Antimicrobial Therapy

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Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics

I- Fluoroquinolone; The discovery of quinolone antimicrobials led to the development of numerous compound 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. Unfortunately, overuse resulted in rising rates of resistance in gram-negative and gram positive organisms, increased frequency of Clostridium difficile infections, and identification of numerous untoward adverse effects. Consequently, these agents have been relegated to second-line options for various indications.

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

Summary of drugs described in this lecture

Mechanism of action

Most bacterial species maintain two distinct type II topoisomerases that assist with deoxyribonucleic acid (DNA) replication, (DNA gyrase), and topoisomerase IV. DNA gyrase is responsible for reducing torsional stress ahead of replicating forks by breaking double-strand DNA and introducing negative supercoils. Topoisomerase IV assists in separating daughter chromosomes once replication is completed. 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.

Antimicrobial spectrum

Fluoroquinolones are bactericidal and exhibit area-under-the-curve/minimum inhibitory concentration (AUC/MIC)-dependent killing. A major facet of their development centered on improving microbiologic coverage. Modifications to the quinolone nucleus steadily improved topoisomerase inhibitory activity and facilitated bacterial cell wall penetration. These changes enhanced activity against a variety of pathogens including Aerobic gram-negative and gram-positive organisms, atypical organisms (for example, chlamydia, legionella, and mycoplasma spp.), and Anaerobes. 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.

Second-generation compounds (for example, ciprofloxacin) exhibit improved intracellular penetration and broadened coverage, which includes Enterobacteriaceae, Pseudomonas aeruginosa, Haemophilus influenzae, Neisseria spp., Chlamydia spp., and Legionella spp.

Third-generation compounds (for example, levofloxacin) maintain the bacterial spectrum of second-generation agents, with improved activity against Streptococcus spp., including S. pneumoniae, methicillin-susceptible Staphylococcus aureus, Stenotrophomonas maltophilia, and Mycobacterium spp.

Fourth-generation compounds (moxifloxacin, gemifloxacin, and delafloxacin) 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. 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 31.2.

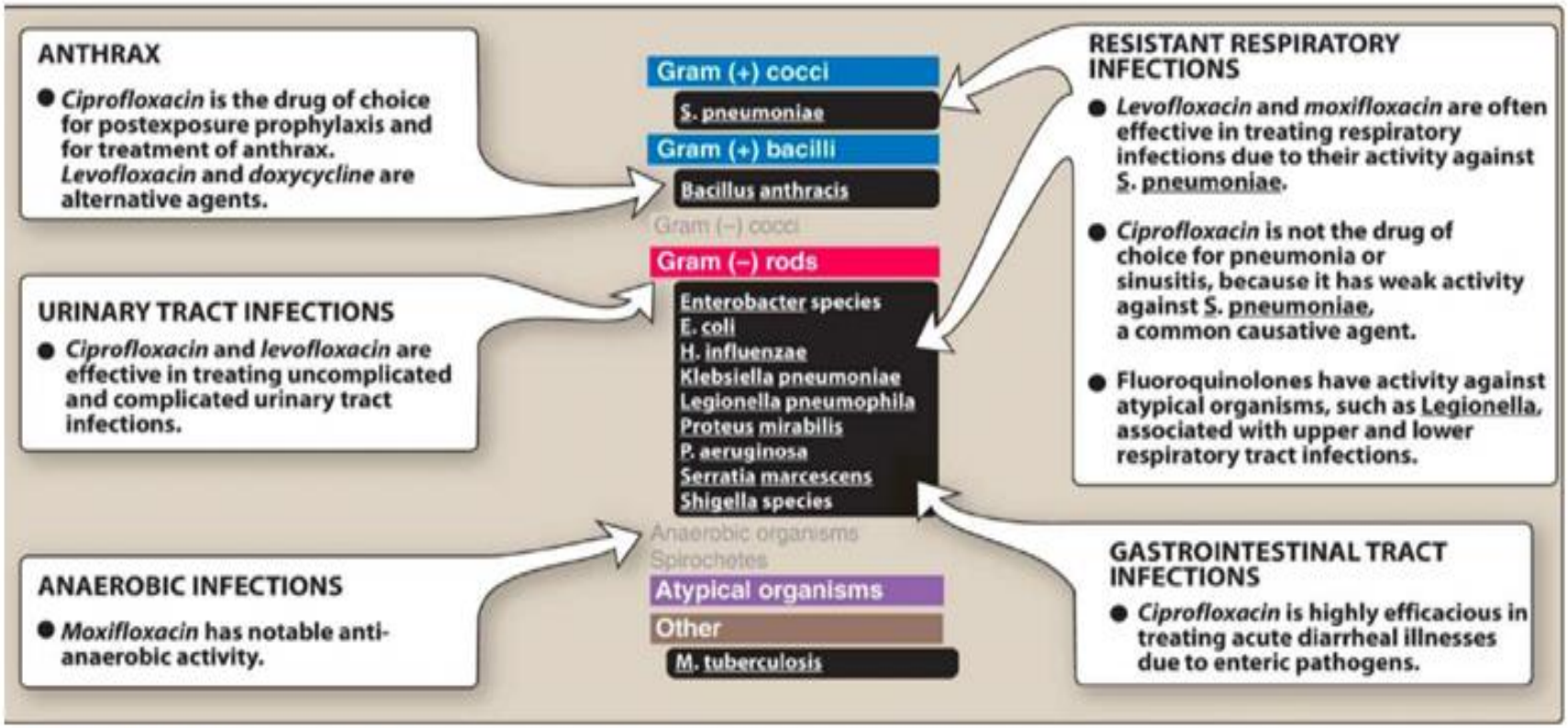


Figure 31.2 Typical therapeutic applications of fluoroquinolones.

Resistance

Numerous mechanisms of fluoroquinolone resistance exist in clinical pathogens. High-level fluoroquinolone resistance is primarily driven by chromosomal mutations within topoisomerases, decreased entry, efflux systems, and modifying enzymes play a role.

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. 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.

3. Fluoroquinolone degradation

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

Pharmacokinetics

1. Absorption

Fluoroquinolones are well absorbed after oral administration, with levofloxacin and moxifloxacin having a bioavailability that exceeds 90% (Figure 31.3). 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 31.4).

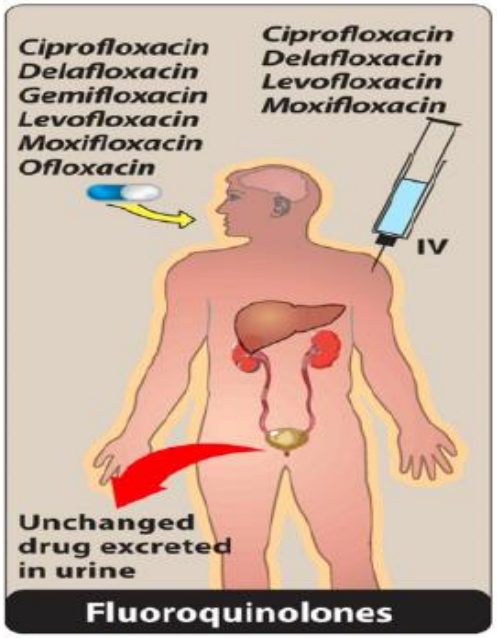


Figure 31.3 Administration and fate of the fluoroquinolones.

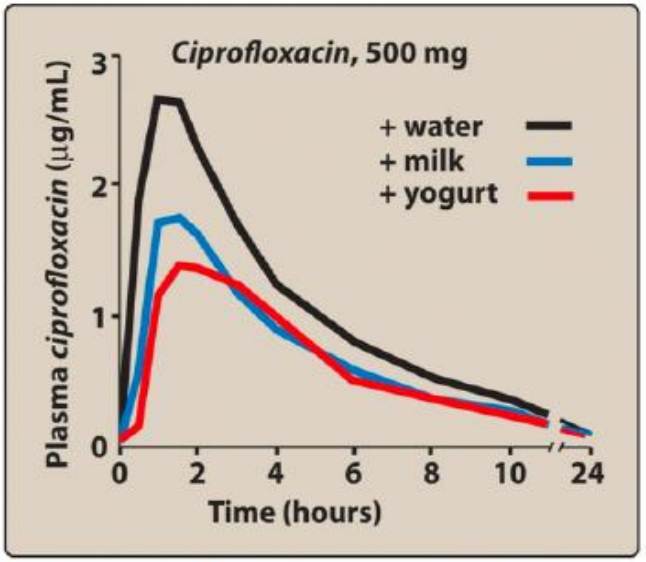


Figure 31.4 Effect of dietary calcium on the absorption of *ciprofloxacin*.

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. Penetration into cerebrospinal fluid is good, and these agents may be considered in certain central nervous system (CNS) infections. Accumulation in macrophages and polymorphonuclear leukocytes results in activity against intracellular organisms such as Listeria, Chlamydia, and Mycobacterium.

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 (see Figure 31.3).

Adverse Reactions

In general, fluoroquinolones are well tolerated (Figure 31.5). Common adverse effects leading to discontinuation are nausea, vomiting, headache, and dizziness. These agents carry boxed warnings for tendinitis, tendon rupture, peripheral neuropathy, and CNS effects (hallucinations, anxiety, insomnia, confusion, and seizures). Patients taking fluoroquinolones are at risk for phototoxicity resulting in exaggerated sunburn reactions. Patients should use sunscreen and avoid excessive exposure to ultraviolet (UV) light. Arthropathy is uncommon, but arthralgia and arthritis are reported with fluoroquinolone use in pediatric patients.

Use in the pediatric population should be limited to distinct clinical scenarios (for example, cystic fibrosis exacerbation). Hepatotoxicity or 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.

Fluoroquinolones may prolong the QTc interval, and these agents should be avoided in patients predisposed to arrhythmias or taking medication associated with QT prolongation. Ciprofloxacin inhibits P450 1A2- and 3A4-mediated metabolism. Serum concentrations of medications such as theophylline, tizanidine, warfarin, ropinirole, duloxetine, caffeine, sildenafil, and zolpidem may be increased (Figure 31.6).

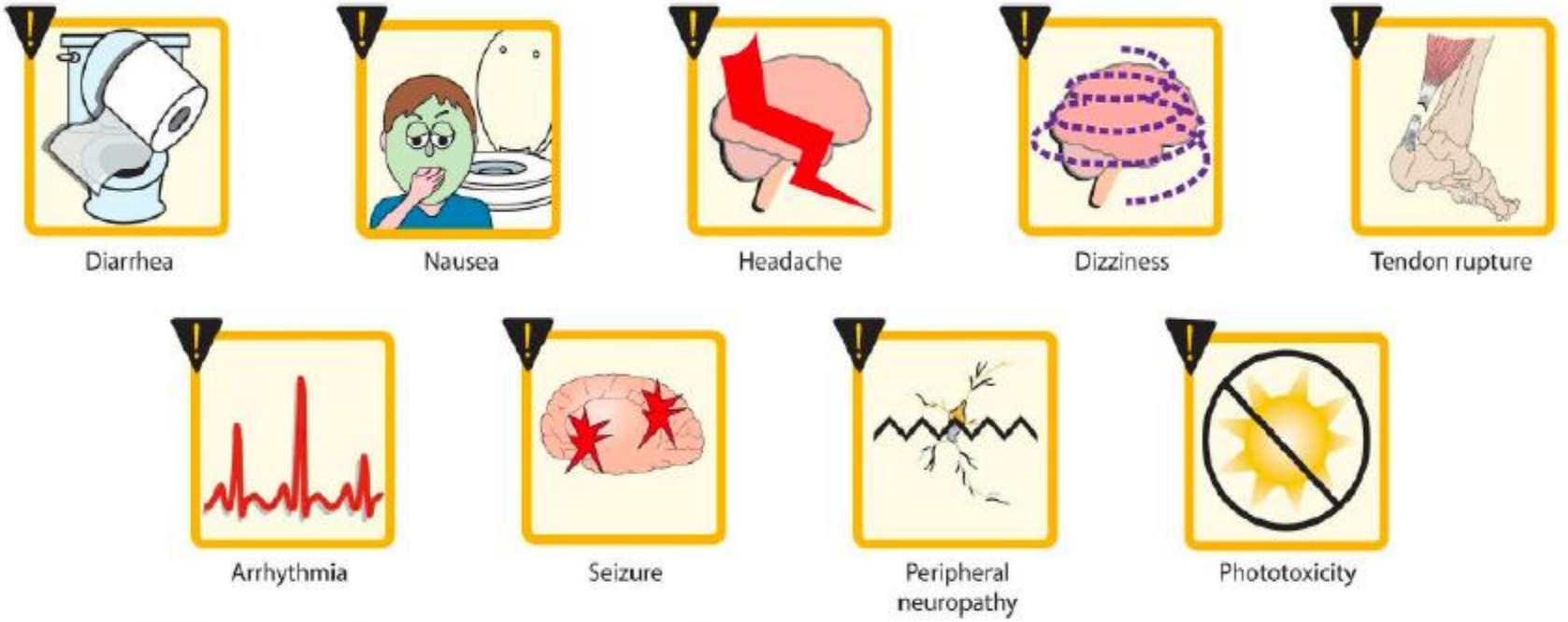


Figure 31.5 Some adverse reactions to fluoroquinolones.

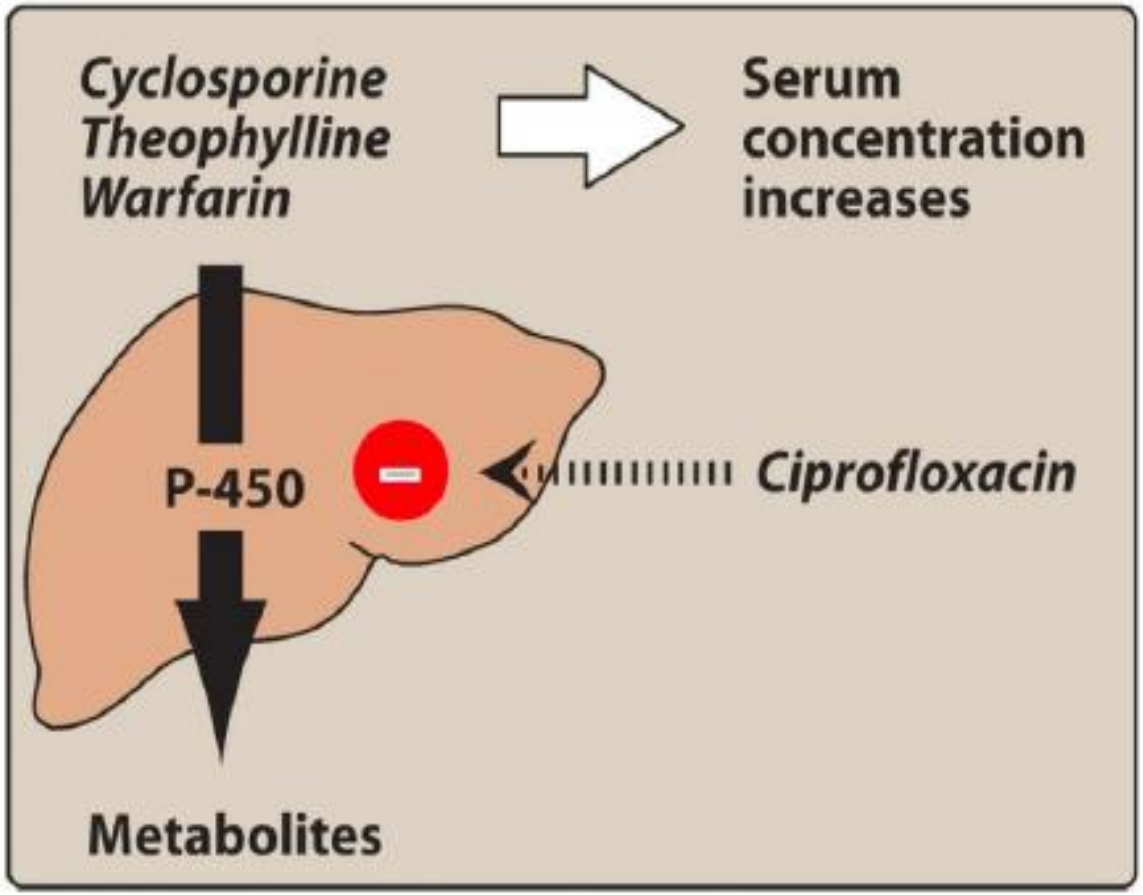


Figure 31.6 Drug interactions with *ciprofloxacin*.

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 patients who do not tolerate other agents (for example, severe beta-lactam allergies) or as definitive therapy once susceptibilities are available.Listed below are potential indications for these agents:

1. Ciprofloxacin

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

2. Levofloxacin

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

3. Moxifloxacin

Moxifloxacin 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. 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. Moxifloxacin may be considered a second-line agent for the management of drug-susceptible tuberculosis.

4. Gemifloxacin

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

5. Delafloxacin

Delafloxacin 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.

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 31.7).

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. 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.

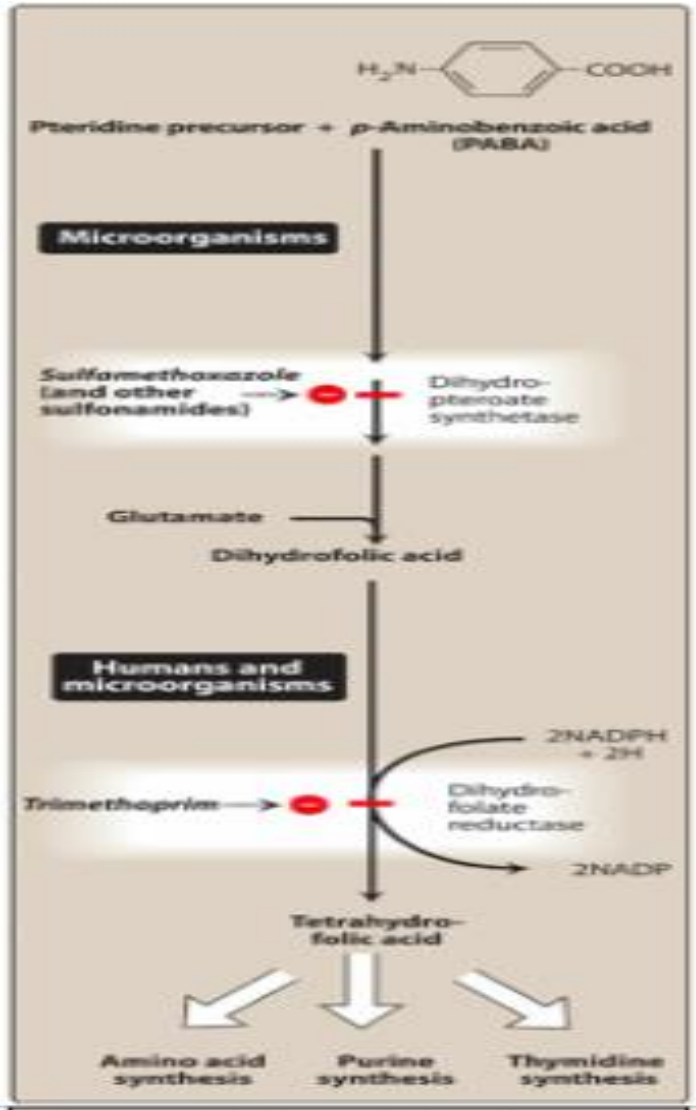
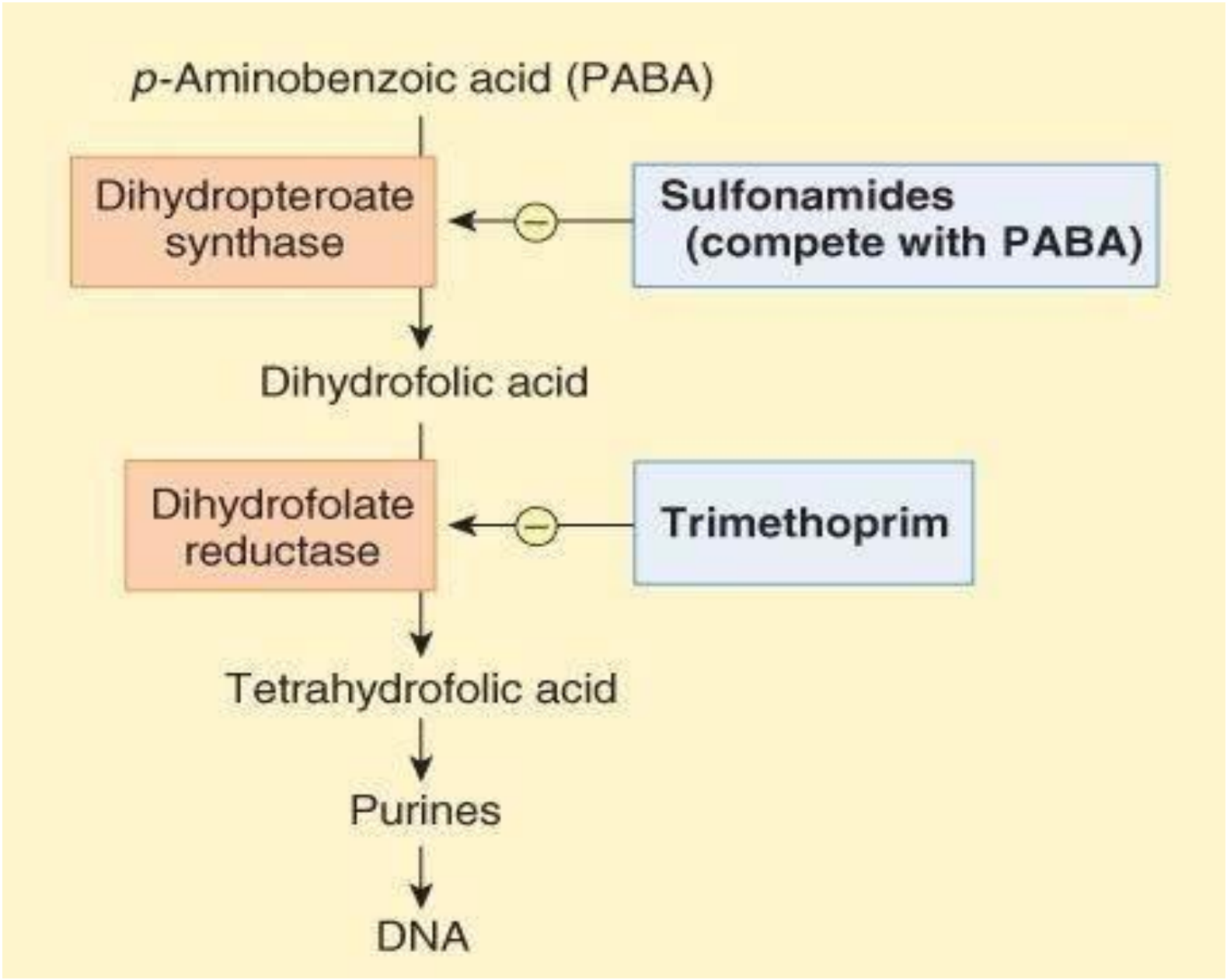


Figure 31.7 Inhibition of tetrahydrofolate synthesis by sulfonamides and trimethoprim


p-Aminobenzoic acid (PABA)
Dihydropteroate synthase
Sulfonamides (compete with PABA)
Dihydrofolic acid
Dihydrofolate reductase
Trimethoprim
Tetrahydrofolic acid
Purines
DNA

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 [sul-fa-DYE-a-zeen] in combination with the dihydrofolate reductase inhibitor pyrimethamine [py-ri- METH-a-meen] is the preferred treatment for toxoplasmosis.

Resistance

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

Pharmacokinetics

1. Absorption

Most sulfa drugs are well absorbed following oral administration (Figure 31.8). 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.] 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.

However, in burn units, silver sulfadiazine or mafenide acetate (α-amino-p-toluenesulfonamide) creams have been effective in reducing burn-associated sepsis because they prevent colonization of bacteria. [Note: Silver sulfadiazine is preferred because mafenide produces pain on application and its absorption may contribute to acid–base disturbances.]

2. Distribution

Sulfa drugs are bound to serum albumin in circulation and widely distributed 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.

3. Metabolism

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

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.

Adverse effects

1. Crystalluria

Nephrotoxicity may develop as a result of crystalluria (Figure 31.9). 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

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.

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.

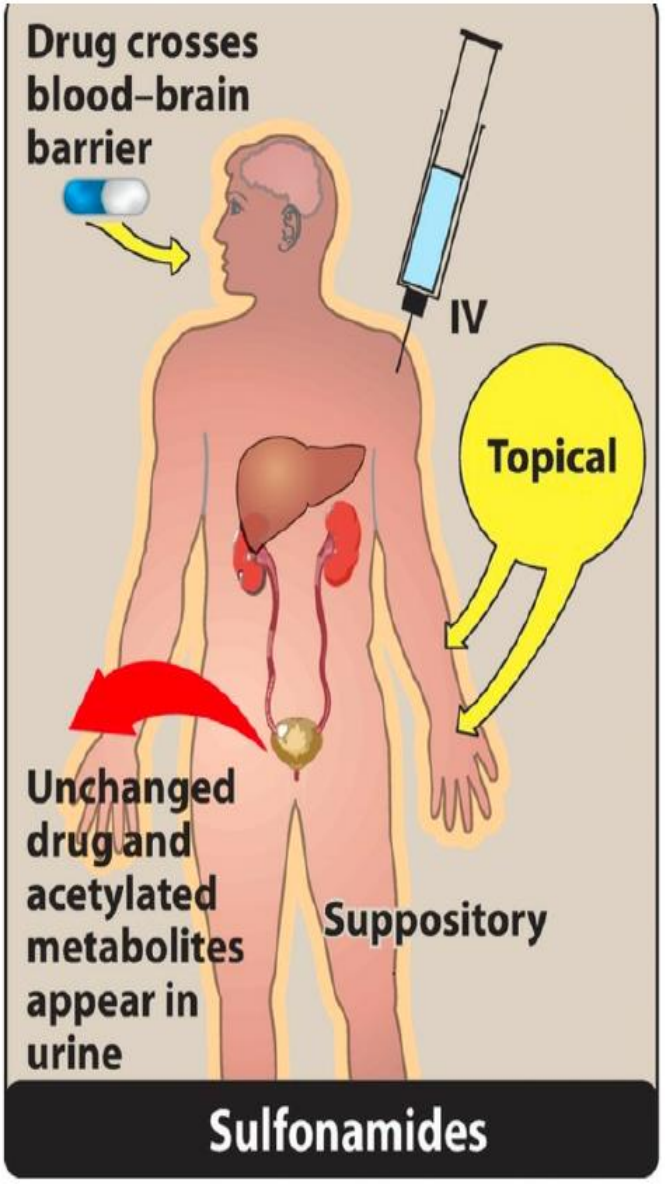


Figure 31.8 Administration and fate of the sulfonamides.

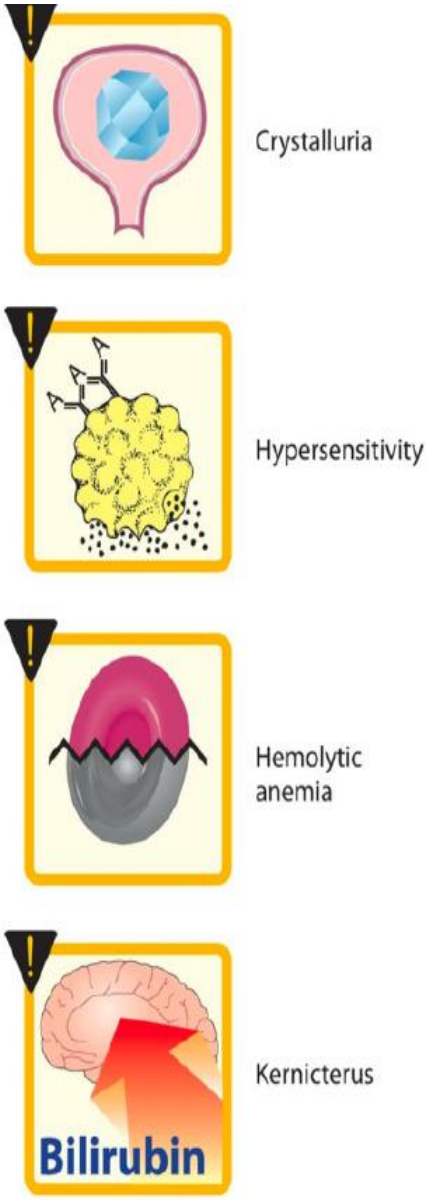


Figure 31.9 Some adverse reactions to sulfonamides.

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, a potent inhibitor of bacterial dihydrofolate reductase, was initially available in combination with the sulfonamide sulfamethoxazole [sul-fa-meth-OX-a-zole], and later approved for use as a single agent. Today, trimethoprim is most commonly used in combination with sulfamethoxazole.

Mechanism of action

Mechanism of action

Trimethoprim is a potent inhibitor of bacterial dihydrofolate reductase (see Figure 31.7). 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.

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).

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.

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.

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 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 (Figure 31.10). The combination was selected because of the synergistic activity and the similarity in the half-lives of the two drugs.

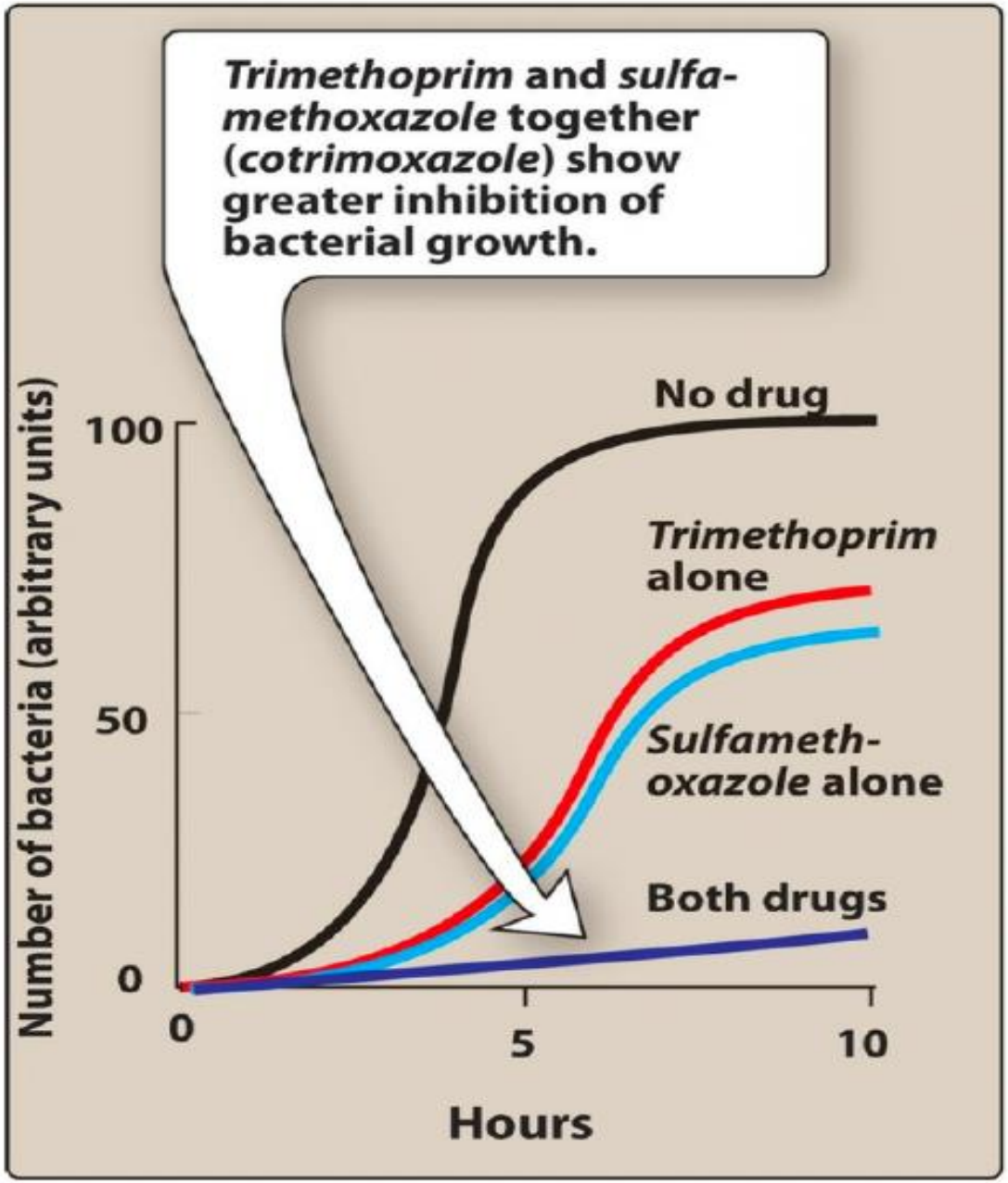


Figure 31.10 Synergism between *trimethoprim* and *sulfamethoxazole* inhibits growth of E. coli.

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 (Figure 31.7).

Antibacterial spectrum

Cotrimoxazole has a broader spectrum of antibacterial action than the sulfa drugs alone (Figure 31.11). 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.

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.

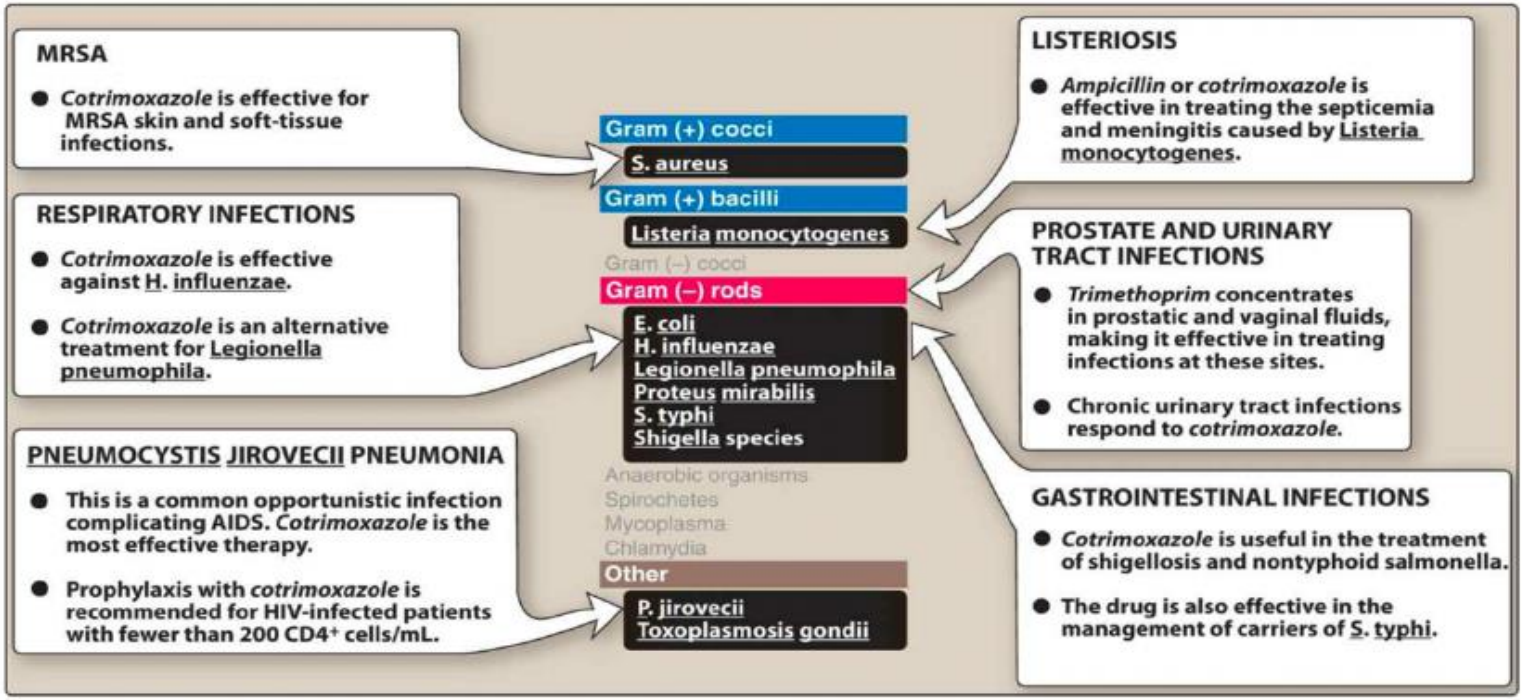


Figure 31.11 Typical therapeutic applications of *cotrimoxazole* (*sulfamethoxazole* plus *trimethoprim*).

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.

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.

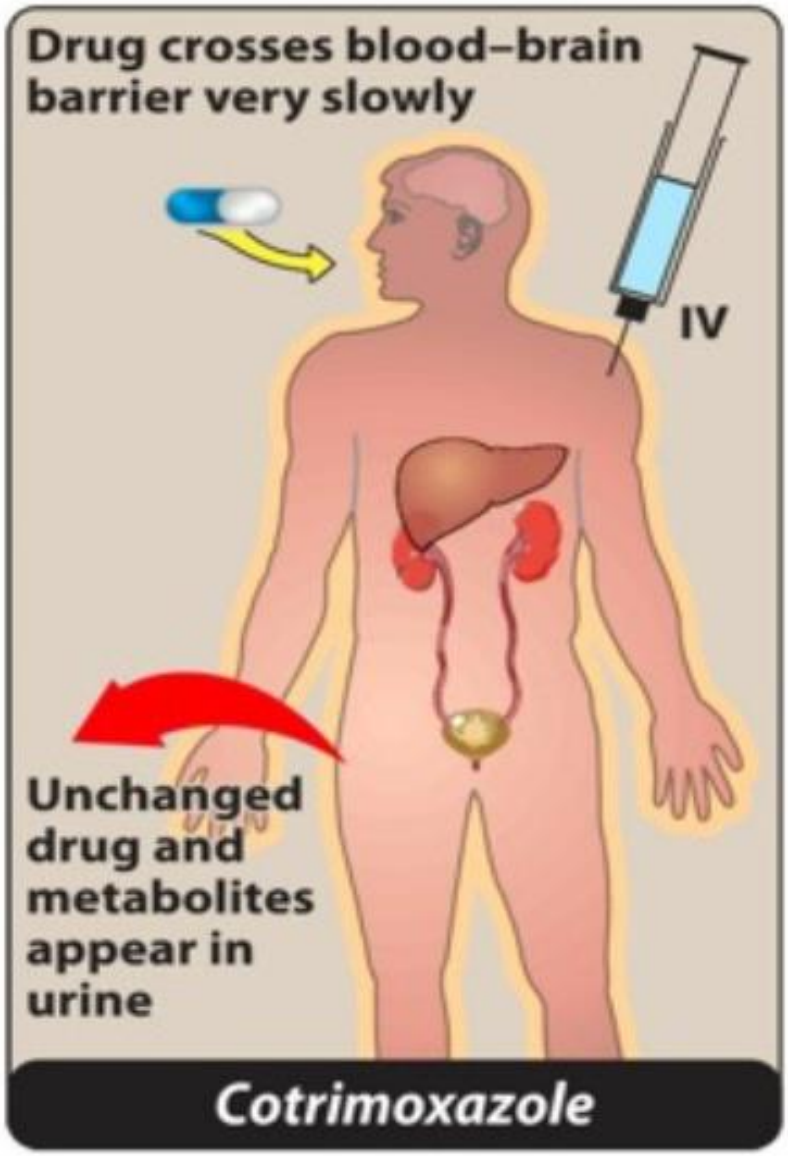


Figure 31.12 Administration and fate of cotrimoxazole

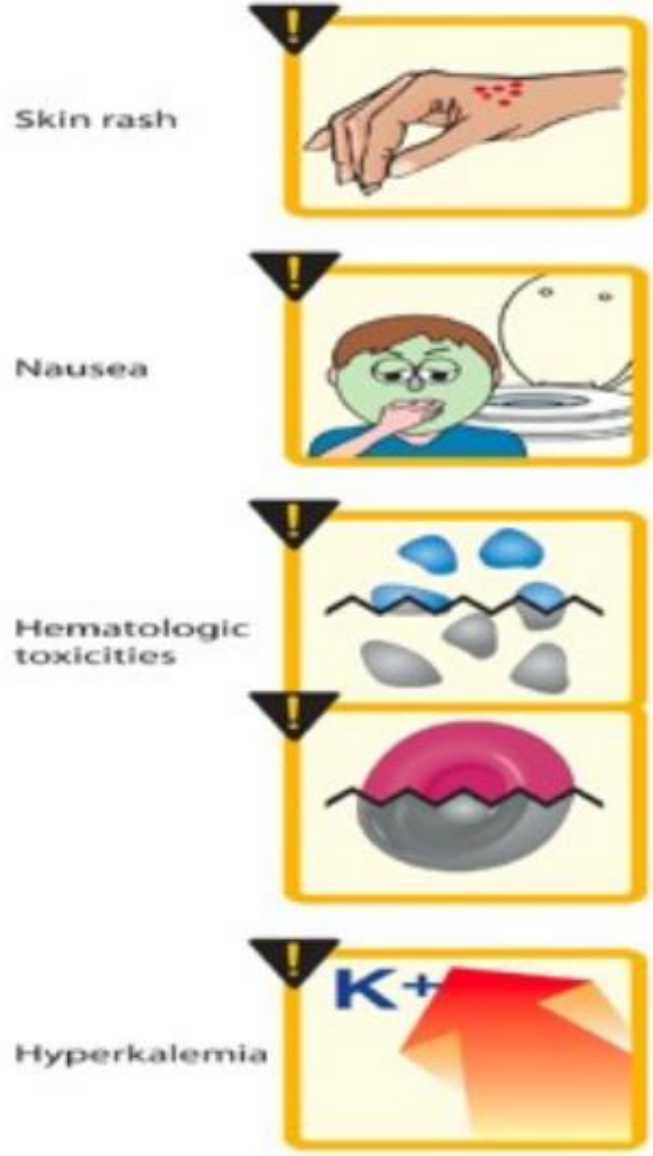


Figure 31.13 Some adverse reactions to cotrimoxazole

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.

A. Methenamine

Mechanism of action

Methenamine salts are hydrolyzed to ammonia and formaldehyde in acidic urine ($pH \leq 5.5$). 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 (Figure 31.14).

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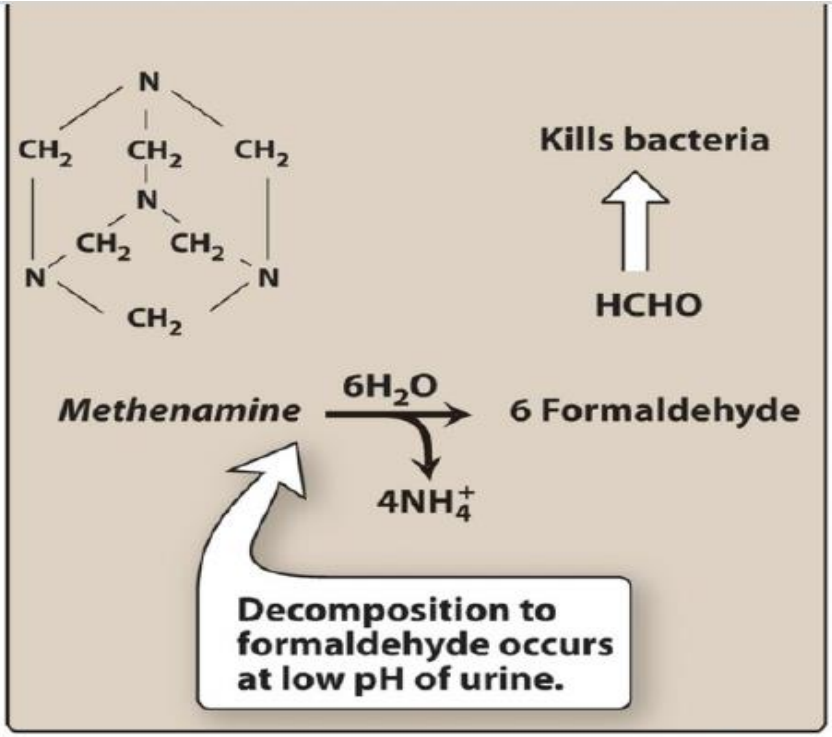

Figure 31.14 Formation of formaldehyde from *methenamine* at acid pH.

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.

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.

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.]

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 resurrected 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.

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.

Antimycobacterial Drugs

Mycobacteria are rod-shaped aerobic bacilli that multiply slowly, every 18 to 24 hours in vitro. Their cell walls contain mycolic acids, which give the genus its name. Mycolic acids are long-chain, β-hydroxylated fatty acids. Mycobacteria produce highly lipophilic cell walls that stain poorly with Gram stain. Once stained, the bacilli are not decolorized easily by acidified organic solvents. Hence, the organisms are called "acid-fast bacilli." Mycobacterial infections classically result in the formation of slow-growing, granulomatous lesions that cause tissue destruction anywhere in the body.

DRUGS USED TO TREAT TUBERCULOSIS
Ethambutol MYAMBUTOL
Isoniazid GENERIC ONLY
Pyrazinamide GENERIC ONLY
Rifabutin MYCOBUTIN
Rifampin RIFADIN
Rifapentine PRIFTIN
DRUGS USED TO TREAT TUBERCULOSIS (2ND LINE)
Aminoglycosides
Aminosalicylic acid PASER
Bedaquiline SIRTURO
Capreomycin CAPASTAT
Cycloserine SEROMYCIN
Ethionamide TRECATOR
Fluoroquinolones
Macrolides
DRUGS USED TO TREAT LEPROSY
Clofazimine LAMPRENE
Dapsone GENERIC ONLY
Rifampin (*Rifampicin*) RIFADIN

Mycobacterium tuberculosis can cause latent tuberculosis infection (LTBI) and the disease known as tuberculosis (TB). [Note: In LTBI, the patient is infected with M. tuberculosis without signs or symptoms of active TB disease.] TB is the leading infectious cause of death worldwide, and a quarter of the world's population is infected with TB. Increasing in frequency are diseases caused by nontuberculous mycobacteria (NTM).

These species include M. avium-intracellulare, M. chelonae, M. abscessus, M. kansasii, and M. fortuitum. Finally, M. leprae causes leprosy.TB treatment generally includes four first-line drugs (Figure 32.1). Second-line drugs are typically less effective, more toxic, and less extensively studied. They are used for patients who cannot tolerate first-line drugs or who are infected with resistant TB. No drugs are specifically developed for NTM infections. Macrolides, rifamycins, and aminoglycosides are frequently included, but NTM regimens vary widely by organism.

II. Chemotherapy for Tuberculosis

M. tuberculosis is slow-growing and requires treatment for months to years. LTBI can be treated for 9 months with isoniazid (INH) monotherapy or with 12 once-weekly

higher doses of INH and rifapentine. In contrast, active TB disease must be treated with several drugs. Treatment for drug-susceptible TB lasts for at least 6 months, while treatment of multidrug-resistant TB (MDR-TB) typically lasts for about 2 years.

A. Strategies for addressing drug resistance

Populations of M. tuberculosis contain small numbers of organisms that are naturally resistant to a particular drug. Under selective pressure from inadequate treatment, especially from monotherapy, these resistant organisms can emerge as the dominant population. Figure 32.2 shows that resistance develops rapidly in TB patients given only streptomycin.

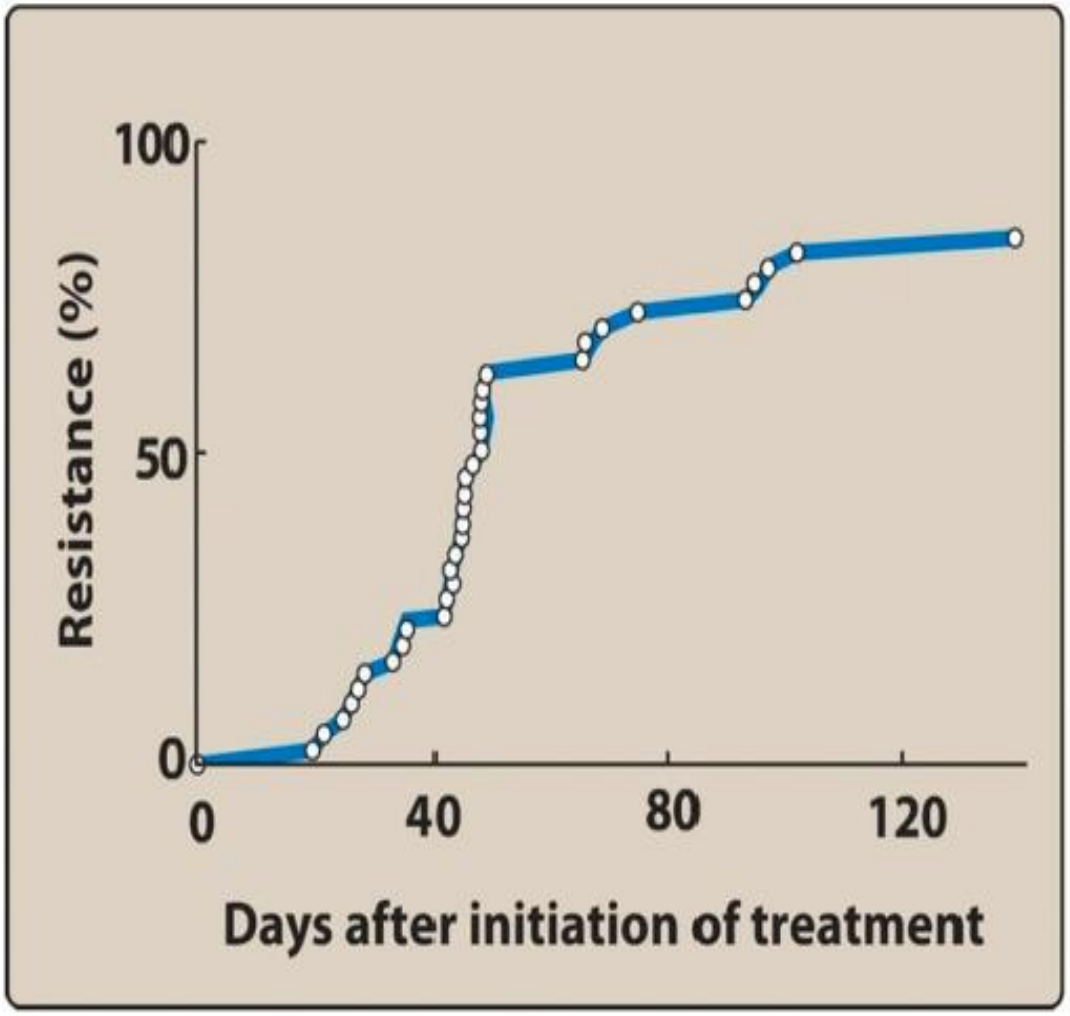

Figure 32.2 Cumulative percentage of strains of Mycobacterium tuberculosis showing resistance to *streptomycin*.

Multidrug therapy is employed to suppress these resistant organisms. The first-line drugs isoniazid, rifampin, ethambutol, and pyrazinamide are preferred because of their high efficacy and acceptable incidence of toxicity. Rifabutin or rifapentine may replace rifampin under certain circumstances. Active disease always requires treatment with multidrug regimens, and preferably three or more drugs with proven in vitro activity against the isolate. Although clinical improvement can occur in the first several weeks of treatment, therapy is continued much longer to eradicate persistent organisms and to prevent relapse. Standard short-course chemotherapy for tuberculosis includes isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months (the intensive phase), followed by isoniazid and rifampin for 4 months (the continuation phase; Figure 32.3).

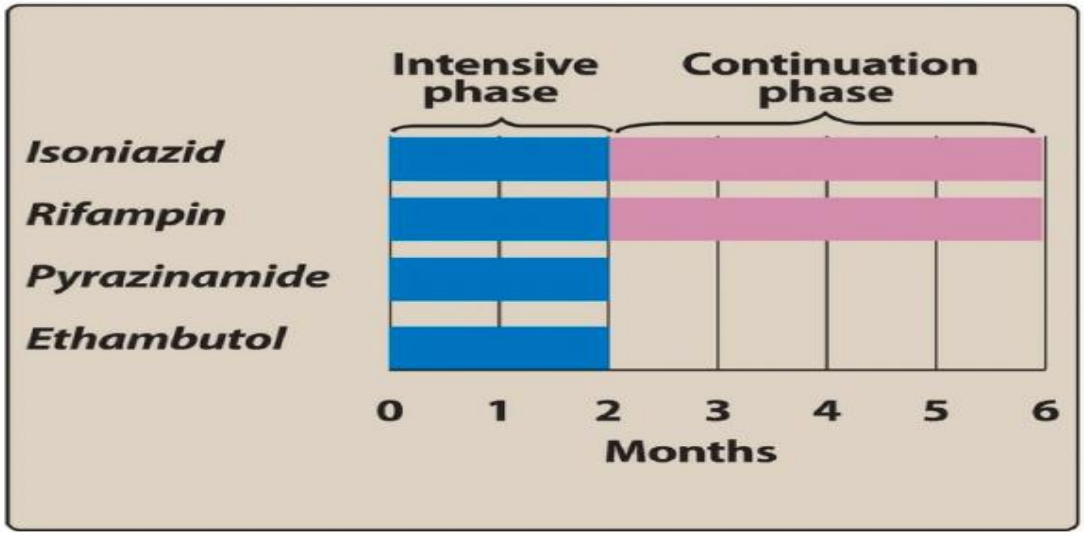

Figure 32.3 One of several recommended multidrug schedules for the treatment of tuberculosis.

Once susceptibility data are available, the drug regimen can be individually tailored. Second-line regimens for MDR-TB (TB resistant to at least isoniazid and rifampin) normally include an aminoglycoside (streptomycin, kanamycin, or amikacin) or capreomycin (all injectable agents), a fluoroquinolone (typically levofloxacin or moxifloxacin), any first-line drugs that remain active, and one or more of the following: cycloserine, ethionamide, or p-aminosalicylic acid. For extensively drug-resistant TB (XDR-TB), other drugs such as clofazimine and linezolid may be employed empirically. Patient adherence can be low when multidrug regimens last for 6 months or longer. One successful strategy for achieving better treatment completion rates is directly observed therapy (DOT). Patients take the medications under the observation of a member of the health care team. DOT decreases drug resistance and improves cure rates. Most public health departments offer DOT services.