# Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics

# 40

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## I. FLUOROQUINOLONES

*Nalidixic acid* is the predecessor to all fluoroquinolones, a class of man-made antibiotics. Over 10,000 fluoroquinolone analogs have been synthesized, including several with wide clinical applications. Fluoroquinolones in use today typically offer greater efficacy, a broader spectrum of antimicrobial activity, and a better safety profile than their predecessors. 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*). The fluoroquinolones and other antibiotics discussed in this chapter are listed in Figure 40.1.

### 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. 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.

**FLUOROQUINOLONES**
***Ciprofloxacin*** CIPRO
***Levofloxacin*** LEVAQUIN
***Moxifloxacin*** AVELOX
***Nalidixic acid***
***Norfloxacin*** NOROXIN
***Ofloxacin***

**INHIBITORS OF FOLATE SYNTHESIS**
***Mafenide*** SULFAMYLON
***Silver sulfadiazine*** SILVADENE
***Sulfasalazine*** AZULFIDINE

**INHIBITORS OF FOLATE REDUCTION**
***Pyrimethamine*** DARAPRIM
***Trimethoprim***

**COMBINATION OF INHIBITORS OF FOLATE SYNTHESIS AND REDUCTION**
***Cotrimoxazole*** (***trimethoprim*** + ***sulfamethoxazole***) BACTRIM

**URINARY TRACT ANTISEPTICS**
***Methenamine*** MANDELAMINE, HIPREX
***Nitrofurantoin*** MACROBID

**Figure 40.1**
Summary of drugs described in this chapter.

### 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 nonfluorinated 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 (Figure 40.2). 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.

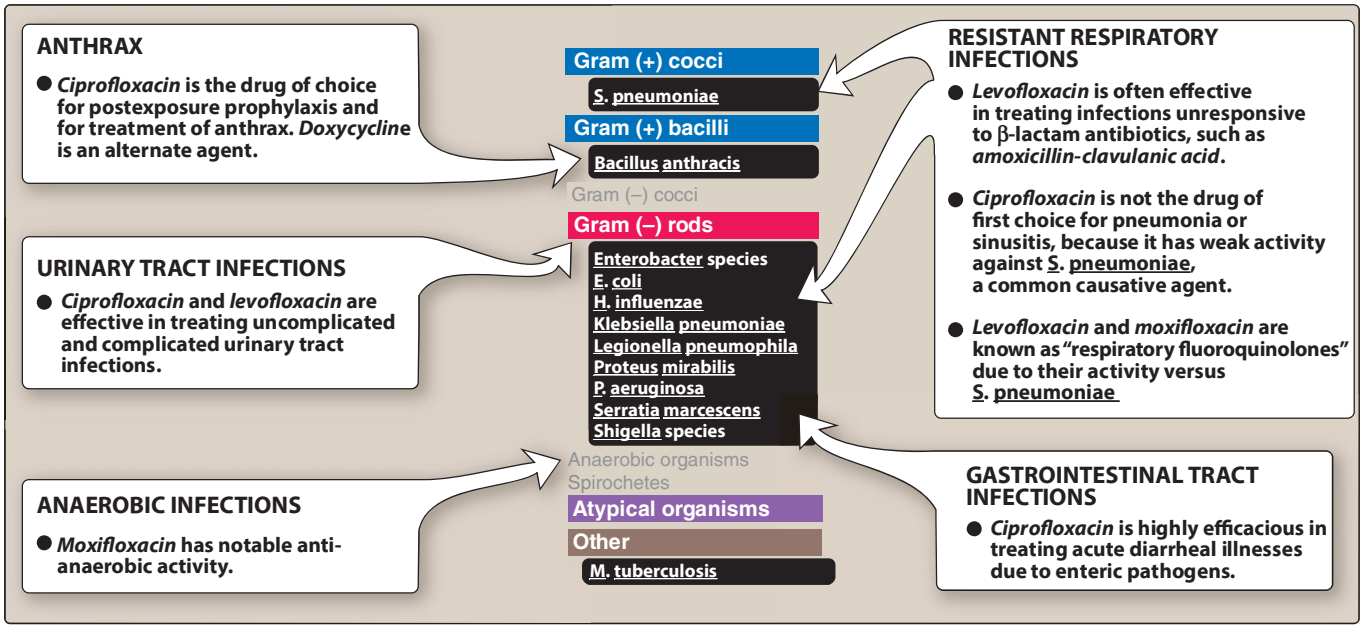


**Figure 40.2**
Typical therapeutic applications of fluoroquinolones.

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] not only has 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

Although plasmid-mediated resistance or resistance via enzymatic degradation is not of great concern, high levels of fluoroquinolone resistance have emerged in gram-positive and gram-negative bacteria, primarily due to chromosomal mutations. Cross-resistance exists among the quinolones. 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 and 2) efflux pumps. The former involves a decreased number of porin proteins in the outer

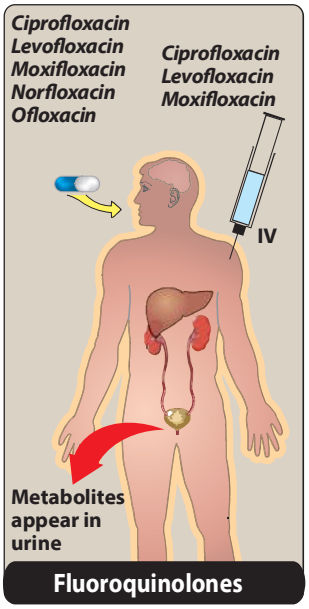


**Figure 40.3**
Administration and fate of the fluoroquinolones.

membrane of the resistant cell, thereby impairing access of the drugs to the intracellular topoisomerases. The latter mechanism pumps drug out of the cell.

## E. Pharmacokinetics

1. **Absorption:** Only 35% to 70% of orally administered *norfloxacin* is absorbed, compared with 80% to 99% of the other fluoroquinolones (Figure 40.3). 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 (Figure 40.4).

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. Levels are high in bone, urine (except *moxifloxacin*), kidney, and prostatic tissue (but not prostatic fluid), and concentrations in the lungs exceed those in serum. 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 (Figure 40.5). Like most antibiotics, 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. If phototoxicity occurs, discontinuation of the drug is advisable. 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 $QT_c$ 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 (Figure 40.6). Quinolones may also raise the serum levels of *warfarin*, *caffeine*, and *cyclosporine*.

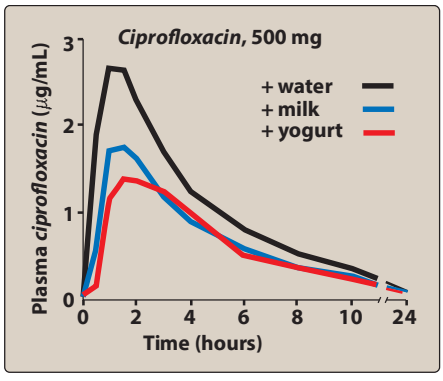


**Figure 40.4**
Effect of dietary calcium on the absorption of *ciprofloxacin*.

## II. OVERVIEW OF THE 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

The sulfa drugs are seldom prescribed alone except in developing countries, where they are still employed because of their low cost and efficacy.

### A. Mechanism of action

In many microorganisms, dihydrofolic acid is synthesized from *p*-aminobenzoic acid (PABA), pteridine, and glutamate (Figure 40.7). 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 (see Chapter 43).

### 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.

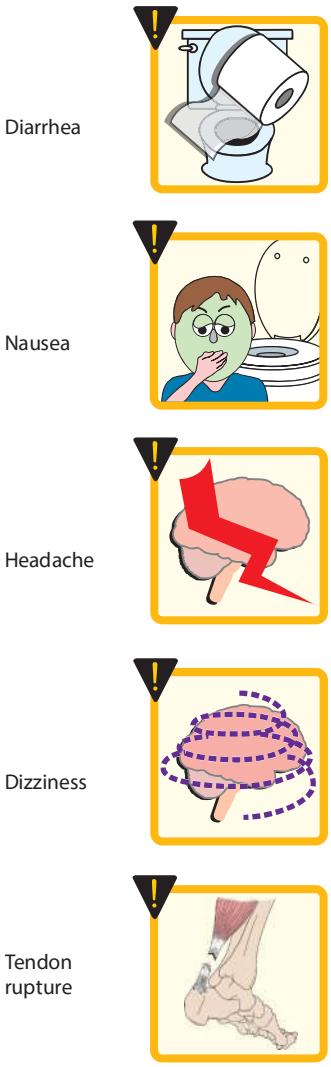


**Figure 40.5**
Some adverse reactions to fluoroquinolones.

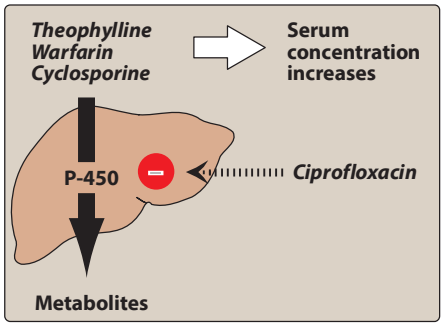


**Figure 40.6**
Drug interactions with fluoroquinolones.

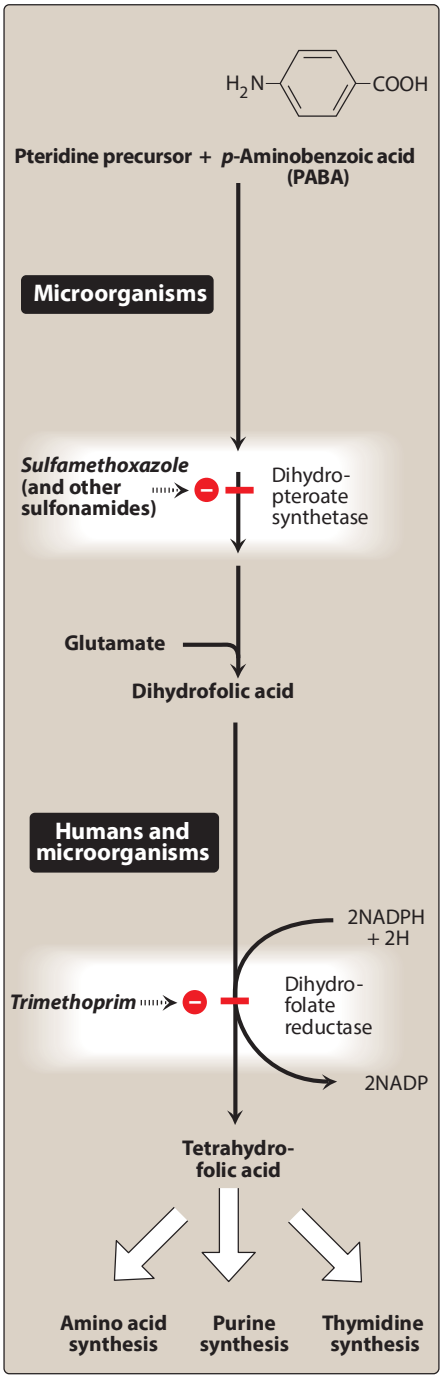


**Figure 40.7**
Inhibition of tetrahydrofolate synthesis by sulfonamides and *trimethoprim*.

## D. Pharmacokinetics

1. **Absorption:** After oral administration, most sulfa drugs are well absorbed (Figure 40.8). 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 ($pK_a$) of the drug. In general, the smaller the $pK_a$ 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 (Figure 40.9). Adequate hydration and alkalinization of urine can prevent the problem by reducing the concentration of drug and promoting its ionization.

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.

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.

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 (Figure 40.10).

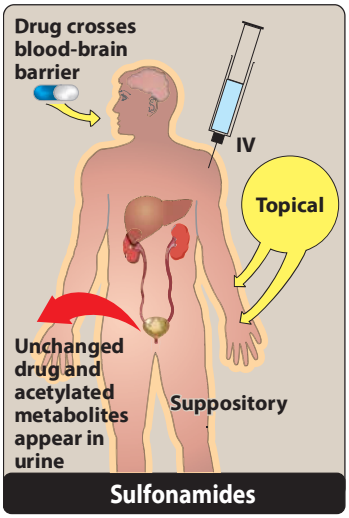


**Figure 40.8**
Administration and fate of the sulfonamides.

## 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 (Figure 40.7) 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

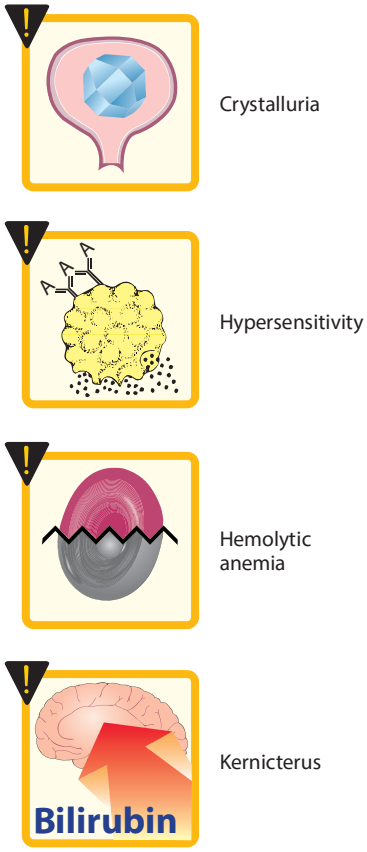


**Figure 40.9**
Some adverse reactions to sulfonamides.

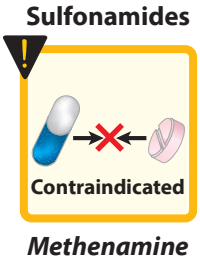


**Figure 40.10**
Contraindication for sulfonamide treatment.

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. These effects include 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* [co-try-MOX-a-zole], shows greater antimicrobial activity than equivalent quantities of either drug used alone (Figure 40.11). The combination was selected because of the synergistic activity and the similarity in the half-lives of the two drugs.

### A. 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 reduction of dihydrofolate to tetrahydrofolate (Figure 40.7).

### B. Antibacterial spectrum

*Cotrimoxazole* has a broader spectrum of antibacterial action than the sulfa drugs alone (Figure 40.12). 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.

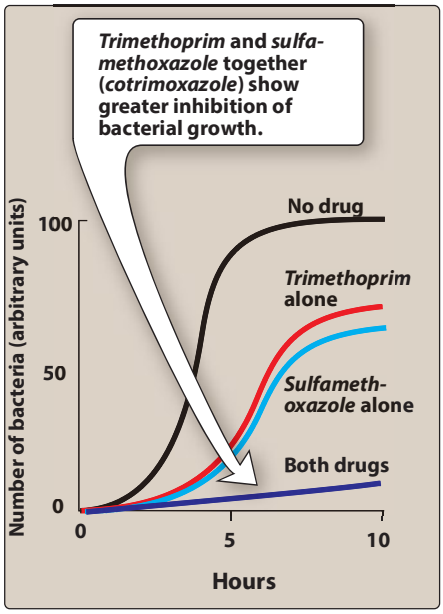


**Figure 40.11**
Synergism between *trimethoprim* and *sulfamethoxazole* inhibits growth of E. coli.

### 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.

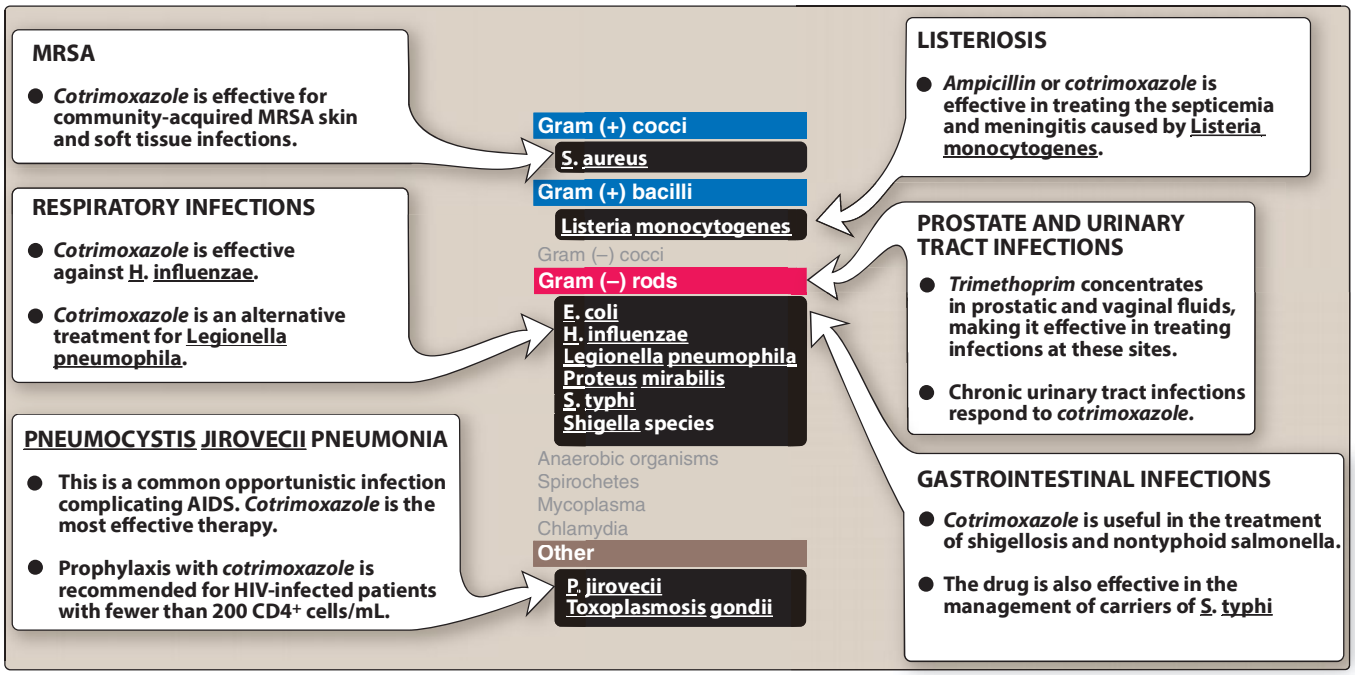


**Figure 40.12**
Typical therapeutic applications of *cotrimoxazole* (*sulfamethoxazole* plus *trimethoprim*).

### E. Adverse effects

Reactions involving the skin are very common and may be severe in the elderly (Figure 40.14). 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, and increased monitoring is recommended when the drugs are used concurrently. 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*.

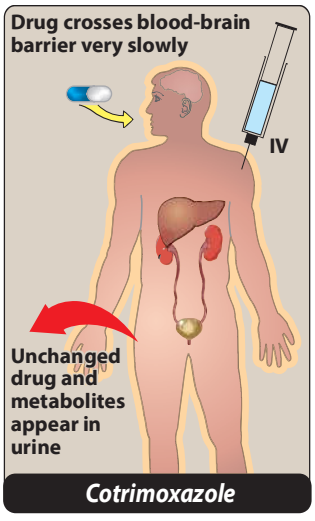


**Figure 40.13**
Administration and fate of *cotrimoxazole*.

## 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,

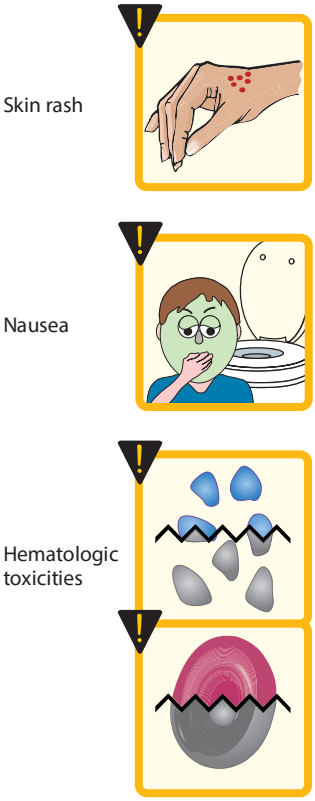


**Figure 40.14**
Some adverse reactions to *cotrimoxazole*.

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 (Figure 40.15). 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.]

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*.

3. **Pharmacokinetics:** *Methenamine* is administered orally. In addition to formaldehyde, ammonium ions are produced in the bladder. Because the liver rapidly metabolizes ammonia to form urea, *methenamine* is contraindicated in patients with hepatic insufficiency, as ammonia can accumulate. *Methenamine* is distributed throughout the body fluids, but no decomposition of the drug occurs at pH 7.4. Thus, systemic toxicity does not occur, and the drug is eliminated in the urine.

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*. The combination increases the risk of crystalluria and mutual antagonism.]

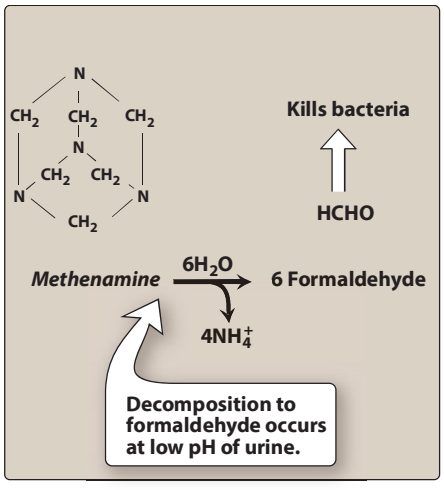


**Figure 40.15**
Formation of formaldehyde from *methenamine* at acid pH.

## B. Nitrofurantoin

*Nitrofurantoin* [nye-troe-FYOOR-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. Gram-positive 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.

## Study Questions

**Choose the ONE best answer.**

40.1 A 32-year-old male presents to an outpatient clinic with a 5-day history of productive cough, purulent sputum, and shortness of breath. He is diagnosed with community-acquired pneumonia (CAP). It is noted that this patient has a severe ampicillin allergy (anaphylaxis). Which of the following would be an acceptable treatment for this patient?

A. Levofloxacin.
B. Ciprofloxacin.
C. Penicillin VK.
D. Nitrofurantoin.

Correct answer = A. Streptococcus pneumoniae is a common cause of CAP, and the respiratory fluoroquinolones levofloxacin and moxifloxacin provide good coverage. Ciprofloxacin does not cover S. pneumoniae well and is a poor choice for treatment of CAP. Penicillin would be a poor choice due to allergy. Nitrofurantoin has no clinical utility for respiratory tract infections.

40.2 A 22-year-old female presents with a 2-day history of dysuria with increased urinary frequency and urgency. A urine culture and urinalysis are done. She is diagnosed with a urinary tract infection (UTI) caused by E. coli. All of the following would be considered appropriate therapy for this patient except:

A. Levofloxacin.
B. Cotrimoxazole.
C. Moxifloxacin.
D. Nitrofurantoin.

Correct answer = C. Moxifloxacin does not concentrate in the urine and would be ineffective for treatment of a UTI. All other answers are viable alternatives, and the resistance profile for the E. coli can be utilized to direct therapy.

40.3 Which of the following drugs is correctly matched with the appropriate adverse effect?

A. Levofloxacin—hyperkalemia.
B. Nitrofurantoin—pulmonary fibrosis.
C. Cotrimoxazole—hepatic encephalopathy.
D. Methenamine—nystagmus.

Correct answer = B. Hyperkalemia may be caused by cotrimoxazole, not fluoroquinolones. Hepatic encephalopathy may be related to therapy with methenamine in patients with hepatic insufficiency. Nystagmus is not associated with methenamine therapy.

40.4 Cotrimoxazole would be expected to provide coverage for all of the following organisms except:

A. Pseudomonas aeruginosa.
B. Community-acquired MRSA.
C. Nocardia asteroides.
D. Stenotrophomonas maltophilia.

Correct answer = A. Cotrimoxazole is generally the drug of choice for answers C and D. It is also an excellent option for treatment of community-acquired MRSA skin and soft tissue infections.