Azithromycin, clarithromycin, and telithromycin all have broader spectra of activity than erythromycin, which is less frequently used. These agents are commonly used in the treatment of upper and lower respiratory tract infections caused by *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and atypical organisms (e.g., *Chlamydia pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae*); group A streptococcal pharyngitis in penicillin-allergic patients; and nontuberculous mycobacterial infections (e.g., caused by *M. marinum* and *M. chelonae*) as well as in the prophylaxis and treatment of *M. avium-intracellulare* infection in patients with HIV/AIDS and in combination therapy for *H. pylori* infection and bartonellosis. Enterobacteriaceae, *Pseudomonas* species, and *Acinetobacter* species are intrinsically resistant to macrolides as a result of decreased membrane permeability, although azithromycin is active against gram-negative diarrheal pathogens. The major adverse effects of this drug class include nausea, vomiting, diarrhea and abdominal pain, prolongation of QT_c interval, exacerbation of myasthenia gravis, and tinnitus. Azithromycin specifically has been associated with an increased risk of death, especially among patients with underlying heart disease, because of the risk of QT_c interval prolongation and torsades de pointes. Erythromycin, clarithromycin, and telithromycin inhibit the CYP3A4 hepatic drug-metabolizing enzyme and can result in increased levels of coadministered drugs, including benzodiazepines, statins, warfarin, cyclosporine, and tacrolimus. Azithromycin does not inhibit CYP3A4 and lacks these drug–drug interactions.

CLINDAMYCIN

Clindamycin is a lincosamide antibiotic and is bacteriostatic against some organisms and bactericidal against others. It is used most often to treat bacterial infections caused by anaerobes (e.g., *B. fragilis*, *Clostridium perfringens*, *Fusobacterium* species, *Prevotella melaninogenicus*, and *Peptostreptococcus* species) and susceptible staphylococci and streptococci. Clindamycin is used for treatment of dental infections, anaerobic lung abscess, and skin and soft tissue infections. It is used together with bactericidal agents (penicillins or vancomycin) to inhibit new toxin synthesis in the treatment of streptococcal or staphylococcal toxic shock syndrome. Other uses include treatment of infections caused by *Capnocytophaga canimorsus*, a component of combination therapy for malaria and babesiosis, and therapy for toxoplasmosis. Clindamycin has excellent oral bioavailability. Adverse effects include nausea, vomiting, diarrhea, *C. difficile*–associated diarrhea and pseudomembranous colitis, maculopapular rash, and (rarely) Stevens-Johnson syndrome.

TETRACYCLINES AND GLYCYLCYCLINES

The tetracyclines (doxycycline, minocycline, and tetracycline) and the glycylcyclines (tigecycline) inhibit protein synthesis and are bacteriostatic. These drugs have wide clinical uses. They are used in the treatment of skin and soft tissue infections caused by gram-positive cocci (including MRSA), spirochetal infections (e.g., Lyme disease, syphilis, leptospirosis, and relapsing fever), rickettsial infections (e.g., Rocky Mountain spotted fever), atypical pneumonia, sexually transmitted infections (e.g., *Chlamydia trachomatis* infection, lymphogranuloma venereum, and granuloma inguinale), infections with *Nocardia* and *Actinomyces*, brucellosis, tularemia, Whipple's disease, and malaria. Tigecycline, the only approved agent in the glycylcycline class, is a derivative of minocycline and is indicated in the treatment of infections due to MRSA, vancomycin-sensitive enterococci, many Enterobacteriaceae, and *Bacteroides* species. Tigecycline has no activity against *P. aeruginosa*. It has been used in combination with colistin for the treatment of serious infections with multidrug-resistant gram-negative organisms. A pooled analysis of 13 clinical trials found an increased risk of death and treatment failure among patients treated with tigecycline alone. Tetracyclines have reduced absorption when coadministered with calcium- and iron-containing compounds, including milk, and doses should be spaced at least 2 h apart. The major adverse reactions to both of these classes are nausea, vomiting, diarrhea, and photosensitivity. Tetracyclines have been associated with fetal bone-growth abnormalities and should be avoided during pregnancy and in the treatment of children <8 years old.

TRIMETHOPRIM-SULFAMETHOXAZOLE

Trimethoprim-sulfamethoxazole (TMP-SMX) is an antibiotic whose two components both inhibit folate synthesis and produce antibacterial activity. TMP-SMX is active against gram-positive bacteria such as staphylococci and streptococci; however, its use against MRSA is usually limited to community-acquired infections, and its activity against *Streptococcus pyogenes* may not be reliable. TMP-SMX is also active against many gram-negative bacteria, including *H. influenzae*, *E. coli*, *P. mirabilis*, *N. gonorrhoeae*, and *S. maltophilia*. TMP-SMX does not have activity against anaerobes or *P. aeruginosa*. It has many uses because of its wide spectrum of activity and high oral bioavailability. Urinary tract infections, skin and soft tissue infections, and respiratory tract infections are among the common uses. Another important indication is for both prophylaxis and treatment of *Pneumocysitis jirovecii* infections in immunocompromised patients. Resistance to TMP-SMX has limited its use against many Enterobacteriaceae. Resistance rates among urinary isolates of *E. coli* are almost 25% in the United States. The most common adverse reactions associated with TMP-SMX are gastrointestinal effects such as nausea, vomiting, and diarrhea. In addition, rash is a common allergic reaction and may preclude the subsequent use of other sulfonamides. With prolonged use, leukopenia, thrombocytopenia, and granulocytopenia can develop. TMP-SMX can also cause nephrotoxicity, hyperkalemia, and hyponatremia, which are more common at high doses. TMP-SMX has several important interactions with other drugs (Table 170-4), including warfarin, phenytoin, and methotrexate.

FLUOROQUINOLONES

The fluoroquinolones include norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, and gemifloxacin. Ciprofloxacin and levofloxacin have the broadest spectrum of activity against gram-negative bacteria, including *P. aeruginosa* (similar to that of third-generation cephalosporins). Because of the risk of selection of resistance during fluoroquinolone treatment of serious pseudomonal infections, these agents are usually used in combination with an antipseudomonal β-lactam. Levofloxacin, moxifloxacin, and gemifloxacin have additional gram-positive activity, including that against *S. pneumoniae* and some strains of MSSA, and are used for treatment of community-acquired pneumonia. Strains of MRSA are commonly resistant to all fluoroquinolones. Moxifloxacin is used as one component of second-line regimens for multidrug-resistant tuberculosis. Fluoroquinolones exhibit concentration-dependent killing, are well absorbed orally, and have elimination half-lives that usually support once- or twice-daily dosing. Oral coadministration with compounds containing high concentrations of aluminum, magnesium, or calcium can reduce fluoroquinolone absorption. Their penetration into prostate tissue supports their use for bacterial prostatitis. Fluoroquinolones are generally well tolerated but can cause CNS stimulatory effects, including seizures; glucose dysregulation; and tendinopathy associated with Achilles tendon rupture, particularly in older patients, organ transplant recipients, and patients taking glucocorticoids. Worsening of myasthenia gravis also has been associated with quinolone use. Moxifloxacin causes modest prolongation of the QT_c interval and should be used with caution in patients receiving other QT_c-prolonging drugs.

RIFAMYCINS

The rifamycins include rifampin, rifabutin, and rifapentine. Rifampin is the most commonly used rifamycin. For almost all therapeutic indications, it is used in combination with other agents to reduce the likelihood of selection of high-level rifampin resistance. Rifampin is used foremost in the treatment of mycobacterial infections—specifically, as a mainstay of combination therapy for *M. tuberculosis* infection or as a single agent in the treatment of latent *M. tuberculosis* infection. In addition, it is often used in the treatment of nontuberculous mycobacterial infection. Rifampin is used in combination regimens for the treatment of staphylococcal infections, particularly prosthetic valve endocarditis and bone infections with retained hardware. It is a component of combination therapy for brucellosis (with doxycycline) and leprosy (with dapsone for tuberculoid leprosy and with dapsone