazine** [sul-fa-DYE-ah-zeen] or **mafenide** [mah-FEN-ide] acetate (α -amino-*p*-toluenesulfonamide) 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.*]

- **2. Distribution:**

- Sulfa drugs are **bound to serum albumin** in the circulation, where the extent of binding depends on the ionization constant (pKa) of the drug.
- In general, the smaller the pKa value, the greater the binding.
- Sulfa drugs distribute throughout the bodily fluids and penetrate well into cerebrospinal fluid—even in the absence of inflammation.
- They can also pass the **placental barrier** and enter fetal tissues.

- **3. Metabolism:**

- The 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”; see below) and, therefore, potential damage to the kidney.

- **4. Excretion:**

- **Sulfa drugs are eliminated by glomerular filtration** and secretion and require **dose adjustments** for renal dysfunction.
- Sulfonamides may be eliminated in breast milk.

E. Adverse effects

- **1. Crystalluria:**

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

- **2. Hypersensitivity:**

- rashes,
- angioedema or
- Stevens-Johnson syndrome, 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, aplastic anemia, and other blood dyscrasias.

- **4. Kernicterus:**

- This disorder 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.

- **5. Drug potentiation:**

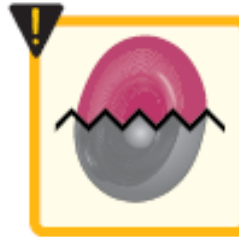
- Transient potentiation of the anticoagulant effect of *warfarin* results from the **displacement** from binding sites on serum albumin.
- Serum *methotrexate* levels may also rise through its displacement.



Crystalluria



Hypersensitivity



Hemolytic
anemia

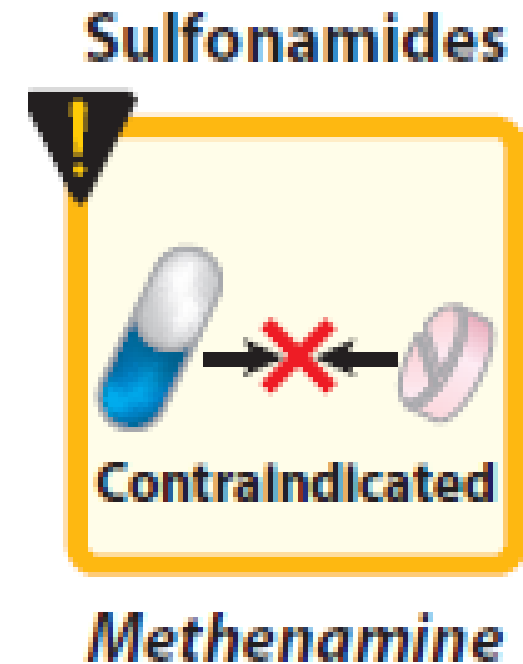


Kernicterus

Figure 40.9
Some adverse reactions to
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* [try-METH-oh-prim], a potent inhibitor of bacterial **dihydrofolate reductase**, exhibits an antibacterial spectrum similar to that of the sulfonamides.
- *Trimethoprim* is most often compounded with *sulfamethoxazole* [sul-fa-meth-OX-a-zole], producing the combination called **cotrimoxazole**.

- **A. Mechanism of action**

- The active form of folate is the tetrahydro derivative that is formed through reduction of **dihydrofolic acid** by **dihydrofolate reductase**.
- This enzymatic reaction is inhibited by *trimethoprim*, leading to a decreased availability of the **tetrahydrofolate** cofactors required for purine, pyrimidine, and amino acid synthesis.
- The bacterial reductase has a much stronger affinity for *trimethoprim* than does the mammalian enzyme, which accounts for the **selective toxicity** of the drug.

- **B. 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 UTIs and in the treatment of bacterial prostatitis (although fluoroquinolones are preferred).

- **C. 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** and decreased permeability to the drug may play a role.

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

- **E. Adverse effects**

- *Trimethoprim* can produce the effects of folic acid deficiency.
 - megaloblastic anemia,
 - leukopenia, and
 - granulocytopenia,
 - especially in pregnant patients and those having very poor diets.
- These blood disorders may be reversed by the simultaneous administration of *folinic acid*, which does not enter bacteria.

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.

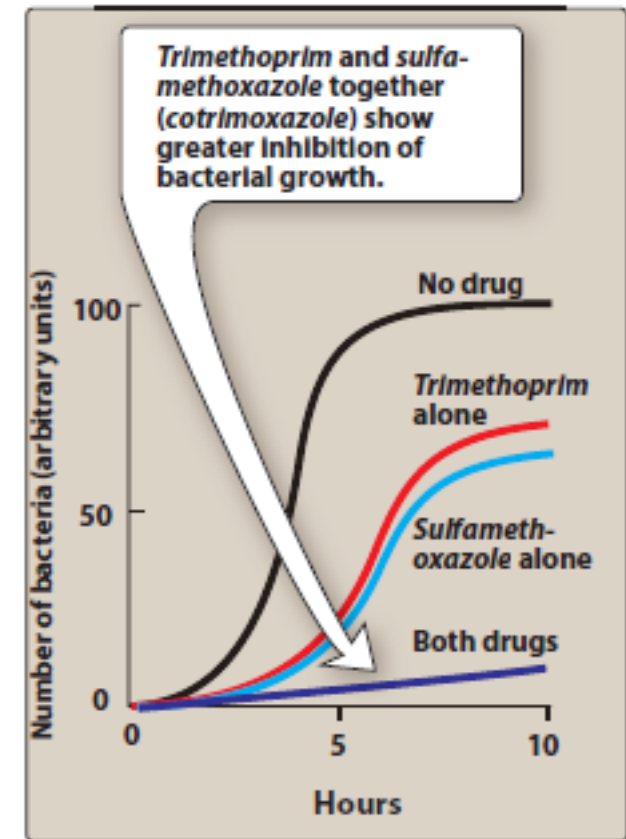


Figure 40.11

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

- **B. 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* pneumonia (PCP), toxoplasmosis, and ampicillin- or chloramphenicol-resistant salmonella infections.
- It has activity against MRSA and can be particularly useful for community-acquired skin and soft tissue infections caused by this organism.
- It is the drug of choice for infections caused by susceptible *Nocardia species* and *Stenotrophomonas maltophilia*.

MRSA

- *Cotrimoxazole* is effective for community-acquired MRSA skin and soft tissue infections.

RESPIRATORY INFECTIONS

- *Cotrimoxazole* is effective against *H. influenzae*.
- *Cotrimoxazole* is an alternative treatment for *Legionella pneumophila*.

PNEUMOCYSTIS JIROVECI PNEUMONIA

- This is a common opportunistic infection complicating AIDS. *Cotrimoxazole* is the most effective therapy.
- Prophylaxis with *cotrimoxazole* is recommended for HIV-infected patients with fewer than 200 CD4⁺ cells/mL.

Gram (+) cocci

S. aureus

Gram (+) bacilli

Listeria monocytogenes

Gram (-) cocci

Gram (-) rods

E. coli
H. influenzae
Legionella pneumophila
Proteus mirabilis
S. typhi
Shigella species

Anaerobic organisms

Spirochetes

Mycoplasma

Chlamydia

Other

P. jirovecii
Toxoplasmosis gondii

LISTERIOSIS

- *Ampicillin* or *cotrimoxazole* is effective in treating the septicemia and meningitis caused by *Listeria monocytogenes*.

PROSTATE AND URINARY TRACT INFECTIONS

- *Trimethoprim* concentrates in prostatic and vaginal fluids, making it effective in treating infections at these sites.
- Chronic urinary tract infections respond to *cotrimoxazole*.

GASTROINTESTINAL INFECTIONS

- *Cotrimoxazole* is useful in the treatment of shigellosis and nontyphoid salmonella.
- The drug is also effective in the management of carriers of *S. typhi*

- **C. Resistance**

- Resistance to the *trimethoprim–sulfamethoxazole* combination is **less frequently encountered** than resistance to either of the drugs alone, because it requires that the bacterium have simultaneous resistance to both drugs.

Significant resistance has been documented in a number of clinically relevant organisms, including **E. coli and MRSA.**

- **D. Pharmacokinetics**
- *Cotrimoxazole* is generally administered orally (Figure 40.13).
- Intravenous administration may be utilized in patients with severe pneumonia caused by PCP.
- Both agents distribute 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.

- **E. Adverse effects**

- Reactions involving the skin are very common and may be severe in the elderly.

Nausea and vomiting are the most common gastrointestinal adverse effects.

Glossitis and stomatitis have been observed.

Hyperkalemia may occur, especially with higher doses.

- Megaloblastic anemia, leukopenia, and thrombocytopenia may occur and have been fatal.
- The hematologic effects may be reversed by the concurrent administration of *folinic acid*, which protects the patient and does not enter the microorganism.

- **Hemolytic anemia** may occur in patients with G6PD deficiency due to the *sulfamethoxazole* component.
- Immunocompromised patients with PCP frequently show drug-induced fever, rashes, diarrhea, and/or pancytopenia.
- Prolonged prothrombin times (increased INR) in patients receiving both *sulfamethoxazole* and *warfarin* have been reported.
- The plasma half-life of *phenytoin* may be increased due to inhibition of its metabolism.
- *Methotrexate* levels may rise due to displacement from albumin-binding sites by *sulfamethoxazole*.

VI. URINARY TRACT ANTISEPTICS/ANTIMICROBIALS

- UTIs are prevalent in women of child-bearing age and in the elderly population.

E. coli is the most common pathogen, causing about 80% of uncomplicated upper and lower UTIs.

Staphylococcus saprophyticus is the second most common bacterial pathogen causing UTIs.

In addition to *cotrimoxazole* and the quinolones previously mentioned, UTIs may be treated with any one of a group of agents called **urinary tract antiseptics**,

- including *methenamine*, *nitrofurantoin*, and the quinolone *nalidixic acid* (not available in the United States).
- These drugs do not achieve antibacterial levels in the circulation, but because they are **concentrated in the urine**, microorganisms at that site can be effectively eradicated

A. Methenamine

- **1. Mechanism of action:**
- *Methenamine* [meth-EN-a-meen] decomposes at an acidic pH of 5.5 or less in the urine, thus producing **formaldehyde**, which acts locally and is **toxic to most bacteria**.
- Bacteria do not develop resistance to formaldehyde, which is an advantage of this drug.
- [Note: *Methenamine* is frequently formulated with a weak acid (for example, mandelic acid or hippuric acid) to **keep the urine acidic**.
- The urinary pH should be maintained below 6. Antacids, such as *sodium bicarbonate*, should be avoided.]

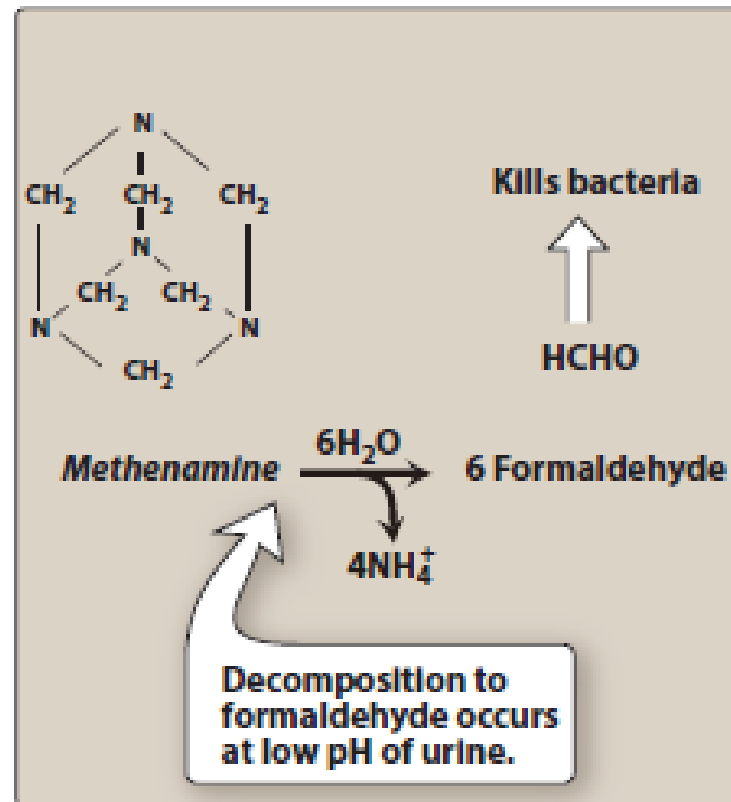


Figure 40.15

Formation of formaldehyde from *methenamine* at acid pH.

- **2. Antibacterial spectrum:**

- *Methenamine* is primarily used for chronic suppressive therapy to reduce the frequency of UTIs.
- Routine use in patients with chronic urinary catheterization to reduce catheter associated bacteriuria or catheter-associated UTI is not generally recommended.
- *Methenamine* should not be used to treat upper UTIs (for example, pyelonephritis).
- Urea-splitting bacteria that alkalinize the urine, such as *Proteus* species, are usually resistant to the action of *methenamine*.

- **4. Adverse effects:**

- The major side 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.
- [Note: Sulfonamides, such as *cotrimoxazole*, react with formaldehyde and must not be used concomitantly with *methenamine*.

B. Nitrofurantoin

- *Nitrofurantoin* [nye-troe-FYLOOR-an-toyn] sensitive bacteria reduce the drug to a highly active intermediate that inhibits various enzymes and damages bacterial DNA.
- It is useful against *E. coli*, but other common urinary tract gram-negative bacteria may be resistant.
- Grampositive cocci (for example, *S. saprophyticus*) are typically susceptible.
- Hemolytic anemia may occur with *nitrofurantoin* use in patients with G6PD deficiency.

- Other adverse effects include gastrointestinal disturbances, acute pneumonitis, and neurologic problems.
- Interstitial pulmonary fibrosis has occurred in patients who take *nitrofurantoin* chronically.
- The drug should not be used in patients with significant renal impairment or women who are 38 weeks or more pregnant.