Chapter 57: DNA Disruptors: Sulfonamides, Quinolones, and Nitroimidazoles

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ABBREVIATIONS

Abbreviations

AIDS: acquired immunodeficiency syndrome

CSF: cerebrospinal fluid

DHFR: dihydrofolate reductase

GI: gastrointestinal

HIV: human immunodeficiency virus

PABA: *para*-aminobenzoic acid

TMP: trimethoprim

SMX: sulfamethoxazole

UTI: urinary tract infection

SULFONAMIDES

HISTORICAL PERSPECTIVE

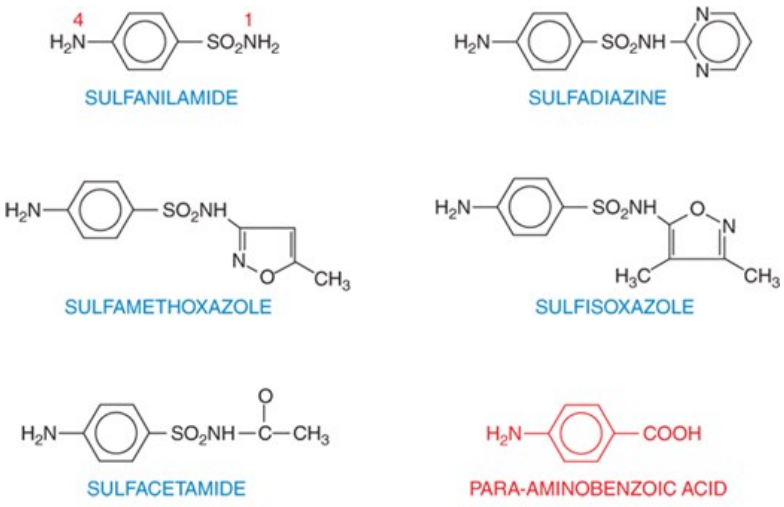
The sulfonamide drugs were the first effective chemotherapeutic agents used systemically for the prevention and cure of bacterial infections in humans. Investigations in 1932 at the I. G. Farbenindustrie in Germany resulted in the patenting of *prontosil* and several other azo dyes containing a sulfonamide group. Because synthetic azo dyes had been studied for their action against streptococci, Domagk tested the new compounds and observed that mice with streptococcal and other infections could be protected by *prontosil*. In 1933, Foerster reported giving *prontosil* to a 10-month-old infant with staphylococcal septicemia and achieving a dramatic cure. Favorable clinical results with *prontosil* and its active metabolite, *sulfanilamide*, in puerperal sepsis and meningococcal infections awakened the medical profession to the new field of antibacterial chemotherapy, and experimental and clinical articles soon appeared in profusion. The development of the carbonic anhydrase inhibitor–type diuretics and the sulfonylurea hypoglycemic agents followed from observations made with the sulfonamide antibiotics. For discovering the chemotherapeutic value of *prontosil*, Domagk was awarded the Nobel Prize in Medicine for 1938 (Lesch, 2007). The advent of *penicillin* and other antibiotics diminished the usefulness of the sulfonamides, but the introduction of the combination of *trimethoprim* (TMP) and *sulfamethoxazole* (SMX) in the 1970s increased the use of sulfonamides for the prophylaxis and treatment of infections.

Sulfonamides are derivatives of *para*-aminobenzenesulfonamide (*sulfanilamide*; Figure 57–1) and are congeners of *para*-aminobenzoic acid (PABA). Most of them are relatively insoluble in water, but their sodium salts are readily soluble. The minimal structural prerequisites for antibacterial action

are all embodied in *sulfanilamide* itself. The sulfur must be linked directly to the benzene ring. The *para*-NH_2 group (the N of which has been designated as N4) is essential and can be replaced only by moieties that can be converted *in vivo* to a free amino group. Substitutions made in the amide NH_2 group (position N1) have variable effects on antibacterial activity of the molecule; substitution of heterocyclic aromatic nuclei at N1 yields highly potent compounds. The sulfone agent *dapsone* is discussed in Chapter 65.

Figure 57–1

Sulfanilamide and PABA. Sulfonamides are derivatives of *sulfanilamide* and act by virtue of being congeners of PABA. The antimicrobial and dermatological anti-inflammatory agent *dapsone* (4,4′-diaminodiphenyl sulfone; see Chapters 65 and 75) also bears a resemblance to PABA and *sulfanilamide*.

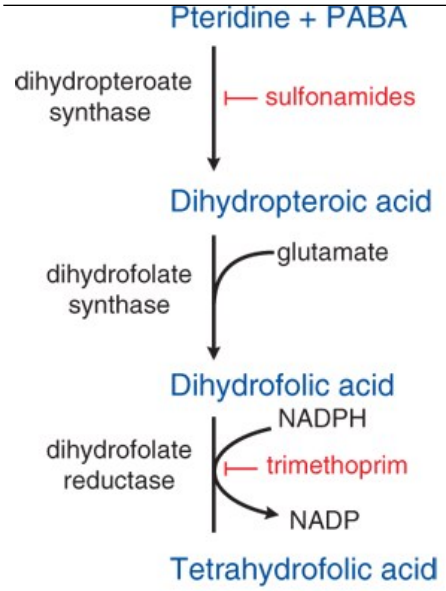


Mechanism of Action

Sulfonamides are competitive inhibitors of *dihydropteroate synthase*, the bacterial enzyme responsible for the incorporation of PABA into *dihydropteroic acid*, the immediate precursor of *folic acid* (Figure 57–2). Sensitive microorganisms are those that must synthesize their own folic acid; those that can use preformed folate are not affected. Sulfonamides administered as single agents are typically *bacteriostatic*; cellular and humoral defense mechanisms of the host are essential for final eradication of the infection. Toxicity is selective for nonmammalian cells because mammalian cells require preformed folic acid, cannot synthesize it, and are thus insensitive to drugs acting by this mechanism (Grayson, 2010).

Figure 57–2

Steps in folate metabolism blocked by sulfonamides and trimethoprim. Coadministration of a sulfonamide and *trimethoprim* introduces sequential blocks in the biosynthetic pathway for tetrahydrofolate; the combination is much more effective than either agent alone.



Synergists of Sulfonamides

Trimethoprim (TMP) exerts a synergistic effect with sulfonamides. It is a potent and selective competitive inhibitor of microbial *dihydrofolate reductase*, the enzyme that reduces *dihydrofolate* to *tetrahydrofolate*, which is required for one-carbon transfer reactions. Coadministration of a sulfonamide and TMP (e.g., trimethoprim-sulfamethoxazole [TMP-SMX]) introduces sequential blocks in the biosynthetic pathway for tetrahydrofolate (see Figure 57–2); the combination is much more effective than either agent alone (Bushby and Hitchings, 1968). Similar complementary activity is seen with *pyrimethamine*, which is generally used in combination with agents such as *sulfadoxine*, *sulfadiazine*, or *dapsone*. The predominant systemic use of sulfonamides is now in such combinations.

Antimicrobial Activity

On their original introduction to therapeutic use, sulfonamides had a wide range of antimicrobial activity against both gram-positive and gram-negative bacteria; a high percentage of isolates of *Streptococcus pyogenes, Streptococcus pneumoniae, Staphylococcus aureus*, and *Haemophilus influenzae* were susceptible to systemically achievable concentrations of sulfonamides. However, the increase in sulfonamide resistance is such that sulfonamide activity against these pathogens in serious infections cannot be assumed, and they play little part in empiric therapy (Grayson, 2010). Potent activity remains against most isolates of *Haemophilus ducreyi, Nocardia* spp., and *Klebsiella granulomatis.* Isolates of *Neisseria meningitidis* and *Shigella* are generally resistant, as are many strains of *Escherichia coli* isolated from patients with urinary tract infections (UTIs) (Olson et al., 2009). Sulfonamides and derivatives also possess important activity against parasites and fungi, and those applications are further discussed in Chapters 61, 65, and 66.

Bacterial Resistance

Bacterial resistance to sulfonamides can originate by random mutation and selection or by transfer of resistance by plasmids; it usually does not involve cross-resistance to other classes of antibiotics except to the extent that other resistance elements may be carried on mobile elements such as plasmids. Resistance to folate antagonists can result from (1) a lower affinity of dihydropteroate synthase for sulfonamides, (2) decreased bacterial permeability or active efflux of the drug, (3) an alternative metabolic pathway for synthesis of an essential metabolite, or (4) increased production of an essential metabolite or drug antagonist (e.g., PABA) (Estrada et al., 2016). Plasmid-mediated resistance is due to plasmid-encoded, drug-resistant dihydropteroate synthetase.

ADME

Except for sulfonamides especially designed for their local effects in the bowel (see Chapter 55), this class of drugs is absorbed rapidly from the gastrointestinal (GI) tract. Typically, 70% to 100% of an oral dose is absorbed and can be found in the urine within 30 min of ingestion. Peak plasma levels are achieved in 2 to 6 h, depending on the drug. Peak plasma drug concentrations achievable *in vivo* are about 100 to 200 µg/mL. The small intestine is the major site of absorption, but some of the drug is absorbed from the stomach. Absorption from other sites, such as the vagina, respiratory tract, or abraded skin, is variable and unreliable, but a sufficient amount may enter the body to cause toxic reactions in susceptible persons or to produce sensitization.

All sulfonamides are bound in varying degree to plasma proteins, particularly to albumin. Sulfonamides are distributed throughout all tissues of the body. The sulfonamides readily enter pleural, peritoneal, synovial, ocular, and similar body fluids and may reach concentrations therein that are 50% to 80% of the simultaneously determined concentration in blood. Because the protein content of body fluids usually is low, the drug is present in the unbound active form. After systemic administration of adequate doses, *sulfadiazine* and *sulfisoxazole* attain concentrations in cerebrospinal fluid (CSF) that may be effective in meningitis. However, because of the emergence of sulfonamide-resistant microorganisms, these drugs are used rarely for the treatment of meningitis. Sulfonamides pass readily through the placenta and reach the fetal circulation. The concentrations attained in the fetal tissues may cause both antibacterial and toxic effects.

Sulfonamides are metabolized in the liver. The major metabolite is the N4-acetylated sulfonamide. Acetylation results in products that have no antibacterial activity but retain the toxic potential of the parent substance. Sulfonamides are eliminated from the body partly as the unchanged drug and partly as metabolic products. The largest fraction is excreted in the urine, and the $t_{1/2}$ depends on renal function. In acid urine, the older sulfonamides are insoluble, and crystalline deposits may form. Small amounts are eliminated in the feces, bile, milk, and other secretions.

Pharmacological Properties of Individual Sulfonamides

Sulfonamides for Systemic Use

Sulfisoxazole

Sulfisoxazole is a rapidly absorbed and excreted sulfonamide. *It* is bound extensively to plasma proteins. Following an oral dose of 2 to 4 g, peak concentrations in plasma of 110 to 250 µg/mL are found in 2 to 4 h. Approximately 30% of *sulfisoxazole* in the blood and about 30% in the urine is in the acetylated form. The kidney excretes about 95% of a single dose in 24 h. Concentrations of the drug in urine thus greatly exceed those in blood and may be bactericidal. *Sulfisoxazole acetyl* is tasteless and hence preferred for oral use in children. *Sulfisoxazole acetyl* in combination with *erythromycin ethylsuccinate* is used in children with otitis media.

Sulfamethoxazole

Sulfamethoxazole is a close congener of *sulfisoxazole*, but its rates of enteric absorption and urinary excretion are slower ($t_{1/2}$ of 11 h). It is administered orally and employed for both systemic infections and UTIs. Precautions must be observed to avoid *sulfamethoxazole*-induced crystalluria because of the high percentage of the acetylated, relatively insoluble form of the drug in the urine. The clinical uses of *sulfamethoxazole* as a single agent are the same as those for *sulfisoxazole*. In the U.S., it is marketed only in fixed-dose combinations with TMP (discussed further in the following section Trimethoprim-Sulfamethoxazole).

Sulfadiazine

Sulfadiazine given orally is absorbed rapidly from the GI tract. Peak blood concentrations are reached within 3 to 6 h, with a $t_{1/2}$ of 10 h. About 55% of the drug is bound to plasma protein. Therapeutic concentrations are attained in CSF within 4 h of a single oral dose of 60 mg/kg. Both free and acetylated forms of *sulfadiazine* are readily excreted by the kidney; 15% to 40% of the excreted drug is in acetylated form. Alkalinization of the urine accelerates the renal clearance of both forms by diminishing their tubular reabsorption. Precaution must be taken to ensure fluid intake adequate to produce a daily urine output of at least 1200 mL in adults and a corresponding quantity in children. If this cannot be accomplished, sodium bicarbonate may be given to reduce the risk of crystalluria.

Sulfadoxine

This agent has a particularly long plasma $t_{1/2}$ of 7 to 9 days. Although no longer marketed in the U.S., its combination with *pyrimethamine* (500 mg *sulfadoxine* plus 25 mg *pyrimethamine*) is listed as a World Health Organization essential medicine and is used for the prophylaxis and treatment of malaria caused by *mefloquine*-resistant strains of *Plasmodium falciparum* (see Chapter 66). However, because of severe and sometimes fatal reactions, including the Stevens-Johnson syndrome, and the emergence of resistant strains, the drug has limited usefulness for the treatment of malaria.

Sulfonamides for Topical Use

Sulfacetamide is the N1-acetyl-substituted derivative of *sulfanilamide*. Its aqueous solubility is about 90 times that of *sulfadiazine*. Solutions of the sodium salt of the drug are employed extensively in the management of ophthalmic infections. Very high aqueous concentrations are not irritating to the eye and are effective against susceptible microorganisms. The drug penetrates into ocular fluids and tissues in high concentration. Sensitivity reactions to *sulfacetamide* are rare, but the drug should not be used in patients with known hypersensitivity to sulfonamides. A 30% solution of the sodium salt has a pH of 7.4, whereas the solutions of sodium salts of other sulfonamides are highly alkaline. See Chapters 74 and 75 for ocular and dermatological uses. *Silver sulfadiazine* and *mafenide* are sulfonamides used topically, primarily in the prevention of infection in burn patients. These agents are covered in Chapter 75.

Therapeutic Uses

Use of sulfonamides as single agents for treatment of systemic infections has become uncommon. Because a significant percentage of UTIs are caused by sulfonamide-resistant microorganisms, sulfonamides are no longer a therapy of first choice; TMP-SMX is preferred (although resistance to this agent is increasing as well). *Sulfisoxazole* may be used effectively for cystitis in areas where the prevalence of resistance is not high. The usual dosage is 2 to 4 g initially, followed by 1 to 2 g orally four times a day for 5 to 10 days. TMP-SMX is most commonly used for infections due to *Nocardia* spp., but *sulfisoxazole* and *sulfadiazine* are alternative agents, given in dosages of 6 to 8 g daily. For serious infections, addition of a second agent, such as *imipenem*, *amikacin*, or *linezolid*, is recommended. The combination of *pyrimethamine* and *sulfadiazine* is the treatment of choice for toxoplasmosis (see Chapter 67). *Pyrimethamine* is given as a loading dose of 2000 mg followed by 50 to 75 mg orally per day, with *sulfadiazine* 1 to 1.5 g orally every 6 h, plus folinic acid (*leucovorin*) 10 to 25 mg orally each day for at least 6 weeks (Panel on Opportunistic Infections, 2020). Patients should receive at least 2 L of fluid intake daily to prevent crystalluria.

Adverse Reactions

Hypersensitivity Reactions

Among the skin and mucous membrane manifestations attributed to sensitization to sulfonamide are morbilliform, scarlatinal, urticarial, erysipeloid, pemphigoid, purpuric, and petechial rashes, as well as erythema nodosum, erythema multiforme of the Stevens-Johnson type, Behçet syndrome, exfoliative dermatitis, and photosensitivity (Khan et al., 2019). Sulfonamide metabolites are hypothesized to be primarily responsible for dermatologic hypersensitivity reactions. These hypersensitivity reactions occur most often after the first week of therapy but may appear earlier in previously sensitized individuals. Fever, malaise, and pruritus frequently are present simultaneously. Patients living with human immunodeficiency virus (HIV) infection manifest a higher frequency of rashes with sulfonamide treatment than do other individuals. Patients who have allergic reactions are often advised to avoid other agents with sulfa moieties; however, only those with a sulfonamide (SO_2NH_2) moiety carry a risk of cross-allergenicity. Further, data suggest most patients who have a reaction to an antimicrobial sulfonamide can tolerate a non-antimicrobial agent with a sulfonamide moiety (e.g., *furosemide*), although avoidance may be preferred for severe reactions.

Disturbances of the Urinary Tract

Crystalluria has occurred in dehydrated patients with HIV who were receiving *sulfadiazine* for *Toxoplasma* encephalitis. Crystalluria can be prevented by maintaining daily urine volume of at least 1200 mL (in adults) or, if necessary, urine alkalinization because the solubility of *sulfadiazine* increases with elevations of pH.

Miscellaneous Reactions

Anorexia, nausea, and vomiting occur in 1% to 2% of persons receiving sulfonamides. Focal or diffuse necrosis of the liver owing to direct drug toxicity

or sensitization occurs in less than 0.1% of patients. Headache, nausea, vomiting, fever, hepatomegaly, jaundice, and laboratory evidence of hepatocellular dysfunction usually appear 3 to 5 days after sulfonamide administration is started, and the syndrome may progress to acute yellow atrophy and death. Aplastic anemia involving complete suppression of bone marrow activity with profound anemia, granulocytopenia, and thrombocytopenia is an extremely rare occurrence with sulfonamide therapy. It probably results from a direct myelotoxic effect and may be fatal. Reversible suppression of the bone marrow is quite common in patients with limited bone marrow reserve (e.g., patients with acquired immunodeficiency syndrome [AIDS] or those receiving myelosuppressive chemotherapy). The administration of sulfonamides to newborn infants, especially if premature, may lead to the displacement of bilirubin from plasma albumin, potentially causing an encephalopathy called *kernicterus*. Sulfonamides should not be given to pregnant women near term because these drugs cross the placenta and are secreted in milk.

Drug Interactions

Drug interactions of the sulfonamides are seen mainly with *warfarin*, the sulfonylurea hypoglycemic agents, and the hydantoin anticonvulsants. In each case, sulfonamides can potentiate the effects of the other drug by inhibiting its metabolism or by displacing it from albumin. Frequent monitoring and dosage adjustment may be necessary when a sulfonamide is given concurrently.

TRIMETHOPRIM-SULFAMETHOXAZOLE

TMP inhibits bacterial dihydrofolate reductase (DHFR), an enzyme downstream from the one that sulfonamides inhibit in the same biosynthetic sequence (see Figure 57–2). The combination of TMP with *sulfamethoxazole* (SMX) was an important advance in the development of clinically effective and synergistic antimicrobial agents. In much of the world, the combination of TMP with SMX is known as *cotrimoxazole*. In addition to its combination with SMX, TMP is available in some countries as a single-entity preparation.

Mechanism of Action

The antimicrobial activity of the combination of TMP-SMX results from actions on sequential steps of the enzymatic pathway for the synthesis of tetrahydrofolic acid (see Figure 57–2). Tetrahydrofolate is essential for one-carbon transfer reactions (e.g., the synthesis of thymidylate from deoxyuridylate) in both bacteria and mammalian cells. However, TMP is a highly selective inhibitor of the DHFR of lower organisms relative to that of mammals: About 100,000 times more drug is required to inhibit human reductase than the bacterial enzyme. The most effective ratio of SMX to TMP across the greatest number of microorganisms is 20:1. The combination is thus formulated to achieve an SMX concentration *in vivo* that is 20 times greater than that of TMP; SMX has pharmacokinetic properties such that the concentrations of the two drugs will thus be relatively constant in the body over a long period. Although each agent alone usually exerts bacteriostatic activity, when the organism is sensitive to both agents, bactericidal activity may be achieved.

Antimicrobial Activity

The antibacterial spectrum of TMP is similar to that of SMX, although TMP is 20 to 100 times more potent.

Spectrum of TMP-SMX in Combination

Although most *S. pneumoniae* are susceptible to TMP-SMX, there has been a disturbing increase in resistance (paralleling the rise in *penicillin* resistance), and its value as empiric therapy for many respiratory tract infections is questionable. The vast majority (>90%) of strains of *S. aureus* remain susceptible, even among *methicillin*-resistant isolates, although geographic variation exists. Activity against *Staphylococcus epidermidis* is more variable. *S. pyogenes* is usually sensitive when proper testing procedures (media with low thymidine content) are followed (Bowen et al., 2012). The *viridans* group of streptococci is typically susceptible, although susceptibility among *penicillin*-resistant strains is low (Diekema et al., 2001). Susceptibility in *E. coli* varies significantly by geographic region, although it has been declining in general, and in many places, TMP-SMX is no longer considered adequate empiric therapy. *Proteus mirabilis, Klebsiella* spp., *Enterobacter* spp., *Salmonella, Shigella, Pseudomonas pseudomallei, Serratia* spp., *Stenotrophomonas maltophila*, and *Alcaligenes* spp. are typically susceptible. Also usually susceptible are *Brucella abortus, Pasteurella haemolytica, Yersinia pseudotuberculosis, Yersinia enterocolitica*, and *Nocardia asteroides*. *Pseudomonas aeruginosa, Bacteroides fragilis*, and enterococci are clinically resistant.

Bacterial Resistance

Bacterial resistance to TMP-SMX has eroded the efficacy of this agent, especially among pneumococci and *E. coli*, although resistance to the combination is lower than it is to either of the agents alone. In addition to the resistance mechanisms to sulfonamides described above, resistance specific to TMP may develop. Resistance is typically due either to point mutations in genes encoding for DHFR or to the acquisition of a plasmid that codes for an altered DHFR (Estrada et al., 2016), both of which are associated with reduced binding of TMP.

ADME

The pharmacokinetic profiles of SMX and TMP are closely, but not perfectly, matched to achieve a near-constant ratio of 20:1 in their concentrations in blood and tissues over the course of their distribution and elimination. After a single oral dose of the combined preparation, TMP is absorbed more rapidly than SMX. Peak blood concentrations of TMP usually occur by 2 h in most patients, whereas peak concentrations of SMX occur by 4 h after a single oral dose. The half-lives of TMP and SMX are 11 and 10 h, respectively.

When 800 mg SMX is given with 160 mg TMP (one “double-strength” tablet; “single-strength” is 400 mg to 80 mg, maintaining the same ratio) twice daily, the peak concentrations of the drugs in plasma are about 40 and 2 µg/mL. Peak concentrations are similar (46 and 3.4 µg/mL) after intravenous infusion of 800 mg SMX and 160 mg TMP over a period of 1 h.

TMP is distributed and concentrated rapidly in tissues; about 40% is bound to plasma protein in the presence of SMX. The volume of distribution of TMP is almost nine times that of SMX. The drug readily enters CSF and sputum. High concentrations of each component of the mixture also are found in bile. About 65% of SMX is bound to plasma protein. About 60% of administered TMP and from 25% to 50% of administered SMX are excreted in the urine in 24 h. Two-thirds of the sulfonamide is unconjugated. Metabolites of TMP also are excreted. The rates of excretion and the concentrations of both compounds in the urine are reduced significantly in patients with uremia.

Therapeutic Uses

Urinary Tract Infections

Treatment of UTIs with TMP-SMX is highly effective for sensitive bacteria. Use for empiric therapy of UTIs is complicated by the increase in resistance among *E. coli*; guidelines recommend avoiding empiric use for UTIs when local resistance among *E. coli* exceeds 20% or if patients have recently received TMP-SMX (Gupta et al., 2011). Most treatment guidelines recommend 160/800 mg administered twice daily for 3 days for uncomplicated cystitis and for 10 to 14 days for complicated disease or pyelonephritis. TMP also is found in therapeutic concentrations in prostatic secretions, and TMP-SMX is a common treatment for acute or chronic bacterial prostatitis.

Bacterial Respiratory Tract Infections

TMP-SMX is effective for outpatients with mild acute exacerbations of chronic bronchitis. TMP-SMX should not be used to treat streptococcal pharyngitis because it does not eradicate the microorganism from the pharynx. It is effective for acute otitis media in children and acute maxillary sinusitis in adults that are caused by susceptible strains of *H. influenzae* and *S. pneumoniae*.

GI Infections

The combination is an alternative to a fluoroquinolone for treatment of shigellosis, but increasing resistance limits its use unless susceptibility is confirmed. TMP and TMP-SMX are no longer recommended for prevention or treatment of traveler’s diarrhea because of increasing resistance worldwide among likely pathogens.

Infection by Pneumocystis jirovecii

High-dose therapy (TMP 15–20 mg/kg per day plus SMX 75–100 mg/kg per day in three or four divided doses; typical maximum dose is 20 mg/kg per day of TMP) is effective for *Pneumocystis jirovecii* pneumonia (Panel on Opportunistic Infections, 2020). Adjunctive corticosteroids should be given at the onset of anti-*Pneumocystis* therapy in patients with a Po_2 less than 70 mmHg or an alveolar-arterial gradient less than 35 mmHg. Prophylaxis with TMP-SMX using a variety of dosing strategies (from daily to several times weekly) is effective in preventing pneumonia caused by this organism in patients with HIV as well as among patients with other immunocompromising conditions (e.g., neutropenia and solid-organ transplantation). Adverse reactions

are less frequent with the lower prophylactic doses of TMP-SMX.

Methicillin-Resistant Staphylococcus aureus Infections

The increasing incidence of community-acquired infections due to *methicillin*-resistant *S. aureus* has provided a role for TMP-SMX as an adjunctive therapy to incision and drainage of complicated abscesses. However, it is less effective than standard therapy in the treatment of invasive *methicillin*-resistant *S. aureus* infections, including bacteremia (Paul et al., 2015).

Miscellaneous Infections

Nocardia infections have been treated successfully with the combination, but failures also have been reported. Although a combination of *doxycycline* and *streptomycin* or *gentamicin* is now considered the treatment of choice for brucellosis, TMP-SMX may be an effective substitute for the *doxycycline* combination. TMP-SMX also has been used successfully for infection by *Stenotrophomonas maltophilia* and infection by the intestinal parasites *Cyclospora* and *Isospora*. TMP-SMX is used as prophylaxis against infection due to *Toxoplasma gondii* in HIV-infected individuals and is an alternative for treatment of toxoplasmosis (see Chapter 67).

Adverse Effects

TMP-SMX extends the toxicity of the sulfonamides. Hematological reactions include various anemias, coagulation disorders, granulocytopenia, agranulocytosis, purpura, Henoch-Schönlein purpura, and sulfhemoglobinemia. TMP-SMX reportedly causes up to three times as many dermatological reactions as does *sulfisoxazole* (5.9% vs. 1.7%). Mild and transient jaundice has been noted and appears to have the histological features of allergic cholestatic hepatitis. Permanent impairment of renal function may follow the use of TMP-SMX in patients with renal disease due to SMX crystalluria; liberal fluid intake should be encouraged to dilute the urine during therapy. An increase in serum creatinine without decrement in glomerular filtration rate may be observed with high-dose therapy due to TMP's inhibition of creatinine secretion. Hyperkalemia can also be observed, as TMP has a similar structure to potassium-sparing diuretics such as *triamterene*. Patients with HIV frequently have hypersensitivity reactions to TMP-SMX (rash, neutropenia, Stevens-Johnson syndrome, Sweet syndrome, and pulmonary infiltrates). Both rapid and slow desensitization protocols have been established for patients intolerant to medically necessary therapy (Khan et al., 2019).

Drug Interactions

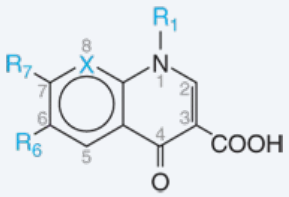
As with the sulfonamides alone, co-administration of TMP-SMX with *warfarin* can inhibit *warfarin* metabolism and lead to excessive anticoagulation with risks for bleeding. Caution is warranted with coadministration of agents that can increase potassium or suppress bone marrow when combined with high-dose TMP-SMX. Administration of TMP-SMX should be avoided in patients receiving high doses of *methotrexate* for treatment of malignancies, as TMP-SMX can increase *methotrexate* concentrations and lead to serious toxicity.

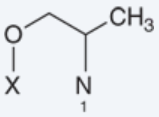
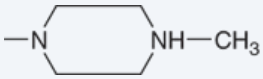
THE QUINOLONES

The first quinolone, *nalidixic acid*, was isolated as a by-product of the synthesis of chloroquine and made available for the treatment of UTIs. The introduction of fluorinated 4-quinolones (fluoroquinolones), such as *norfloxacin*, *ciprofloxacin*, and *levofloxacin* (Table 57–1), represents a particularly important therapeutic advance. These agents have broad antimicrobial activity and are effective after oral administration for the treatment of a wide variety of infectious diseases. However, due to potentially fatal side effects, many quinolones had to be withdrawn from the U.S. market: *lomefloxacin* and *sparfloxacin* (phototoxicity, QTc prolongation); *gatifloxacin* (systemic forms only: hypoglycemia); *temafloxacin* (immune hemolytic anemia); *trovafloxacin* (hepatotoxicity); *grepafloxacin* (cardiotoxicity); and *clinafloxacin* (phototoxicity). In all cases, the side effects were discovered during postmarketing surveillance (Sheehan and Chew, 2003). The FDA has issued new warnings for fluoroquinolones still being marketed, calling attention to their toxicities and recommending against their routine use in uncomplicated infections (Food and Drug Administration, 2018).

TABLE 57–1

STRUCTURAL FORMULAS OF SELECTED QUINOLONES AND FLUOROQUINOLONES



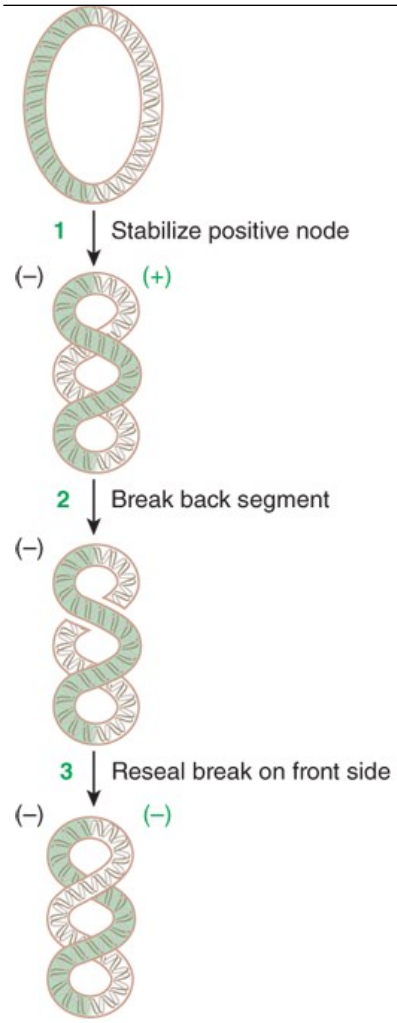
CONGENER	R_1	R_6	R_7	X
Nalidixic acid	$-C_2H_5$	–H	$-CH_3$	–N–
Norfloxacin	$-C_2H_5$	–F		–CH–
Ciprofloxacin		–F		–CH–
Levofloxacin		–F		

Mechanism of Action

The quinolone antibiotics target bacterial *DNA gyrase* and *topoisomerase IV* (Mohammed et al., 2019). For many gram-positive bacteria, topoisomerase IV, which separates interlinked (catenated) daughter DNA molecules that are the product of DNA replication, is the primary target. In contrast, DNA gyrase is the primary quinolone target in many gram-negative microbes. The gyrase introduces negative supercoils into the DNA to combat excessive positive supercoiling that can occur during DNA replication (Figure 57–3) (Cozzarelli, 1980). The quinolones, as a drug-metal complex, inhibit gyrase-mediated DNA supercoiling at concentrations that correlate well with those required to inhibit bacterial growth (0.1–10 µg/mL).

Figure 57–3

Model of the formation of negative DNA supercoils by DNA gyrase. DNA gyrase binds to two segments of DNA (1), creating a node of positive (+) superhelix. The enzyme then introduces a double-strand break in the DNA and passes the front segment through the break (2). The break is then resealed (3), creating a negative (–) supercoil. Quinolones inhibit the nicking and closing activity of the gyrase and, at higher concentrations, block the decatenating activity of topoisomerase IV.



Source: Laurence L. Brunton, Björn C. Knollmann:
Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e:

Eukaryotic cells do not contain DNA gyrase. They do contain a mechanistically similar type II DNA topoisomerase, but quinolones inhibit it only at concentrations (100–1000 µg/mL) much higher than those needed to inhibit the bacterial enzymes.

Antimicrobial Activity

The fluoroquinolones were potent, bactericidal agents against most gram-negative pathogens when first introduced, including *Proteus, E. coli, Klebsiella,* and various species of *Salmonella, Shigella, Enterobacter,* and *Campylobacter*. As with TMP-SMX, resistance has continuously eroded the coverage that fluoroquinolones provide, especially among *E. coli* and *Proteus* spp., such that fluoroquinolones may not be reliable for empiric therapy due to the prevalence of these organisms in some regions (Olson et al., 2009). While once a standard therapy for *Neisseria gonorrhoeae* infections, resistance has increased to the point these agents are no longer recommended in most countries for empiric therapy of gonorrhea (Centers for Disease Control and Prevention, 2021). *Ciprofloxacin* and *levofloxacin* have sufficient activity against *Pseudomonas* spp. for use in systemic infections; a newly introduced agent, *delafloxacin*, also possesses *in vitro* activity, but to date, few patients with *Pseudomonas* infections have been treated with this agent. Fluoroquinolones have good *in vitro* activity against staphylococci, but they are less active against *methicillin*-resistant strains, and there is concern over development of resistance during therapy. Activity against streptococci is significantly greater with the newer agents, including *levofloxacin*, *gemifloxacin*, *moxifloxacin*, and *delafloxacin*. Several intracellular bacteria are inhibited by fluoroquinolones at concentrations that can be achieved in plasma; these include species of *Chlamydia, Mycoplasma, Legionella, Brucella*, and *Mycobacterium* (including *Mycobacterium tuberculosis*). *Ciprofloxacin*, *ofloxacin*, *levofloxacin*, and *moxifloxacin* have activity against *Mycobacterium fortuitum, Mycobacterium kansasii*, and *M. tuberculosis*. *Moxifloxacin* also has useful activity against intestinal anaerobes, such as *Bacteroides fragilis*.

Bacterial Resistance

Resistance to quinolones may develop during therapy via mutations in the bacterial chromosomal genes encoding DNA gyrase or topoisomerase IV, leading to reduced binding affinity for the fluoroquinolones (Correia et al., 2017). Chromosomal mutations leading to upregulation of efflux pump–mediated active transport of the drug out of the bacteria or the reduction in expression of porin channels allowing quinolones to transit the outer membrane also contribute to resistance. Less commonly, plasmids can transfer genes that encode proteins capable of binding to and protecting the topoisomerases from quinolone effects or that directly modify the quinolone itself. Resistance emerging during the course of therapy can occur, especially in *E. coli*, *Pseudomonas*, and staphylococci.

ADME

Most quinolones are well absorbed after oral administration. Peak serum levels of the fluoroquinolones are obtained within 1 to 3 h of an oral dose. The volume of distribution of quinolones is high, with concentrations in urine, kidney, lung, and prostate tissue and stool, bile, and macrophages and neutrophils higher than serum levels. Food may delay the time to peak serum concentrations. Many fluoroquinolones have been detected in human breast milk; because of their excellent bioavailability, the potential exists for substantial exposure of nursing infants. Except for *moxifloxacin*, quinolones are cleared predominantly by the kidney, and dosages must be adjusted for renal failure.

Pharmacological Properties of Individual Quinolones

Norfloxacin

The gram-negative activity of *norfloxacin* (not available in the United States) is similar to, but somewhat less potent than, that of *ciprofloxacin*. However, the relatively low serum levels reached with *norfloxacin* limit its usefulness in the treatment of UTIs and gastrointestinal infections. The serum $t_{1/2}$ is 3 to 5 h for *norfloxacin*; approximately 25% of the drug is eliminated unchanged in the urine, with hepatic metabolism also occurring.

Ciprofloxacin

Ciprofloxacin's bioavailability is approximately 70%. Typical oral doses are 250 to 750 mg and intravenous doses are 200 to 400 mg twice daily (maximum dose 1.5 g/day orally). The elimination $t_{1/2}$ is about 5 h, and the drug is typically dosed twice daily, with the exception of an extended-release formulation, which can be dosed once daily.

Ofloxacin/Levofloxacin

Ofloxacin has somewhat more potent gram-positive activity than *ciprofloxacin*; separation of the more active S- or levorotatory isomer yields *levofloxacin*, which has even better antistreptococcal activity. Bioavailability of both of these agents is excellent, such that intravenous and oral doses are the same; *levofloxacin* is dosed once daily (250–750 mg) as opposed to twice-daily dosing for *ofloxacin* (200–400 mg daily divided every 12 h).

Moxifloxacin

Moxifloxacin improves further on the gram-positive potency of *levofloxacin*, typically having minimal inhibitory concentrations one to two dilutions lower against *S. pneumoniae*. It also has expanded activity against anaerobic pathogens but is substantially less active than *ciprofloxacin* or *levofloxacin* against *P. aeruginosa*. *Moxifloxacin* is well absorbed, with equivalent intravenous and oral doses; the $t_{1/2}$ is about 12 h, allowing for daily dosing (usual dose 400 mg daily). *Moxifloxacin* undergoes hepatic sulfation and glucuronidation. Less than a quarter of systemic *moxifloxacin* is excreted unchanged via the kidneys, and because high concentrations are not achieved in the urine, it is not recommended for UTIs.

Gatifloxacin, Gemifloxacin

The agents *gatifloxacin* and *gemifloxacin* have a similar spectrum of activity to *moxifloxacin*, with enhanced potency against gram-positive organisms and poor activity versus *Pseudomonas*. They are less active than *moxifloxacin* against *B. fragilis*. Both have high bioavailability and renal elimination. *Gatifloxacin* is no longer available for systemic use in the U.S. due to toxicity concerns, but an ophthalmic preparation is licensed for the treatment of bacterial conjunctivitis.

Delafloxacin

Delafloxacin is a newly approved fluoroquinolone with potent activity against staphylococci; minimal inhibitory concentrations are at least 6-fold lower than *levofloxacin* for most isolates of *S. aureus*. Activity against gram-negatives, including *Pseudomonas*, is similar to that of *levofloxacin*. It is available for intravenous and oral administration and undergoes mixed renal and nonrenal elimination.

Therapeutic Uses

Urinary Tract Infections

The fluoroquinolones are a mainstay of treatment of upper and lower UTIs, being more efficacious than TMP-SMX or oral β-lactams. Because of their broad spectrum of activity and adverse effects, however, recent guidelines suggest reserving their use for complicated cystitis or pyelonephritis when possible (Gupta et al., 2011). *Moxifloxacin* does not accumulate in the urine and is not approved for treatment of UTIs. Typical treatment durations for quinolones are 3 days for uncomplicated cystitis and 5 to 7 days for uncomplicated pyelonephritis.

Prostatitis

Norfloxacin, *ciprofloxacin*, *ofloxacin*, and *levofloxacin* achieve good levels in prostatic secretions and are effective in the treatment of prostatitis caused by sensitive bacteria. Fluoroquinolones administered for 4 to 6 weeks appear to be effective in patients not responding to TMP-SMX.

Sexually Transmitted Diseases

Fluoroquinolones lack activity for *Treponema pallidum* but have activity *in vitro* against *Chlamydia trachomatis* and *H. ducreyi*. For chlamydial urethritis/cervicitis, a 7-day course of *ofloxacin* or *levofloxacin* is an alternative to a 7-day treatment with *doxycycline* or a single dose of *azithromycin*; other available quinolones have not been reliably effective. Previously, a single oral dose of a fluoroquinolone such as *ciprofloxacin* had been effective treatment of sensitive strains of *N. gonorrhoeae*, but increasing resistance to fluoroquinolones has led to *ceftriaxone* being the first-line agent for this infection. A study of *delafloxacin* for single-dose therapy failed to meet its endpoint for efficacy. Chancroid (infection by *H. ducreyi*) can be treated with 3 days of *ciprofloxacin*.

GI and Abdominal Infections

Norfloxacin, *ciprofloxacin*, *ofloxacin*, and *levofloxacin* given for 1 to 3 days all have been effective in the treatment of patients with traveler's diarrhea, reducing the duration of loose stools by 1 to 3 days. *Ciprofloxacin* in a single daily dose has been used for prophylaxis of traveler's diarrhea, but resistance among *Campylobacter* and *Shigella* and increasing recognition of fluoroquinolone adverse effects have led to authorities discouraging this use. *Ciprofloxacin* and *ofloxacin* can cure most patients with enteric fever caused by *Salmonella typhi*, as well as bacteremic nontyphoidal infections in patients with HIV, and clear chronic fecal carriage. Quinolones should be avoided in the treatment of diarrhea due to Shiga toxin–producing *E. coli*. *Ciprofloxacin* and *levofloxacin*, when combined with *metronidazole*, or *moxifloxacin* alone, may be useful in the management of intra-abdominal infections if local susceptibilities allow.

Respiratory Tract Infections

Many newer fluoroquinolones, including *levofloxacin*, *moxifloxacin*, *gemifloxacin*, and *delafloxacin*, have excellent activity against *S. pneumoniae, H. influenzae,* and the atypical respiratory pathogens. Thus, these agents are frequently used in the management of community-acquired pneumonia. *Ciprofloxacin* and *levofloxacin* also play a role in the treatment of respiratory exacerbations owing to *P. aeruginosa* in patients with cystic fibrosis and in combination with a β-lactam agent to provide broad gram-negative coverage for nosocomial pneumonia in patients at high risk for resistant isolates.

Bone, Joint, and Soft-Tissue Infections

The treatment of chronic osteomyelitis may require prolonged (weeks to months) antimicrobial therapy with agents active against *S. aureus* or gram-negative rods. Failures are often associated with the development of resistance, particularly in *S. aureus*. Combination therapy with a fluoroquinolone

and *rifampin* is an option for the management of early-onset prosthetic joint infections. *Levofloxacin*, *moxifloxacin*, and *delafloxacin* are approved for the treatment of skin and soft-tissue infections; although, they should generally be reserved for situations where their expanded spectrum of activity can be leveraged, such as diabetic foot infections.

Other Infections

Ciprofloxacin and *levofloxacin* are used for the prophylaxis of anthrax and are effective for the treatment of tularemia and plague due to *Yersinia pestis* (Hendricks et al., 2014). *Levofloxacin* and *moxifloxacin* may be used as part of multiple-drug regimens for the treatment of multidrug-resistant tuberculosis and atypical mycobacterial infections as well as *Mycobacterium avium* complex infections in AIDS (see Chapter 65). Quinolones, when used as prophylaxis in neutropenic patients, have decreased the incidence of gram-negative rod bacteremias (Freifeld et al., 2011).

Adverse Effects

Gastrointestinal Adverse Effects

Common adverse reactions involve the GI tract, with 3% to 17% of patients reporting mild nausea, vomiting, and abdominal discomfort. Fluoroquinolones have emerged as a leading cause of *Clostridium difficile* colitis due to the spread of quinolone-resistant strains.

Neurologic Adverse Effects

Common side effects (1%–11%) involving the CNS include mild headaches, dizziness, insomnia, and anxiety. Rarely, hallucinations, delirium, and seizures have occurred, especially in patients who were also receiving *theophylline* or nonsteroidal anti-inflammatory drugs. Patients with a history of epilepsy are at higher risk for fluoroquinolone-induced convulsions. Recently, the fluoroquinolones have been recognized as rare causes of peripheral neuropathy and possibly optic neuritis, which in some cases has been irreversible.

Musculoskeletal Adverse Effects

Arthralgias and joint pain are occasionally reported with fluoroquinolones. Tendon rupture or tendinitis (usually of the Achilles tendon) is a recognized serious adverse effect, especially in those more than 60 years old, in patients taking corticosteroids, and in solid-organ transplant recipients. Early animal studies suggested an increased risk of cartilage damage and malformation among young animals (Burkhardt et al., 1997). While arthralgias and joint pain during therapy are more common among children receiving quinolones relative to comparators during the course of therapy, studies have not noted long-term joint abnormalities or growth inhibition among children exposed to fluoroquinolones. The American Academy of Pediatrics suggests that fluoroquinolone use in children is appropriate when limited treatment options exist or when oral administration offers a significant risk/benefit advantage (Jackson and Schutze, 2016). Similarly, limited data suggest that fluoroquinolone use may be appropriate in pregnant women in the absence of alternative therapies.

Other Adverse Effects

Among the quinolones available in the U.S., *moxifloxacin* carries the highest risk for QT interval prolongation and torsades de pointes arrhythmias; *gemifloxacin*, *levofloxacin*, and *ofloxacin* appear to have lower risk; and *ciprofloxacin* has the lowest risk. However, the overall risk of torsades de pointes is small with the use of fluoroquinolones. *Gatifloxacin*'s propensity to cause both hypo- and hyperglycemia, especially in older adults, led to its removal for systemic use in the U.S. (Park-Wyllie et al., 2006). Other agents such as *levofloxacin* may rarely be associated with dysglycemias among at-risk patients. Rashes, including photosensitivity reactions, also can occur; patients with frequent sun exposure should be advised to protect themselves with clothing or sunscreen.

Drug Interactions

All quinolones form complexes with divalent and trivalent cations (e.g., calcium, iron, aluminum). When coadministered orally with quinolones, these cations can chelate the quinolone and reduce systemic bioavailability. Thus, a separation of at least 2 h between oral administration of quinolones and these cations is recommended. *Ciprofloxacin* inhibits the metabolism of theophylline, and toxicity from elevated concentrations of the methylxanthine may occur. Nonsteroidal anti-inflammatory drugs may augment displacement of γ-aminobutyric acid (GABA) from its receptors by the quinolones, enhancing neurological adverse effects (Halliwell et al., 1993). Due to risk for QT prolongation, quinolones should be used with caution in patients on

class III (*amiodarone*) and class IA (*quinidine*, *procainamide*) antiarrhythmics.

NITROIMIDAZOLES

Metronidazole and *tinidazole* are nitroimidazoles with activity against anaerobic bacteria and parasites. Here, we will discuss the antibacterial activity of *metronidazole*; an in-depth discussion of *metronidazole* and *tinidazole*, including their pharmacokinetics, adverse effects, and antiparasitic uses, will be reserved for Chapter 67; applications for treatment of *Helicobacter pylori* disease are discussed in Chapter 53 and for inflammatory bowel disease in Chapter 55.

Metronidazole

Antibacterial Activity and Resistance

Metronidazole is essentially a prodrug: The nitro group of *metronidazole* is reduced in anaerobic bacteria, some microaerophilc bacteria, and protozoans, producing the active form of the drug. The activation leads to formation of reactive compounds that interact with DNA, possibly disrupting its structure and inhibiting replication (Dingsang and Hunter, 2018). *Metronidazole* displays excellent activity against most anaerobic bacteria, including *Bacteroides*, *Clostridium*, *Fusobacterium*, *Peptococcus*, *Peptostreptococcus*, and *Eubacterium*. It is less active against *Gardnerella* and *Helicobacter*, and the gram-positive anaerobes *Actinomyces, Propionibacterium*, and *Lactobacillus* are typically resistant. Acquired resistance among normally susceptible organisms is uncommon, and resistance mechanisms are complex and incompletely described. In the case of *Bacteroides* spp., *metronidazole* resistance has been linked to a family of nitroimidazole (*nim*) resistance genes, which can be encoded chromosomally or episomally. These *nim* genes appear to encode a nitroimidazole reductase capable of converting a 5-nitroimidazole to a 5-aminoimidazole, thus stopping the formation of the reactive nitroso group responsible for microbial killing.

Therapeutic Uses and Dosage

Metronidazole is a relatively inexpensive agent with efficacy against a broad spectrum of anaerobic bacteria. Typical doses are 250 to 500 mg twice or three times daily, via the intravenous or oral routes. The drug is frequently given in combination with other antimicrobial agents to treat polymicrobial infections with aerobic and anaerobic bacteria. *Metronidazole* is used as a component of prophylaxis for colorectal surgery and is employed as a single agent to treat bacterial vaginosis. It is used in combination with other antibiotics and a proton pump inhibitor in regimens to treat infection with *H. pylori* (see Chapter 53). *Metronidazole* has been used as therapy for nonsevere *C. difficile* infection, although *vancomycin* or *fidaxomicin* are now preferred agents. For patients with fulminant, life-threatening *C. difficile* infection, intravenous *metronidazole* is administered in combination with oral *vancomycin*.

DRUG SUMMARY TABLE

Drug Facts for Your Personal Formulary: *DNA Disruptors: Sulfonamides, Quinolones, and Nitroimidazoles*

Drug	Therapeutic Uses	Clinical Pharmacology and Tips
Sulfonamides: Competitive inhibitors of bacterial dihydropteroate synthase, thereby disrupting folate synthesis General: Bacteriostatic; limited efficacy as monotherapy, renal elimination, hypersensitivity reactions		
Sulfadiazine (PO)	• Toxoplasmosis (with pyrimethamine)	• Good activity against *T. gondii* • Reasonable CSF penetration • Higher risk of crystalluria, requires hydration
Sulfadoxine (PO)	• Prophylaxis and treatment of malaria (with pyrimethamine)	• Some activity vs. *P. falciparum* • Long $t_{1/2}$

Sulfonamide and Dihydrofolate Reductase Inhibitor Combination: Sequential inhibition of folate synthesis, often bactericidal		
Trimethoprim-sulfamethoxazole (IV, PO)	• UTI • Upper respiratory tract infections • Shigellosis • *P. jirovecii* pneumonia • Skin/soft-tissue infections due to *S. aureus* • Infections due to *Nocardia*, *S. maltophila, Cyclospora, Isospora*	• Excellent activity vs. *S. aureus*, *S. epidermidis*, *S. pyogenes* • Good activity vs. *Proteus, E. coli, Klebsiella, Enterobacter, Serratia, Nocardia, Brucella* • Some activity vs. *S. pneumoniae* • Formulated in 5:1 (SMX:TMP) ratio, giving 20:1 serum levels • Well absorbed on oral administration • Good penetration into CSF • Metabolized and renally eliminated • Hypersensitivity reactions (i.e., rash) common • Dose-related bone marrow suppression, hyperkalemia
Quinolones: Bactericidal inhibitors of bacterial gyrase and topoisomerase, prevent DNA unwinding **General: Drug interactions with cations, neurological adverse effects, tendonitis/tendon rupture, photosensitivity, QT prolongation; typically avoided in children and pregnant women except for compelling indications**		
Norfloxacin (PO)	• UTI, prostatitis • Traveler's diarrhea	• Good activity vs. *E. coli, Klebsiella, Proteus, Serratia, Salmonella, Shigella* • Some activity vs. *Pseudomonas* • Effective concentrations only achieved in GI and urinary tracts
Ciprofloxacin (IV, PO)	• UTI, prostatitis • Traveler's diarrhea • Intra-abdominal infections (with metronidazole) • *Pseudomonas* infections • Anthrax, tularemia	• Excellent activity vs. *E. coli, Klebsiella, Proteus, Serratia, Salmonella, Shigella* • Good activity vs. *Pseudomonas* • Some activity vs. *S. aureus*, streptococci • Good bioavailability and tissue distribution • Renal and nonrenal elimination
Levofloxacin (IV, PO)	• Respiratory tract infections • UTI, prostatitis • *Chlamydia* • Traveler's diarrhea • Intra-abdominal infections (with metronidazole) • *Pseudomonas* infections	• Excellent activity vs. *E. coli, Klebsiella, Proteus, Serratia, Salmonella, Shigella,* streptococci, *H. influenzae, Legionella, Chlamydia* • Good activity vs. *Pseudomonas, S. aureus* • Good bioavailability and tissue distribution • Renal elimination • S-isomer of ofloxacin
Moxifloxacin (IV, PO)	• Respiratory tract infections • Intra-abdominal infections • Mycobacterial infections	• Excellent activity vs. *E. coli, Klebsiella, Proteus, Serratia,* streptococci, *H. influenzae, Legionella, Chlamydia* • Good activity vs. *S. aureus, B. fragilis* • Good bioavailability and tissue distribution • Renal and nonrenal elimination; not for UTI • QT prolongation
Nitroimidazoles: Bactericidal DNA-damaging agents; require activation by reductases present in anaerobes		
Metronidazole (IV,	• *C. difficile* colitis	• Bacterial spectrum limited to anaerobic organisms, including *B.*

PO, topical)	• Empiric coverage of anaerobic organisms, as in intra-abdominal and skin and soft-tissue infections • *H. pylori* gastritis (in combination with other agents) • Bacterial vaginosis	*fragilis* and *Clostridium* • Excellent absorption • Wide distribution including CNS • Hepatic elimination • Inhibitor of CYP enzymes; drug interactions with warfarin • Peripheral neuropathy with prolonged use

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