Certain gram-positive bacilli are sensitive to chloramphenicol. *Corynebacterium diphtheriae, L. monocytogenes*, and *B. anthracis* are almost always susceptible, whereas *Corynebacterium jeikeium* and *Nocardia* spp. are usually resistant.[344,374,375]

Gram-Negative Bacteria

Chloramphenicol has variable activity against gram-negative organisms. It is highly active against community-acquired organisms, such as *H. influenzae* and *M. catarrhalis*.[366] *N. meningitidis* and *N. gonorrhoeae* are also both highly susceptible.[376,377]

Activity against *E. coli* is variable worldwide. A surveillance study demonstrated a wide range of chloramphenicol-resistant isolates, from 8% in Curaçao to 82% in Ghana.[378] Another study in the United Kingdom showed that rates of resistance declined from 20.2% in 1991 to 7.9% in 2004.[379] Chloramphenicol generally has good activity against some other members of the Enterobacteriaceae, such as *P. mirabilis, Salmonella* spp., *Shigella* spp., and *Yersinia* spp., whereas others, such as *Klebsiella* spp., *Serratia* spp., *Morganella* spp., and *Enterobacter* spp., are usually more resistant.[380–383] The combination of chloramphenicol with polymyxin B was found to be synergistic in vitro against New Delhi metallo-β-lactamase (NDM)-producing MDR *K. pneumoniae*.[384]

P. aeruginosa is generally resistant to chloramphenicol by means of an active efflux pump.[385] *Acinetobacter* spp. are also generally resistant, whereas *S. maltophilia* is usually susceptible.[386,387] Chloramphenicol has activity against *B. pseudomallei,* whereas *B. cepacia* is usually resistant owing to decreased drug permeability.[388,389]

Anaerobic Bacteria

Most gram-positive and gram-negative anaerobic bacteria are susceptible to chloramphenicol. Anaerobic gram-positive cocci, such as *Peptostreptococcus* spp., are all susceptible at achievable concentrations. Anaerobic gram-positive bacilli, such as *Clostridium, Lactobacillus,* and *Propionibacterium* spp., are also readily susceptible.[390] However, resistant strains of *Clostridium perfringens* and *C. difficile* have been isolated.[391,392] Against gram-negative anaerobic bacteria, chloramphenicol is one of the most active antimicrobial agents. *Bacteroides* spp., *Fusobacterium* spp., and *Prevotella* spp. are all highly susceptible.[390] A US study of 5225 *B. fragilis* group isolates demonstrated that every single one was susceptible to chloramphenicol.[393]

Other Organisms

Chloramphenicol has activity against chlamydiae, mycoplasma, rickettsiae, *T. pallidum, C. burnetii,* and leptospirae.[344,394–396] It is not active against mycobacteria and protozoa.

Clinical Uses

In the developed world, chloramphenicol is generally reserved for serious infections with limited alternative antimicrobial choices because of its well-known toxicities. In the developing world, it is still commonly used because it may be the only broad-spectrum agent available. It also has the advantage of an oral formulation and is available without a prescription in many parts of the world.

Bacterial Meningitis and Brain Abscess

Chloramphenicol remains a useful drug for the treatment of bacterial meningitis in countries that do not have access to third-generation cephalosporins. The use of single-dose intramuscular injections of oily chloramphenicol has been suggested as a nationwide antibiotic of choice for meningitis epidemics.[397] Conclusions from a meta-analysis determined that in circumstances in which ceftriaxone or cefotaxime is not available or affordable, an ampicillin-chloramphenicol combination may be used as an alternative because the two treatment groups did not have important clinical differences.[398] In a Nigerian study of childhood bacterial meningitis, similar results were seen in children treated with chloramphenicol as compared with those given cephalosporins.[399] Another study during a meningococcal meningitis epidemic in sub-Saharan Africa demonstrated that single-dose intramuscular ceftriaxone had clinical outcomes at 72 hours that were comparable to those of single-dose intramuscular oily chloramphenicol and was actually cheaper.[400] Unfortunately, poor outcome was noted in areas with high rates of chloramphenicol-resistant *H. influenzae* type b. This was seen in children treated in Papua New Guinea, where resistance rates were 20%.[401] Areas with penicillin-resistant pneumococcal meningitis also have poor outcomes. In one study in South Africa, 20 of 25 children with chloramphenicol-susceptible, penicillin-resistant strains had poor outcomes, including death.[402]

Chloramphenicol had been used extensively for the treatment of brain abscesses until the availability of safer agents. It may still have a role in treating this infection, particularly in patients with severe penicillin allergies.[403] A case report of a patient with a culture-negative brain abscess in whom multiple antibiotic regimens had failed had dramatic clinical and radiographic improvement after 7 days of chloramphenicol therapy.[404]

Salmonella Infections

Chloramphenicol was once the drug of choice for typhoid fever.[405] It has been largely replaced by the more efficacious and safer fluoroquinolones and ceftriaxone.[406–408] In areas previously burdened with chloramphenicol-resistant *Salmonella* Typhi, sensitive strains are reappearing.[409] Usual treatment for typhoid fever is a 2-week course.[410] Clinical failure rates are rather low (estimated 4.8%), but relapse rates approach 5.6%.[411]

Treatment of acute *Salmonella* gastroenteritis with chloramphenicol is not indicated and usually prolongs fecal excretion after clinical recovery.[412,413] There does not appear to be any benefit with antibiotics in general with mild disease. Infections due to *Salmonella enterica* serotype Choleraesuis and *S. enterica* serotype Typhimurium can be treated with chloramphenicol, but resistance rates as high as 83% have been reported.[414] Third-generation cephalosporins seem to be the drug of choice.

Other Infections

There are various other potential uses of chloramphenicol. It may be the drug of choice in rickettsial infections, such as RMSF, in pregnant women, or in patients allergic to tetracyclines.[415] Overall, it is inferior to the tetracyclines for the treatment of RMSF.[416] It may be useful when it is clinically difficult to distinguish between RMSF and meningococcemia. Chloramphenicol is also effective therapy for Mediterranean spotted fever, tick typhus, epidemic louse-borne typhus, murine typhus, and scrub typhus.[92]

Renewed interest was previously seen in chloramphenicol for treatment of serious VRE infections, including bacteremia.[417,418] However, this enthusiasm has since subsided with the availability of newer agents, such as daptomycin, linezolid, quinupristin-dalfopristin, and tigecycline. Other serious infections may find roles for chloramphenicol, such as a case report of successful treatment in combination with ciprofloxacin for prosthetic valve endocarditis due to *S. maltophilia*.[34,419]

Chloramphenicol has fallen out of favor as inclusion in multidrug therapy for the maintenance treatment of melioidosis, caused by *B. pseudomallei.* In an open-label, randomized study looking at chloramphenicol, doxycycline, and TMP-SMX versus doxycycline and TMP-SMX, the latter group was just as effective and better tolerated than the traditional four-drug group.[175]

Topical chloramphenicol can be used for treatment of bacterial conjunctivitis, and it has excellent intraorbital penetration.[420] It was also found to be superior to topical povidone-iodine in preventing neonatal chlamydial conjunctivitis in a trachoma-endemic area of Mexico.[421] However, two randomized trials have trivialized the early use of topical chloramphenicol. In one trial, 326 children with infective conjunctivitis (250 cases were bacterial) were randomized to chloramphenicol or placebo. There was no significant difference in clinical cure rates at day 7 or with further episodes of conjunctivitis. AEs were rare in both groups.[422] Another trial of 307 patients with infective conjunctivitis compared early topical chloramphenicol, delayed treatment, and no treatment. Delaying antibiotics was found to reduce antibiotic use, resulted in similar duration and severity of symptoms as immediate prescribing, and reduced reattendance for eye infections.[423]

Because of its activity against tularemia, plague, and anthrax, chloramphenicol has been suggested by the Working Group on Civilian Biodefense as an effective alternative agent in the setting of biologic warfare.[424–426]

Mechanism of Resistance

Resistance to chloramphenicol occurs by various mechanisms. The most common is by enzymatic acetylation and inactivation by chloramphenicol acetyltransferases (CATs).[427] Most CAT genes are located on mobile genetic elements, can be distributed to other bacteria, and often confer resistance to other classes of antimicrobial drugs.[428,429] The plasmid-mediated spread of these resistant genes was the cause of the global decrease in *Salmonella* Typhi susceptibility.[430]

Other mechanisms of resistance occur by decreasing membrane permeability, which prevents uptake of chloramphenicol. Some gram-negative bacteria prevent drug penetration by a change in their outer membrane proteins.[431] This was demonstrated to be plasmid mediated in *P. aeruginosa* and chromosomally mediated in *H. influenzae*.[432,433]

Transmembrane efflux pumps have also been shown to confer resistance to both gram-positive and gram-negative organisms.[434,435] Lastly, alteration of a 50S ribosomal subunit was found to reduce chloramphenicol binding in *Bacillus subtilis*.[436]

Adverse Reactions

Hematologic Toxicity

Bone Marrow Suppression

The most significant toxic effect of chloramphenicol is its effect on the bone marrow. There are two types of adverse effects. The first is the more common reversible bone marrow suppression that is a direct pharmacologic effect of the antibiotic and results from inhibition of mitochondrial synthesis. It has been postulated that chloramphenicol does this by binding to the 70S ribosomes in mammalian mitochondria, and by suppressing the activity of ferrochelatase. Ferrochelatase is an enzyme that normally catalyzes hemoglobin synthesis in the mitochondria of bone marrow erythroid cells.[349] As a result, any combination of reticulocytopenia, anemia, leukopenia, or thrombocytopenia may occur. Serum iron levels may also increase in association with a reduced uptake of radioactive iron by the red blood cells, indicating diminished hemoglobin synthesis. Within the bone marrow, there is vacuolization of the erythroid and myeloid precursors. These findings are common, are dose related, and occur during therapy.[437] They are more likely to occur in patients receiving at least 4 g/day or in patients with serum levels over 25 mg/L. The effect is reversible once chloramphenicol is discontinued.[438]

Hemolytic anemia has also been described in patients with glucose-6-phosphate dehydrogenase deficiency who have been treated with chloramphenicol.[439]

Aplastic Anemia

The other hematologic toxicity is the rare, but often fatal, aplastic anemia. This is the reason why chloramphenicol use has been widely replaced by other antibiotics. In an epidemiologic US study, aplastic anemia was estimated to occur in 1 in 24,500 to 1 in 40,800 courses of treatment. It was felt that fatal aplastic anemia appeared to be 13 times more frequent after the use of chloramphenicol than in the general population. It was also not related to dosage.[440] Most cases occur after the completion of therapy, and only about 20% occur during active treatment.[362] Mortality from aplastic anemia has been estimated to be higher than 50%.[441]

The mechanism appears to be different from the previously described dose-related bone marrow suppression and is not completely understood. It is believed to occur as a result of the metabolism of chloramphenicol to toxic nitro derivatives, which subsequently damage hematopoietic stem cell DNA.[442–444] Thiamphenicol, which has not been reported to cause aplastic anemia, does not have a p-NO_2 group. There also appears to be a possible host factor. Aplastic anemia has been reported in identical twins, suggesting a genetic predisposition.[445] A study involving mice demonstrated that mice given chloramphenicol after treatment with busulfan had a progressive decline in pluripotential stem cells as opposed to control mice. This suggests that aplastic anemia might occur in patients with unrecognized preexisting residual bone marrow damage, either genetic or acquired.[446]

It was previously thought that only the oral administration of chloramphenicol was associated with aplastic anemia.[447] This belief changed in the late 1970s after reports of aplastic anemia associated with parenteral administration started surfacing.[448–451] Whether or not chloramphenicol eyedrops cause aplastic anemia has been a topic of debate. In a British study, estimates of serious hematologic toxicity were reported to be 3 in 442,543.[452] Another study from Spain found that the risk of aplastic anemia could not be totally excluded but was less than 1 per million treatment courses.[453] In a review of 426 cases of aplastic anemia, no patient was found to have used chloramphenicol eyedrops.[454]

Chloramphenicol as a cause of childhood leukemia has also been a concern, but reports have been conflicting. A Chinese population-based case-control interview study of 309 childhood leukemia cases and 618 age- and sex-matched control subjects showed a significant dose-response relationship between chloramphenicol and the risk for acute leukemia.[455] However, another study from the same area failed to demonstrate a similar association.[456] Interesting to note, another study from the United States actually found that the odds ratio for total leukemia was decreased among patients who took chloramphenicol.[457]

Gray Baby Syndrome

The gray baby syndrome is a type of circulatory collapse that can occur in premature and newborn infants and is associated with excessively high serum levels of chloramphenicol.[458] It is characterized by an ashen-gray color, abdominal distention, vomiting, flaccidity, cyanosis, circulatory collapse, and death. It usually starts 2 to 9 days after treatment is started. The syndrome is a result of chloramphenicol impairing myocardial contractility by directly interfering with myocardial tissue respiration and oxidative phosphorylation.[459,460] It is believed to occur more often in neonates owing to their diminished ability to conjugate chloramphenicol and to excrete the active form in the urine. There have also been reports in small children and adults who have had accidental overdoses of the drug.[461] The syndrome is generally associated with serum levels of chloramphenicol greater than 50 mg/L and may occur with unexplained metabolic acidosis.[462] To accelerate drug removal, exchange transfusion and charcoal hemoperfusion have been used.[463,464]

Optic Neuritis and Neurologic Side Effects

Optic atrophy and blindness have been described in patients receiving prolonged chloramphenicol therapy.[465] Symptoms typically tend to be reversible, although permanent vision loss may occur. Fundal changes may not necessarily be seen. Supplementation with B vitamins has been used for treatment.[466] Other neurologic manifestations of chloramphenicol use include peripheral neuritis, headache, ophthalmoplegia, depression, and confusion.

Other Reactions

Gastrointestinal adverse reactions, including nausea, vomiting, diarrhea, glossitis, and stomatitis, may occur but are usually not a significant problem. Hypersensitivity reactions, including rashes, drug fever, and anaphylaxis, are rare. Jarisch-Herxheimer reactions have been observed during therapy for syphilis, brucellosis, and typhoid fever.[344] With prolonged oral administration, chloramphenicol may induce bleeding. This may be a result of either bone marrow suppression or reduction in intestinal flora with consequential inhibition of vitamin K synthesis.[467] Chloramphenicol has also been associated with acute porphyria attacks and should be avoided in patients with porphyria.[468] If given during active immunization, chloramphenicol may interfere with the development of immunity.[469]

Drug Interactions

Significant interactions between chloramphenicol and other drugs are listed in Table 26.5. Particular attention needs to be paid to monitoring serum drug levels of chloramphenicol when other agents metabolized by the liver are used concurrently. Chloramphenicol inhibits the activity of several liver enzymes, including CYP2C9 and CYP3A4. Chloramphenicol may prolong the half-life of tolbutamide, chlorpropamide, phenytoin, cyclophosphamide, and warfarin.[470] Concurrent administration of phenytoin and chloramphenicol may result in potentially toxic serum chloramphenicol levels.[471] Rifampin and phenobarbital have been observed to increase the total body clearance of chloramphenicol, thus decreasing the serum concentration. This is felt

TABLE 26.5 Important Drug-Drug Interactions With Chloramphenicol

OBJECT DRUG	EFFECT
Cimetidine	Possible additive or synergistic bone marrow–suppressant effects with concomitant administration Two case reports of fatal aplastic anemia
Cyanocobalamin	Can diminish the therapeutic effect of cyanocobalamin The expected response for the treatment of anemia may be opposed
Cyclophosphamide	Reduced effectiveness of cyclophosphamide due to decreased metabolism to active cyclophosphamide metabolite by chloramphenicol
Cyclosporine	Increased concentration of cyclosporine due to inhibition of metabolism by chloramphenicol Increased risk of renal dysfunction, cholestasis, paresthesias
Phenobarbital	Reduced serum concentration of chloramphenicol by 30%–40% Increased serum concentration of phenobarbital by up to 50%
Phenytoin (and fosphenytoin)	Can increase or decrease chloramphenicol serum concentration Chloramphenicol can inhibit the metabolism of phenytoin, resulting in increased serum concentration of phenytoin
Rifampin, rifabutin	Decreased serum concentrations of chloramphenicol due to induction of chloramphenicol metabolism
Sulfonylureas	May decrease the metabolism of sulfonylureas
Tacrolimus	Increased blood concentrations of tacrolimus due to decreased metabolism of chloramphenicol
Typhoid vaccine	May diminish the therapeutic effect of the live-attenuated Ty21a strain of typhoid vaccine

to occur by the induction of hepatic microsomal enzymes, and serum concentrations should be monitored when these drugs are administered concurrently.[472]

Chloramphenicol, which is primarily a bacteriostatic agent, may antagonize the bactericidal activity of certain penicillins, cephalosporins, fluoroquinolones, and aminoglycosides in vitro.[473–475] The clinical significance may be minimal in most instances. However, caution should be implemented in the event of such combinations for infections requiring bactericidal activity for efficacy, such as meningitis. Chloramphenicol may also delay the response of various anemias to supplementation with iron, folic acid, and vitamin B_{12}.[470]

ACKNOWLEDGMENT

The authors wish to thank Drs. Mirella Salvatore and Burt Meyers for the use of a figure and several tables from a previous edition of this chapter.

Key References

The complete reference list is available online at Expert Consult.

2. Eisen D. Tetracycline. In: Grayson ML, ed. *Kucers' the Use of Antibiotics*. 6th ed. Boca Raton, FL: CRC Press; 2010:843–850.
3. Sabundayo BP, Standiford HC. Tetracyclines and analogues. In: Yu VL, Edwards G, McKinnon PS, et al, eds. *Antimicrobial Therapy and Vaccines*. Vol. II: Antimicrobial Agents. 2nd ed. Pittsburgh: ESun Technologies LLC; 2005:461–476.
6. Thaker M, Spanogiannopoulos P, Wright GD. The tetracycline resistome. *Cell Mol Life Sci*. 2010;67:419–431.
8. Chopra I, Roberts M. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. *Microbiol Mol Biol Rev*. 2001;65:232–260.
10. Eisen D. Doxycycline. In: Grayson ML, ed. *Kucers' the Use of Antibiotics*. 6th ed. Boca Raton, FL: CRC Press; 2010:851–869.
13. Kunin CM. A guide to use of antibiotics in patients with renal disease. A table of recommended doses and factors governing serum levels. *Ann Intern Med*. 1967;67:151–158.
14. Heaney D, Eknoyan G. Minocycline and doxycycline kinetics in chronic renal failure. *Clin Pharmacol Ther*. 1978;24:233–239.
16. Thiim M, Friedman LS. Hepatotoxicity of antibiotics and antifungals. *Clin Liver Dis*. 2003;7:381–399, vi–vii.
17. Horrevorts A, Pluim M. Minocycline. In: Grayson ML, ed. *Kucers' the Use of Antibiotics*. 6th ed. Boca Raton, FL: CRC Press; 2010:870–880.
18. Carney S, Butcher RA, Dawborn JK, et al. Minocycline excretion and distribution in relation to renal function in man. *Clin Exp Pharmacol Physiol*. 1974;1:299–308.
22. Jonas M, Cunha BA. Minocycline. *Ther Drug Monit*. 1982;4:137–145.
26. Welling PG, Koch PA, Lau CC, et al. Bioavailability of tetracycline and doxycycline in fasted and nonfasted subjects. *Antimicrob Agents Chemother*. 1977;11:462–469.
28. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. *J Antimicrob Chemother*. 2006;58:256–265.
30. Macdonald H, Kelly RG, Allen ES, et al. Pharmacokinetic studies on minocycline in man. *Clin Pharmacol Ther*. 1973;14:852–861.
33. Chow AW, Jewesson PJ. Pharmacokinetics and safety of antimicrobial agents during pregnancy. *Rev Infect Dis*. 1985;7:287–313.
44. Yim CW, Flynn NM, Fitzgerald FT. Penetration of oral doxycycline into the cerebrospinal fluid of patients with latent or neurosyphilis. *Antimicrob Agents Chemother*. 1985;28:347–348.
53. Diekema DJ, Pfaller MA, Schmitz FJ, et al. Survey of infections due to *Staphylococcus* species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the western pacific region for the SENTRY antimicrobial surveillance program, 1997–1999. *Clin Infect Dis*. 2001;32(suppl 2):114–132.
57. Jones RN, Sader HS, Fritsche TR. Doxycycline use for community-acquired pneumonia: contemporary in vitro spectrum of activity against *Streptococcus pneumoniae* (1999-2002). *Diagn Microbiol Infect Dis*. 2004;49:147–149.
84. Roblin PM, Hammerschlag MR. In vitro activity of GAR-936 against *Chlamydia pneumoniae* and *Chlamydia trachomatis*. *Int J Antimicrob Agents*. 2000;16:61–63.
91. Raoult D, Roussellier P, Vestris G, et al. In vitro antibiotic susceptibility of *Rickettsia rickettsii* and *Rickettsia conorii*: plaque assay and microplaque colorimetric assay. *J Infect Dis*. 1987;155:1059–1062.
96. Wallace RJ, Brown-Elliott BA, Crist CJ, et al. Comparison of the in vitro activity of the glycylcycline tigecycline (formerly GAR-936) with those of tetracycline, minocycline, and doxycycline against isolates of nontuberculous mycobacteria. *Antimicrob Agents Chemother*. 2002;46:3164–3167.
101. Brown BA, Wallace RJ Jr, Onyi G. Activities of the glycylcyclines N,N-dimethylglycylamido-minocycline and N,N-dimethylglycylamido-6-demethyl-6-deoxytetracycline against *Nocardia* spp. and tetracycline-resistant isolates of rapidly growing mycobacteria. *Antimicrob Agents Chemother*. 1996;40:874–878.
102. Cercenado E, Marin M, Sanchez-Martinez M, et al. In vitro activities of tigecycline and eight other antimicrobials against different *Nocardia* species identified by molecular methods. *Antimicrob Agents Chemother*. 2007;51:1102–1104.
106. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27–S72.
123. Doernberg SB, Winston LG, Deck DH, et al. Does doxycycline protect against development of *Clostridium difficile* infection? *Clin Infect Dis*. 2012;55:615–620.
125. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(RR–03):1–137.
193. Roberts MC. Tetracycline therapy: update. *Clin Infect Dis*. 2003;36:462–467.
205. Smith K, Leyden JJ. Safety of doxycycline and minocycline: a systematic review. *Clin Ther*. 2005;27:1329–1342.
206. Lebrun-Vignes B, Kreft-Jais C, Castot A, et al. Comparative analysis of adverse drug reactions to tetracyclines: results of a French national survey and review of the literature. *Br J Dermatol*. 2012;166:1333–1341.
209. Fanning WL, Gump DW, Sofferman RA. Side effects of minocycline: a double-blind study. *Antimicrob Agents Chemother*. 1977;11:712–717.
241. Ellis-Grosse EJ, Babinchak T, Dartois N, et al. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. *Clin Infect Dis*. 2005;41(suppl 5):S341–S353.
242. Babinchak T, Ellis-Grosse E, Dartois N, et al. The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: analysis of pooled clinical trial data. *Clin Infect Dis*. 2005;41(suppl 5):S354–S367.
243. Tanaseanu C, Bergallo C, Teglia O, et al. Integrated results of 2 phase 3 studies comparing tigecycline and levofloxacin in community-acquired pneumonia. *Diagn Microbiol Infect Dis*. 2008;61:329–338.
244. Dartois N, Castaing N, Gandjini H, et al. Tigecycline versus levofloxacin for the treatment of community-acquired pneumonia: European experience. *J Chemother*. 2008;20(suppl 1):28–35.
247. McGovern PC, Wible M, El-Tahtawy A, et al. All-cause mortality imbalance in the tigecycline phase 3 and 4 clinical trials. *Int J Antimicrob Agents*. 2013;41:463–467.
249. Bauer G, Berens C, Projan SJ, et al. Comparison of tetracycline and tigecycline binding to ribosomes mapped

by dimethylsulphate and drug-directed fe2+ cleavage of 16s rRNA. *J Antimicrob Chemother*. 2004;53:592–599.
253. Wyeth. Tygacil (tigecycline) package insert. In: *Wyeth Pharmaceuticals I, ed*. Philadelphia: 2011.
256. Muralidharan G, Fruncillo RJ, Micalizzi M, et al. Effects of age and sex on single-dose pharmacokinetics of tigecycline in healthy subjects. *Antimicrob Agents Chemother*. 2005;49:1656–1659.
257. Muralidharan G, Micalizzi M, Speth J, et al. Pharmacokinetics of tigecycline after single and multiple doses in healthy subjects. *Antimicrob Agents Chemother*. 2005;49:220–229.
274. Fritsche TR, Sader HS, Stilwell MG, et al. Potency and spectrum of tigecycline tested against an international collection of bacterial pathogens associated with skin and soft tissue infections (2000-2004). *Diagn Microbiol Infect Dis*. 2005;52:195–201.
281. Nabuurs-Franssen M, Mouton JW. Tigecycline. In: Grayson ML, ed. *Kucers' the Use of Antibiotics*. 6th ed. Boca Raton, FL: CRC Press; 2010:881–892.
284. Zhanel GG, Karlowsky JA, Rubinstein E, et al. Tigecycline: a novel glycylcycline antibiotic. *Expert Rev Anti Infect Ther*. 2006;4:9–25.
302. Lauf L, Ozsvar Z, Mitha I, et al. Phase 3 study comparing tigecycline and ertapenem in patients with diabetic foot infections with and without osteomyelitis. *Diagn Microbiol Infect Dis*. 2014;78:469–480.
341a. US Food and Drug Administration. Xerava: highlights of prescribing information; revised 8/2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211109lbl.pdf. Accessed November 3, 2018.
341b. US Food and Drug Administration. FDA briefing document: omadacycline injection and oral tablets; August 8, 2018. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM615848.pdf. Accessed November 3, 2018.
341c. US Food and Drug Administration. Antimicrobial resistance information from FDA; page last updated 11/5/18. https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm620149.htm. Accessed November 9, 2018.
344. MacLaren G, Shann F. Chloramphenicol and thiamphenicol. In: Grayson ML, ed. *Kucers' the Use of Antibiotics*. 6th ed. Boca Raton, FL: CRC Press; 2010:1008–1029.
349. Manyan DR, Arimura GK, Yunis AA. Chloramphenicol-induced erythroid suppression and bone marrow ferrochelatase activity in dogs. *J Lab Clin Med*. 1972;79:137–144.
353. Smith AL, Weber A. Pharmacology of chloramphenicol. *Pediatr Clin North Am*. 1983;30:209–236.
356. Koup JR, Lau AH, Brodsky B, et al. Chloramphenicol pharmacokinetics in hospitalized patients. *Antimicrob Agents Chemother*. 1979;15:651–657.
365. Neuhauser M, Pendland S. Chloramphenicol. In: Yu VL, Edwards G, McKinnon PS, et al, eds. *Antimicrobial Therapy and Vaccines*. Vol. II: Antimicrobial Agents. 2nd ed. Pittsburgh: ESun Technologies LLC; 2005:121–129.
440. Wallerstein RO, Condit PK, Kasper CK, et al. Statewide study of chloramphenicol therapy and fatal aplastic anemia. *JAMA*. 1969;208:2045–2050.
454. Wiholm BE, Kelly JP, Kaufman D, et al. Relation of aplastic anaemia to use of chloramphenicol eye drops in two international case-control studies. *BMJ*. 1998;316:666.

References

1. Duggar BM. Aureomycin: a product of the continuing search for new antibiotics. *Ann N Y Acad Sci*. 1948;51:177–181.
2. Eisen D. Tetracycline. In: Grayson ML, ed. *Kucers' the Use of Antibiotics*. 6th ed. Boca Raton, FL: CRC Press; 2010:843–850.
3. Sabundayo BP, Standiford HC. Tetracyclines and analogues. In: Yu VL, Edwards G, McKinnon PS, et al, eds. *Antimicrobial Therapy and Vaccines*. Vol. II: Antimicrobial Agents. 2nd ed. Pittsburgh: ESun Technologies LLC; 2005:461–476.
4. Levy SB, FitzGerald GB, Macone AB. Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm. *N Engl J Med*. 1976;295:583–588.
5. DuPont H, Steele JH. Use of antimicrobial agents in animal feeds: implications for human health. *Rev Infect Dis*. 1987;9:447–460.
6. Thaker M, Spanogiannopoulos P, Wright GD. The tetracycline resistome. *Cell Mol Life Sci*. 2010;67:419–431.
7. Perks WH, Walters EH, Tams IP, et al. Demeclocycline in the treatment of the syndrome of inappropriate secretion of antidiuretic hormone. *Thorax*. 1979;34:324–327.
8. Chopra I, Roberts M. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. *Microbiol Mol Biol Rev*. 2001;65:232–260.
9. Chopra I, Hacker K. Inhibition of K88-mediated adhesion of *Escherichia coli* to mammalian receptors by antibiotics that affect bacterial protein synthesis. *J Antimicrob Chemother*. 1986;18:441–451.
10. Eisen D. Doxycycline. In: Grayson ML, ed. *Kucers' the Use of Antibiotics*. 6th ed. Boca Raton, FL: CRC Press; 2010:851–869.
11. Dahl EL, Shock JL, Shenai BR, et al. Tetracyclines specifically target the apicoplast of the malaria parasite *Plasmodium falciparum*. *Antimicrob Agents Chemother*. 2006;50:3124–3131.
12. Ribush N, Morgan T. Tetracyclines and renal failure. *Med J Aust*. 1972;1:53–55.
13. Kunin CM. A guide to use of antibiotics in patients with renal disease. A table of recommended doses and factors governing serum levels. *Ann Intern Med*. 1967;67:151–158.
14. Heaney D, Eknoyan G. Minocycline and doxycycline kinetics in chronic renal failure. *Clin Pharmacol Ther*. 1978;24:233–239.
15. Whelton A, Schach von Wittenau M, Twomey TM, et al. Doxycycline pharmacokinetics in the absence of renal function. *Kidney Int*. 1974;5:365–371.
16. Thiim M, Friedman LS. Hepatotoxicity of antibiotics and antifungals. *Clin Liver Dis*. 2003;7:381–399, vi–vii.
17. Horrevorts A, Pluim M. Minocycline. In: Grayson ML, ed. *Kucers' the Use of Antibiotics*. 6th ed. Boca Raton, FL: CRC Press; 2010:870–880.
18. Carney S, Butcher RA, Dawborn JK, et al. Minocycline excretion and distribution in relation to renal function in man. *Clin Exp Pharmacol Physiol*. 1974;1:299–308.
19. Welling PG, Shaw WR, Uman SJ, et al. Pharmacokinetics of minocycline in renal failure. *Antimicrob Agents Chemother*. 1975;8:532–537.
20. Bernard B, Yin EJ, Simon HJ. Clinical pharmacologic studies with minocycline. *J Clin Pharmacol New Drugs*. 1971;11:332–348.
21. George CR, Guinness MD, Lark DJ, et al. Minocycline toxicity in renal failure. *Med J Aust*. 1973;1:640–641.
22. Jonas M, Cunha BA. Minocycline. *Ther Drug Monit*. 1982;4:137–145.
23. Wood MJ, Farrell W, Kattan S, et al. Activity of minocycline and tetracycline against respiratory pathogens related to blood levels. *J Antimicrob Chemother*. 1975;1:323–331.
24. Sklenar I, Spring P, Dettli L. One-dose and multiple-dose kinetics of minocycline in patients with renal disease. *Agents Actions*. 1977;7:369–377.
25. Smith C, Woods CG, Woods MJ. Absorption of minocycline. *J Antimicrob Chemother*. 1984;13:93.
26. Welling PG, Koch PA, Lau CC, et al. Bioavailability of tetracycline and doxycycline in fasted and nonfasted subjects. *Antimicrob Agents Chemother*. 1977;11:462–469.
27. Neuvonen PJ. Interactions with the absorption of tetracyclines. *Drugs*. 1976;11:45–54.
28. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. *J Antimicrob Chemother*. 2006;58:256–265.
29. Fabre J, Milek E, Kalfopoulos P, et al. [Kinetics of tetracyclines in human. II. Excretion, penetration into normal and inflammed tissues, behavior in a case of renal insufficiency and in hemodialysis]. *Schweiz Med Wochenschr*. 1971;101:625–633.
30. Macdonald H, Kelly RG, Allen ES, et al. Pharmacokinetic studies on minocycline in man. *Clin Pharmacol Ther*. 1973;14:852–861.
31. Lundberg C, Malmborg AS. Concentration of penicillin V and tetracycline in maxillary sinus secretion after repeated doses. *Scand J Infect Dis*. 1973;5:123–133.
32. Ruhen RW, Tandon MK. Comparative effectiveness of tetracycline, minocycline and doxycycline in treatment of acute-on-chronic bronchitis. A study based on sputum levels. *Med J Aust*. 1976;1:151–153.
33. Chow AW, Jewesson PJ. Pharmacokinetics and safety of antimicrobial agents during pregnancy. *Rev Infect Dis*. 1985;7:287–313.
34. Alestig K. Studies on doxycycline during intravenous and oral treatment with reference to renal function. *Scand J Infect Dis*. 1973;5:193–198.
35. Andersson KE, Mardh PA, Akerlund M. Passage of doxycycline into extracellular fluid. *Scand J Infect Dis Suppl*. 1976;9:7–11.
36. Eliasson R, Malmborg AS. Concentrations of doxycycline in human seminal plasma. *Scand J Infect Dis Suppl*. 1976;9:32–36.
37. Lode H. Penetration of antibiotics into the pleural fluid. *J Antimicrob Chemother*. 1979;5:122–124.
38. Schreiner A, Digranes A. Pharmacokinetics of lymecycline and doxycycline in serum and suction blister fluid. *Chemotherapy*. 1985;31:261–265.
39. Marlin GE, Cheng S, Thompson PJ. Sputum and plasma doxycycline concentrations after a single oral 600 mg doxycycline dose in patients with chronic bronchitis. *Eur J Respir Dis*. 1981;62:276–280.
40. Dornbusch K. The detection of doxycycline activity in human bone. *Scand J Infect Dis Suppl*. 1976;9:47–53.
41. Gnarpe H, Dornbusch K, Hagg O. Doxycycline concentration levels in bone, soft tissue and serum after intravenous infusion of doxycycline. A clinical study. *Scand J Infect Dis Suppl*. 1976;9:54–57.
42. Bystedt H, DAhlbäck A, Dornbusch K, et al. Concentrations of azidocillin, erythromycin, doxycycline and clindamycin in human mandibular bone. *Int J Oral Surg*. 1978;7:442–449.
43. Dotevall L, Hagberg L. Penetration of doxycycline into cerebrospinal fluid in patients treated for suspected Lyme neuroborreliosis. *Antimicrob Agents Chemother*. 1989;33:1078–1080.
44. Yim CW, Flynn NM, Fitzgerald FT. Penetration of oral doxycycline into the cerebrospinal fluid of patients with latent or neurosyphilis. *Antimicrob Agents Chemother*. 1985;28:347–348.
45. Nikaido H, Thanassi DG. Penetration of lipophilic agents with multiple protonation sites into bacterial cells: tetracyclines and fluoroquinolones as examples. *Antimicrob Agents Chemother*. 1993;37:1393–1399.
46. Bergogne-Berezin E, Lambert-Zechovsky N, Morel C. [Pharmacokinetics of antibiotics in bronchial secretions. 250 cases]. *Nouv Presse Med*. 1977;6:3548.
47. Hensle TW, Prout GR Jr, Griffin P. Minocycline diffusion into benign prostatic hyperplasia. *J Urol*. 1977;118:609–611.
48. Hoeprich PD, Warshauer DM. Entry of four tetracyclines into saliva and tears. *Antimicrob Agents Chemother*. 1974;5:330–336.
49. Steigbigel NH, Reed CW, Finland M. Absorption and excretion of five tetracycline analogues in normal young men. *Am J Med Sci*. 1968;255:296–312.
50. Mahon WA, Johnson GE, Endrenyl L, et al. The elimination of tritiated doxycycline in normal subjects and in patients with severely impaired renal function. *Scand J Infect Dis Suppl*. 1976;9:24–31.
51. Saivin S, Houin G. Clinical pharmacokinetics of doxycycline and minocycline. *Clin Pharmacokinet*. 1988;15:355–366.
52. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement*. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.
53. Diekema DJ, Pfaller MA, Schmitz FJ, et al. Survey of infections due to *Staphylococcus* species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the western pacific region for the SENTRY antimicrobial surveillance program, 1997–1999. *Clin Infect Dis*. 2001;32(suppl 2):114–132.
54. Holmes RL, Jorgensen JH. Inhibitory activities of 11 antimicrobial agents and bactericidal activities of vancomycin and daptomycin against invasive methicillin-resistant *Staphylococcus aureus* isolates obtained from 1999 through 2006. *Antimicrob Agents Chemother*. 2008;52:757–760.
55. Zhanel GG, Palatnick L, Nichol KA, et al. Antimicrobial resistance in respiratory tract *Streptococcus pneumoniae* isolates: results of the Canadian respiratory organism susceptibility study, 1997 to 2002. *Antimicrob Agents Chemother*. 2003;47:1867–1874.
56. Koeth LM, Felmingham D, Jacobs MR, et al. Antimicrobial resistance of *Streptococcus pneumoniae* and *Haemophilus influenzae* in sao paulo, Brazil from 1996 to 2000. *Int J Antimicrob Agents*. 2004;23:356–361.
57. Jones RN, Sader HS, Fritsche TR. Doxycycline use for community-acquired pneumonia: contemporary in vitro spectrum of activity against *Streptococcus pneumoniae* (1999-2002). *Diagn Microbiol Infect Dis*. 2004;49:147–149.
58. Wimmerstedt A, Kahlmeter G. Associated antimicrobial resistance in *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumoniae* and *Streptococcus pyogenes*. *Clin Microbiol Infect*. 2008;14:315–321.
59. Persson E, Berg S, Bergseng H, et al. Antimicrobial susceptibility of invasive group B streptococcal isolates from south-west Sweden 1988-2001. *Scand J Infect Dis*. 2008;40:308–313.
60. Low DE, Keller N, Barth A, et al. Clinical prevalence, antimicrobial susceptibility, and geographic resistance patterns of enterococci: results from the SENTRY antimicrobial surveillance program, 1997-1999. *Clin Infect Dis*. 2001;32(suppl 2):S133–S145.
61. Holmberg K, Nord CE, Dornbusch K. Antimicrobial in vitro susceptibility of *Actinomyces israelii* and *Arachnia propionica*. *Scand J Infect Dis*. 1977;9:40–45.
62. Vitas AI, Sanchez RM, Aguado V, et al. Antimicrobial susceptibility of *Listeria monocytogenes* isolated from food and clinical cases in navarra, Spain. *J Food Prot*. 2007;70:2402–2406.
63. Mohammed MJ, Marston CK, Popovic T, et al. Antimicrobial susceptibility testing of *Bacillus anthracis*: comparison of results obtained by using the national committee for clinical laboratory standards broth microdilution reference and etest agar gradient diffusion methods. *J Clin Microbiol*. 2002;40:1902–1907.
64. Frean J, Klugman KP, Arntzen L, et al. Susceptibility of *Bacillus anthracis* to eleven antimicrobial agents including novel fluoroquinolones and a ketolide. *J Antimicrob Chemother*. 2003;52:297–299.
65. Hernandez E, Girardet M, Ramisse F, et al. Antibiotic susceptibilities of 94 isolates of *Yersinia pestis* to 24 antimicrobial agents. *J Antimicrob Chemother*. 2003;52:1029–1031.
66. Smith MD, Vinh DX, Nguyen TT, et al. In vitro antimicrobial susceptibilities of strains of *Yersinia pestis*. *Antimicrob Agents Chemother*. 1995;39:2153–2154.
67. Schonberg-Norio D, Hanninen ML, Katila ML, et al. Activities of telithromycin, erythromycin, fluoroquinolones, and doxycycline against *Campylobacter* strains isolated from finnish subjects. *Antimicrob Agents Chemother*. 2006;50:1086–1088.
68. Morris JG Jr, Black RE. Cholera and other vibrioses in the United States. *N Engl J Med*. 1985;312:343–350.
69. Ottaviani D, Bacchiocchi I, Masini L, et al. Antimicrobial susceptibility of potentially pathogenic halophilic vibrios isolated from seafood. *Int J Antimicrob Agents*. 2001;18:135–140.
70. Midani S, Rathore MH. Vibrio species infection of a catfish spine puncture wound. *Pediatr Infect Dis J*. 1994;13:333–334.
71. Fernandez-Cuenca F, Tomas-Carmona M, Caballero-Moyano F, et al. In vitro activity of 18 antimicrobial agents against clinical isolates of *Acinetobacter* spp.: multicenter national study GEIH-REIPI-ab. *Enferm Infecc Microbiol Clin*. 2010;2012.
72. Jenney AW, Lum G, Fisher DA, et al. Antibiotic susceptibility of *Burkholderia pseudomallei* from tropical northern Australia and implications for therapy of melioidosis. *Int J Antimicrob Agents*. 2001;17:109–113.
73. Nicodemo AC, Araujo MR, Ruiz AS, et al. In vitro susceptibility of *Stenotrophomonas maltophilia* isolates: comparison of disc diffusion, Etest and agar dilution methods. *J Antimicrob Chemother*. 2004;53:604–608.
74. Janda JM, Guthertz LS, Kokka RP, et al. *Aeromonas* species in septicemia: laboratory characteristics and clinical observations. *Clin Infect Dis*. 1994;19:77–83.
75. Flamm RK, Castanheira M, Streit JM, et al. Minocycline activity tested against *Acinetobacter baumannii* complex, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* species complex isolates from a global surveillance program (2013). *Diagn Microbiol Infect Dis*. 2016;85:352–355.
76. Schaumann R, Ackermann G, Pless B, et al. In vitro activities of fourteen antimicrobial agents against obligately anaerobic bacteria. *Int J Antimicrob Agents*. 2000;16:225–232.
77. Baykam N, Esener H, Ergonul O, et al. In vitro antimicrobial susceptibility of *Brucella* species. *Int J Antimicrob Agents*. 2004;23:405–407.
78. Dorbecker C, Sander A, Oberle K, et al. In vitro susceptibility of *Bartonella* species to 17 antimicrobial compounds: comparison of etest and agar dilution. *J Antimicrob Chemother*. 2006;58:784–788.

79. Bebear C, Pereyre S, Peuchant O. *Mycoplasma pneumoniae*: susceptibility and resistance to antibiotics. *Future Microbiol*. 2011;6:423–431.
80. Bebear CM, Renaudin H, Bryskier A, et al. Comparative activities of telithromycin (HMR 3647), levofloxacin, and other antimicrobial agents against human mycoplasmas. *Antimicrob Agents Chemother*. 2000;44:1980–1982.
81. Bebear CM, Renaudin H, Charron A, et al. In vitro activity of trovafloxacin compared to those of five antimicrobials against mycoplasmas including *Mycoplasma hominis* and *Ureaplasma urealyticum* fluoroquinolone-resistant isolates that have been genetically characterized. *Antimicrob Agents Chemother*. 2000;44:2557–2560.
82. Schulin T, Wennersten CB, Ferraro MJ, et al. Susceptibilities of *Legionella* spp. to newer antimicrobials in vitro. *Antimicrob Agents Chemother*. 1998;42:1520–1523.
83. Critchley IA, Jones ME, Heinze PD, et al. In vitro activity of levofloxacin against contemporary clinical isolates of *Legionella pneumophila, Mycoplasma pneumoniae* and *Chlamydia pneumoniae* from north America and Europe. *Clin Microbiol Infect*. 2002;8:214–221.
84. Roblin PM, Hammerschlag MR. In vitro activity of GAR-936 against *Chlamydia pneumoniae* and *Chlamydia trachomatis*. *Int J Antimicrob Agents*. 2000;16:61–63.
85. Butaye P, Ducatelle R, De Backer P, et al. In vitro activities of doxycycline and enrofloxacin against European *Chlamydia psittaci* strains from turkeys. *Antimicrob Agents Chemother*. 1997;41:2800–2801.
86. Samra Z, Rosenberg S, Soffer Y, et al. In vitro susceptibility of recent clinical isolates of *Chlamydia trachomatis* to macrolides and tetracyclines. *Diagn Microbiol Infect Dis*. 2001;39:177–179.
87. Wormser GP, Nadelman RB, Dattwyler RJ, et al. Practice guidelines for the treatment of Lyme disease. The infectious diseases society of America. *Clin Infect Dis*. 2000;31(suppl 1):1–14.
88. Ates L, Hanssen-Hubner C, Norris DE, et al. Comparison of in vitro activities of tigecycline, doxycycline, and tetracycline against the spirochete *Borrelia burgdorferi*. *Ticks Tick Borne Dis*. 2010;1:30–34.
89. Murray CK, Ellis MW, Hospenthal DR. Susceptibility of *Leptospira* serovars to antimalarial agents. *Am J Trop Med Hyg*. 2004;71:685–686.
90. Norris SJ, Edmondson DG. In vitro culture system to determine MICs and MBCs of antimicrobial agents against *Treponema pallidum* subsp. *pallidum* (nichols strain). *Antimicrob Agents Chemother*. 1988;32:68–74.
91. Raoult D, Roussellier P, Vestris G, et al. In vitro antibiotic susceptibility of *Rickettsia rickettsii* and *Rickettsia conorii*: plaque assay and microplaque colorimetric assay. *J Infect Dis*. 1987;155:1059–1062.
92. Raoult D, Drancourt M. Antimicrobial therapy of rickettsial diseases. *Antimicrob Agents Chemother*. 1991;35:2457–2462.
93. Branger S, Rolain JM, Raoult D. Evaluation of antibiotic susceptibilities of *Ehrlichia canis, Ehrlichia chaffeensis,* and *Anaplasma phagocytophilum* by real-time PCR. *Antimicrob Agents Chemother*. 2004;48:4822–4828.
94. Brown-Elliott BA, Wallace RJ Jr. Clinical and taxonomic status of pathogenic nonpigmented or late-pigmenting rapidly growing mycobacteria. *Clin Microbiol Rev*. 2002;15:716–746.
95. Uslan DZ, Kowalski TJ, Wengenack NL, et al. Skin and soft tissue infections due to rapidly growing mycobacteria: comparison of clinical features, treatment, and susceptibility. *Arch Dermatol*. 2006;142:1287–1292.
96. Wallace RJ, Brown-Elliott BA, Crist CJ, et al. Comparison of the in vitro activity of the glycylcycline tigecycline (formerly GAR-936) with those of tetracycline, minocycline, and doxycycline against isolates of nontuberculous mycobacteria. *Antimicrob Agents Chemother*. 2002;46:3164–3167.
97. Rhomberg PR, Jones RN. In vitro activity of 11 antimicrobial agents, including gatifloxacin and GAR936, tested against clinical isolates of *Mycobacterium marinum*. *Diagn Microbiol Infect Dis*. 2002;42:145–147.
98. da Silva Telles MA, Chimara E, Ferrazoli L, et al. *Mycobacterium kansasii*: antibiotic susceptibility and PCR-restriction analysis of clinical isolates. *J Med Microbiol*. 2005;54(Pt 10):975–979.
99. Balabanova Y, Ruddy M, Hubb J, et al. Multidrug-resistant tuberculosis in Russia: clinical characteristics, analysis of second-line drug resistance and development of standardized therapy. *Eur J Clin Microbiol Infect Dis*. 2005;24:136–139.
100. Walker NF, Clark SO, Oni T, et al. Doxycycline and HIV infection suppress tuberculosis-induced matrix metalloproteinases. *Am J Respir Crit Care Med*. 2012;185:989–997.
101. Brown BA, Wallace RJ Jr, Onyi G. Activities of the glycylcyclines N,N-dimethylglycylamido-minocycline and N,N-dimethylglycylamido-6-demethyl-6-deoxytetracycline against *Nocardia* spp. and tetracycline-resistant isolates of rapidly growing mycobacteria. *Antimicrob Agents Chemother*. 1996;40:874–878.
102. Cercenado E, Marin M, Sanchez-Martinez M, et al. In vitro activities of tigecycline and eight other antimicrobials against different *Nocardia* species identified by molecular methods. *Antimicrob Agents Chemother*. 2007;51:1102–1104.
103. Chang HR, Comte R, Pechere JC. In vitro and in vivo effects of doxycycline on *Toxoplasma gondii*. *Antimicrob Agents Chemother*. 1990;34:775–780.
104. Edlind TD. Tetracyclines as antiparasitic agents: lipophilic derivatives are highly active against *Giardia lamblia* in vitro. *Antimicrob Agents Chemother*. 1989;33:2144–2145.
105. Chopra I, Hawkey PM, Hinton M. Tetracyclines, molecular and clinical aspects. *J Antimicrob Chemother*. 1992;29:245–277.
106. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27–S72.
107. Klein NC, Cunha BA. Treatment of legionnaires' disease. *Semin Respir Infect*. 1998;13:140–146.
108. Cunha BA. The atypical pneumonias: clinical diagnosis and importance. *Clin Microbiol Infect*. 2006;12(suppl 3):12–24.
109. Shames JM, George RB, Holliday WB, et al. Comparison of antibiotics in the treatment of mycoplasmal pneumonia. *Arch Intern Med*. 1970;125:680–684.
110. Jawetz E. Chemotherapy of chlamydial infections. *Adv Pharmacol Chemother*. 1969;7:253–282.
111. Yung AP, Grayson ML. Psittacosis–a review of 135 cases. *Med J Aust*. 1988;148:228–233.
112. Khatib R, Thirumoorthi MC, Kelly B, et al. Severe psittacosis during pregnancy and suppression of antibody response with early therapy. *Scand J Infect Dis*. 1995;27:519–521.
113. Lindenbaum J, Greenough WB, Islam MR. Antibiotic therapy of cholera. *Bull World Health Organ*. 1967;36:871–883.
114. McCormack WM, Chowdhury AM, Jahangir N, et al. Tetracycline prophylaxis in families of cholera patients. *Bull World Health Organ*. 1968;38:787–792.
115. Islam MR. Single dose tetracycline in cholera. *Gut*. 1987;28:1029–1032.
116. Rabbani GH, Islam MR, Butler T, et al. Single-dose treatment of cholera with furazolidone or tetracycline in a double-blind randomized trial. *Antimicrob Agents Chemother*. 1989;33:1447–1450.
117. De S, Chaudhuri A, Dutta P, et al. Doxycycline in the treatment of cholera. *Bull World Health Organ*. 1976;54:177–179.
118. Yamamoto T, Nair GB, Albert MJ, et al. Survey of in vitro susceptibilities of *Vibrio cholerae* O1 and O139 to antimicrobial agents. *Antimicrob Agents Chemother*. 1995;39:241–244.
119. Gisbert JP, Calvet X, Gomollon F, et al. Treatment for the eradication of *Helicobacter pylori*. Recommendations of the Spanish consensus conference]. *Med Clin (Barc)*. 2000;114:185–195.
120. Gene E, Calvet X, Azagra R, et al. Triple vs. quadruple therapy for treating *Helicobacter pylori* infection: a meta-analysis. *Aliment Pharmacol Ther*. 2003;17:1137–1143.
121. Cammarota G, Martino A, Pirozzi G, et al. High efficacy of 1-week doxycycline- and amoxicillin-based quadruple regimen in a culture-guided, third-line treatment approach for *Helicobacter pylori* infection. *Aliment Pharmacol Ther*. 2004;19:789–795.
122. Sack DA, Kaminsky DC, Sack RB, et al. Prophylactic doxycycline for travelers' diarrhea. Results of a prospective double-blind study of peace corps volunteers in Kenya. *N Engl J Med*. 1978;298:758–763.
123. Doernberg SB, Winston LG, Deck DH, et al. Does doxycycline protect against development of *Clostridium difficile* infection? *Clin Infect Dis*. 2012;55:615–620.
124. Baxter R, Ray GT, Fireman BH. Case-control study of antibiotic use and subsequent *Clostridium difficile*-associated diarrhea in hospitalized patients. *Infect Control Hosp Epidemiol*. 2008;29:44–50.
125. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(RR–03):1–137.
126. Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. *Sex Transm Dis*. 2002;29:497–502.
127. Geisler WM, Uniyal A, Lee JY, et al. Azithromycin versus doxycycline for urogenital *Chlamydia trachomatis* infection. *N Engl J Med*. 2015;373:2512–2521.
128. Bachmann LH, Stephens J, Richey CM, et al. Measured versus self-reported compliance with doxycycline therapy for chlamydia-associated syndromes: high therapeutic success rates despite poor compliance. *Sex Transm Dis*. 1999;26:272–278.
129. Taylor-Robinson D, Furr PM. Clinical antibiotic resistance of *Ureaplasma urealyticum*. *Pediatr Infect Dis*. 1986;5(6 suppl):S335–S337.
130. Wikstrom A, Jensen JS. *Mycoplasma genitalium*: a common cause of persistent urethritis among men treated with doxycycline. *Sex Transm Infect*. 2006;82:276–279.
131. Bjornelius E, Anagrius C, Bojs G, et al. Antibiotic treatment of symptomatic *Mycoplasma genitalium* infection in scandinavia: a controlled clinical trial. *Sex Transm Infect*. 2008;84:72–76.
132. Orellana MA, Gomez-Lus ML. Which is the best empirical treatment in patients with urethritis? *Rev Esp Quimioter*. 2011;24:136–142.
133. Newman LM, Moran JS, Workowski KA. Update on the management of gonorrhea in adults in the United States. *Clin Infect Dis*. 2007;44(suppl 3):S84–S101.
134. Bolan RK, Beymer MR, Weiss RE, et al. Doxycycline prophylaxis to reduce incident syphilis among HIV-infected men who have sex with men who continue to engage in high-risk sex: a randomized, controlled pilot study. *Sex Transm Dis*. 2015;42:98–103.
135. Greaves AB, Hilleman MR, Taggart SR, et al. Chemotherapy in bubonic lymphogranuloma venereum: a clinical and serological evaluation. *Bull World Health Organ*. 1957;16:277–289.
136. Ness RB, Soper DE, Holley RL, et al. Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the pelvic inflammatory disease evaluation and clinical health (PEACH) randomized trial. *Am J Obstet Gynecol*. 2002;186:929–937.
137. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the infectious diseases society of America. *Clin Infect Dis*. 2006;43:1089–1134.
138. Steere AC, Levin RE, Molloy PJ, et al. Treatment of lyme arthritis. *Arthritis Rheum*. 1994;37:878–888.
139. Berende A, ter Hofstede HJ, Vos FJ, et al. Randomized trial of longer-term therapy for symptoms attributed to lyme disease. *N Engl J Med*. 2016;374:1209–1220.
140. Nadelman RB, Nowakowski J, Fish D, et al. Prophylaxis with single-dose doxycycline for the prevention of lyme disease after an *Ixodes scapularis* tick bite. *N Engl J Med*. 2001;345:79–84.
141. Halperin JJ, Shapiro ED, Logigian E, et al. Practice parameter: treatment of nervous system lyme disease (an evidence-based review): report of the quality standards subcommittee of the American academy of neurology. *Neurology*. 2007;69:91–102.
142. Perine PL, Teklu B. Antibiotic treatment of louse-borne relapsing fever in Ethiopia: a report of 377 cases. *Am J Trop Med Hyg*. 1983;32:1096–1100.
143. Zenker PN, Rolfs RT. Treatment of syphilis, 1989. *Rev Infect Dis*. 1990;12(suppl 6):S590–S609.
144. Ghanem KG, Erbelding EJ, Cheng WW, et al. Doxycycline compared with benzathine penicillin for the treatment of early syphilis. *Clin Infect Dis*. 2006;42:e45–e49.
145. Psomas KC, Brun M, Causse A, et al. Efficacy of ceftriaxone and doxycycline in the treatment of early syphilis. *Med Mal Infect*. 2012;42:15–19.
146. Kang-Birken SL, Castel U, Prichard JG. Oral doxycycline for treatment of neurosyphilis in two patients infected with human immunodeficiency virus. *Pharmacotherapy*. 2010;30:119e–122e.
147. De Maria A, Solaro C, Abbruzzese M, et al. Minocycline for symptomatic neurosyphilis in patients allergic to penicillin. *N Engl J Med*. 1997;337:1322–1323.
148. Farnsworth N, Rosen T. Endemic treponematosis: review and update. *Clin Dermatol*. 2006;24:181–190.
149. Suputtamongkol Y, Niwattayakul K, Suttinont C, et al. An open, randomized, controlled trial of penicillin, doxycycline, and cefotaxime for patients with severe leptospirosis. *Clin Infect Dis*. 2004;39:1417–1424.
150. Brett-Major DM, Lipnick RJ. Antibiotic prophylaxis for leptospirosis. *Cochrane Database Syst Rev*. 2009;(3):CD007342.
151. Griffith KS, Lewis LS, Mali S, et al. Treatment of malaria in the United States: a systematic review. *JAMA*. 2007;297:2264–2277.
152. Pukrittayakamee S, Clemens R, Chantra A, et al. Therapeutic responses to antibacterial drugs in vivax malaria. *Trans R Soc Trop Med Hyg*. 2001;95:524–528.
153. Ohrt C, Richie TL, Widjaja H, et al. Mefloquine compared with doxycycline for the prophylaxis of malaria in indonesian soldiers. A randomized, double-blind,

placebo-controlled trial. *Ann Intern Med*. 1997;126:963–972.

154. Sonmez A, Harlak A, Kilic S, et al. The efficacy and tolerability of doxycycline and mefloquine in malaria prophylaxis of the ISAF troops in Afghanistan. *J Infect*. 2005;51:253–258.
155. Rieckmann KH, Yeo AE, Davis DR, et al. Recent military experience with malaria chemoprophylaxis. *Med J Aust*. 1993;158:446–449.
156. Pang LW, Limsomwong N, Boudreau EF, et al. Doxycycline prophylaxis for falciparum malaria. *Lancet*. 1987;1:1161–1164.
157. Pang L, Limsomwong N, Singharaj P. Prophylactic treatment of vivax and falciparum malaria with low-dose doxycycline. *J Infect Dis*. 1988;158:1124–1127.
158. Shmuklarsky MJ, Boudreau EF, Pang LW, et al. Failure of doxycycline as a causal prophylactic agent against *Plasmodium falciparum* malaria in healthy nonimmune volunteers. *Ann Intern Med*. 1994;120:294–299.
159. Tan KR, Magill AJ, Parise ME, et al. Doxycycline for malaria chemoprophylaxis and treatment: report from the CDC expert meeting on malaria chemoprophylaxis. *Am J Trop Med Hyg*. 2011;84:517–531.
160. Fan MY, Walker DH, Yu SR, et al. Epidemiology and ecology of rickettsial diseases in the People's Republic of China. *Rev Infect Dis*. 1987;9:823–840.
161. Gudiol F, Pallares R, Carratala J, et al. Randomized double-blind evaluation of ciprofloxacin and doxycycline for mediterranean spotted fever. *Antimicrob Agents Chemother*. 1989;33:987–988.
162. Perine PL, Chandler BP, Krause DK, et al. A clinico-epidemiological study of epidemic typhus in Africa. *Clin Infect Dis*. 1992;14:1149–1158.
163. Minniear TD, Buckingham SC. Managing rocky mountain spotted fever. *Expert Rev Anti Infect Ther*. 2009;7:1131–1137.
164. Ariza J, Bosilkovski M, Cascio A, et al. Perspectives for the treatment of brucellosis in the 21st century: the ioannina recommendations. *PLoS Med*. 2007;4:e317.
165. Solera J, Martinez-Alfaro E, Saez L. Meta-analysis of the efficacy of the combination of +rifampicin and doxycycline in the treatment of human brucellosis. *Med Clin (Barc)*. 1994;102:731–738.
166. Hasanjani Roushan MR, Mohraz M, Hajiahmadi M, et al. Efficacy of gentamicin plus doxycycline versus streptomycin plus doxycycline in the treatment of brucellosis in humans. *Clin Infect Dis*. 2006;42:1075–1080.
167. Hasanain A, Mahdy R, Mohamed A, et al. A randomized, comparative study of dual therapy (doxycycline-rifampin) versus triple therapy (doxycycline-rifampin-levofloxacin) for treating acute/subacute brucellosis. *Braz J Infect Dis*. 2016;20:250–254.
168. Pappas G, Seitaridis S, Akritidis N, et al. Treatment of *Brucella* spondylitis: lessons from an impossible meta-analysis and initial report of efficacy of a fluoroquinolone-containing regimen. *Int J Antimicrob Agents*. 2004;24:502–507.
169. Powell OW, Kennedy KP, McIver M, et al. Tetracycline in the treatment of "Q" fever. *Australas Ann Med*. 1962;11:184–188.
170. Spelman DW. Q fever: a study of 111 consecutive cases. *Med J Aust*. 1982;1:547–548, 551, 553.
171. Maurin M, Raoult D. Q fever. *Clin Microbiol Rev*. 1999;12:518–553.
172. Ferrante MA, Dolan MJ. Q fever meningoencephalitis in a soldier returning from the persian gulf war. *Clin Infect Dis*. 1993;16:489–496.
173. Fenollar F, Fournier PE, Carrieri MP, et al. Risks factors and prevention of Q fever endocarditis. *Clin Infect Dis*. 2001;33:312–316.
174. Raoult D, Houpikian P, Tissot Dupont H, et al. Treatment of Q fever endocarditis: comparison of 2 regimens containing doxycycline and ofloxacin or hydroxychloroquine. *Arch Intern Med*. 1999;159:167–173.
175. Chaowagul W, Chierakul W, Simpson AJ, et al. Open-label randomized trial of oral trimethoprim-sulfamethoxazole, doxycycline, and chloramphenicol compared with trimethoprim-sulfamethoxazole and doxycycline for maintenance therapy of melioidosis. *Antimicrob Agents Chemother*. 2005;49:4020–4025.
176. Chaowagul W, Simpson AJ, Suputtamongkol Y, et al. A comparison of chloramphenicol, trimethoprim-sulfamethoxazole, and doxycycline with doxycycline alone as maintenance therapy for melioidosis. *Clin Infect Dis*. 1999;29:375–380.
177. Fredeking TM, Zavala-Castro JE, Gonzalez-Martinez P, et al. Dengue patients treated with doxycycline showed lower mortality associated to a reduction in IL-6 and TNF levels. *Recent Pat Antiinfect Drug Discov*. 2015;10:51–58.
178. Haik S, Marcon G, Mallet A, et al. Doxycycline in Creutzfeldt-Jakob disease: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2014;13:150–158.
179. Varges D, Manthey H, Heinemann U, et al. Doxycycline in early CJD: a double-blinded randomised phase II and observational study. *J Neurol Neurosurg Psychiatry*. 2017;88:119–125.
180. Ritchie DJ, Garavaglia-Wilson A. A review of intravenous minocycline for treatment of multidrug-resistant *Acinetobacter* infections. *Clin Infect Dis*. 2014;59(suppl 6):S374–S380.
181. Pogue JM, Neelakanta A, Mynatt RP, et al. Carbapenem-resistance in gram-negative bacilli and intravenous minocycline: an antimicrobial stewardship approach at the detroit medical center. *Clin Infect Dis*. 2014;59(suppl 6):S388–S393.
182. Hand E, Davis H, Kim T, et al. Monotherapy with minocycline or trimethoprim/sulfamethoxazole for treatment of *Stenotrophomonas maltophilia* infections. *J Antimicrob Chemother*. 2016;71:1071–1075.
183. Tan HH. Antibacterial therapy for acne: a guide to selection and use of systemic agents. *Am J Clin Dermatol*. 2003;4:307–314.
184. Stewart DM, Torok HM, Weiss JS, et al. Dose-ranging efficacy of new once-daily extended-release minocycline for acne vulgaris. *Cutis*. 2006;78(4 suppl):11–20.
185. O'Dell JR, Elliott JR, Mallek JA, et al. Treatment of early seropositive rheumatoid arthritis: doxycycline plus methotrexate versus methotrexate alone. *Arthritis Rheum*. 2006;54:621–627.
186. Tilley BC, Alarcon GS, Heyse SP, et al. Minocycline in rheumatoid arthritis. A 48-week, double-blind, placebo-controlled trial. MIRA trial group. *Ann Intern Med*. 1995;122:81–89.
187. O'Dell JR, Paulsen G, Haire CE, et al. Treatment of early seropositive rheumatoid arthritis with minocycline: four-year followup of a double-blind, placebo-controlled trial. *Arthritis Rheum*. 1999;42:1691–1695.
188. Matsuyama A, Sakai N, Ishigami M, et al. Minocycline for the treatment of takayasu arteritis. *Ann Intern Med*. 2005;143:394–395.
189. Sorensen PS, Sellebjerg F, Lycke J, et al. Minocycline added to subcutaneous interferon beta-1a in multiple sclerosis: randomized RECYCLINE study. *Eur J Neurol*. 2016;23:861–870.
190. Metz LM, Li DKB, Traboulsee AL, et al. Trial of minocycline in a clinically isolated syndrome of multiple sclerosis. *N Engl J Med*. 2017;376:2122–2133.
191. Brouillard JE, Terriff CM, Tofan A, et al. Antibiotic selection and resistance issues with fluoroquinolones and doxycycline against bioterrorism agents. *Pharmacotherapy*. 2006;26:3–14.
192. Roberts MC. Tetracycline resistance determinants: mechanisms of action, regulation of expression, genetic mobility, and distribution. *FEMS Microbiol Rev*. 1996;19:1–24.
193. Roberts MC. Tetracycline therapy: update. *Clin Infect Dis*. 2003;36:462–467.
194. Chopra I. New developments in tetracycline antibiotics: glycylcyclines and tetracycline efflux pump inhibitors. *Drug Resist Updat*. 2002;5:119–125.
195. Paulsen IT, Brown MH, Skurray RA. Proton-dependent multidrug efflux systems. *Microbiol Rev*. 1996;60:575–608.
196. Connell SR, Tracz DM, Nierhaus KH, et al. Ribosomal protection proteins and their mechanism of tetracycline resistance. *Antimicrob Agents Chemother*. 2003;47:3675–3681.
197. Rasmussen BA, Gluzman Y, Tally FP. Inhibition of protein synthesis occurring on tetracycline-resistant, TetM-protected ribosomes by a novel class of tetracyclines, the glycylcyclines. *Antimicrob Agents Chemother*. 1994;38:1658–1660.
198. Melville CM, Scott KP, Mercer DK, et al. Novel tetracycline resistance gene, tet(32), in the *Clostridium*-related human colonic anaerobe K10 and its transmission in vitro to the rumen anaerobe butyrivibrio fibrisolvens. *Antimicrob Agents Chemother*. 2001;45:3246–3249.
199. Speer BS, Salyers AA. Novel aerobic tetracycline resistance gene that chemically modifies tetracycline. *J Bacteriol*. 1989;171:148–153.
200. Yang W, Moore IF, Koteva KP, et al. TetX is a flavin-dependent monooxygenase conferring resistance to tetracycline antibiotics. *J Biol Chem*. 2004;279:52346–52352.
201. Moore IF, Hughes DW, Wright GD. Tigecycline is modified by the flavin-dependent monooxygenase TetX. *Biochemistry*. 2005;44:11829–11835.
202. Cohen SP, McMurry LM, Levy SB. Mara locus causes decreased expression of OmpF porin in multiple-antibiotic-resistant (Mar) mutants of *Escherichia coli*. *J Bacteriol*. 1988;170:5416–5422.
203. Gerrits MM, de Zoete MR, Arents NL, et al. 16S rRNA mutation-mediated tetracycline resistance in *Helicobacter pylori*. *Antimicrob Agents Chemother*. 2002;46:2996–3000.
204. Trieber CA, Taylor DE. Mutations in the 16s rRNA genes of *Helicobacter pylori* mediate resistance to tetracycline. *J Bacteriol*. 2002;184:2131–2140.
205. Smith K, Leyden JJ. Safety of doxycycline and minocycline: a systematic review. *Clin Ther*. 2005;27:1329–1342.
206. Lebrun-Vignes B, Kreft-Jais C, Castot A, et al. Comparative analysis of adverse drug reactions to tetracyclines: results of a French national survey and review of the literature. *Br J Dermatol*. 2012;166:1333–1341.
207. Hey H, Jorgensen F, Sorensen K, et al. Oesophageal transit of six commonly used tablets and capsules. *Br Med J (Clin Res Ed)*. 1982;285:1717–1719.
208. Winckler K. Tetracycline ulcers of the oesophagus, Endoscopy, histology and roentgenology in two cases, and review of the literature. *Endoscopy*. 1981;13:225–228.
209. Fanning WL, Gump DW, Sofferman RA. Side effects of minocycline: a double-blind study. *Antimicrob Agents Chemother*. 1977;11:712–717.
210. Shea CR, Olack GA, Morrison H, et al. Phototoxicity of lumidoxycycline. *J Invest Dermatol*. 1993;101:329–333.
211. Bethell HJ. Photo-onycholysis caused by demethylchlortetracycline. *Br Med J*. 1977;2:96.
212. Fenske NA, Millns JL, Greer KE. Minocycline-induced pigmentation at sites of cutaneous inflammation. *JAMA*. 1980;244:1103–1106.
213. Simons JJ, Morales A. Minocycline and generalized cutaneous pigmentation. *J Am Acad Dermatol*. 1980;3:244–247.
214. Cale AE, Freedman PD, Lumerman H. Pigmentation of the jawbones and teeth secondary to minocycline hydrochloride therapy. *J Periodontol*. 1988;59:112–114.
215. Odell EW, Hodgson RP, Haskell R. Oral presentation of minocycline-induced black bone disease. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1995;79:459–461.
216. Siller GM, Tod MA, Savage NW. Minocycline-induced oral pigmentation. *J Am Acad Dermatol*. 1994;30(2 Pt 2):350–354.
217. Attwood HD. A black thyroid and minocycline therapy. *Med J Aust*. 1983;1:549.
218. Landas SK, Schelper RL, Tio FO, et al. Black thyroid syndrome: exaggeration of a normal process? *Am J Clin Pathol*. 1986;85:411–418.
219. Demers P, Fraser D, Goldbloom RB, et al. Effects of tetracyclines on skeletal growth and dentition. A report by the nutrition committee of the Canadian paediatric society. *Can Med Assoc J*. 1968;99:849–854.
220. Moffitt JM, Cooley RO, Olsen NH. Hefferren JJ. Prediction of tetracycline-induced tooth discoloration. *J Am Dent Assoc*. 1974;88:547–552.
221. Witkop CJ Jr, Wolf RO. Hypoplasia and intrinsic staining of enamel following tetracycline therapy. *JAMA*. 1963;185:1008–1011.
222. McIntosh HA, Storey E. Tetracycline-induced tooth changes.4. Discoloration and hypoplasia induced by tetracycline analogues. *Med J Aust*. 1970;1:114–119.
223. Grossman ER, Walchek A, Freedman H. Tetracyclines and permanent teeth: the relation between dose and tooth color. *Pediatrics*. 1971;47:567–570.
224. Toaff R, Ravid R. Tetracyclines and the teeth. *Lancet*. 1966;2:281–282.
225. Cohlan SQ. Teratogenic agents and congenital malformations. *J Pediatr*. 1963;63:650–659.
226. Schultz JC, Adamson JS Jr, Workman WW, et al. Fatal liver disease after intravenous administration of tetracycline in high dosage. *N Engl J Med*. 1963;269:999–1004.
227. Carson JL, Strom BL, Duff A, et al. Acute liver disease associated with erythromycins, sulfonamides, and tetracyclines. *Ann Intern Med*. 1993;119(7 Pt 1):576–583.
228. Vial T, Biour M, Descotes J, et al. Antibiotic-associated hepatitis: update from 1990. *Ann Pharmacother*. 1997;31:204–220.
229. Shils ME. Renal disease and the metabolic effects of tetracycline. *Ann Intern Med*. 1963;58:389–408.
230. Montoliu J, Carrera M, Darnell A, et al. Lactic acidosis and Fanconi's syndrome due to degraded tetracycline. *Br Med J (Clin Res Ed)*. 1981;283:1576–1577.
231. Lander CM. Minocycline-induced benign intracranial hypertension. *Clin Exp Neurol*. 1989;26:161–167.
232. Koch-Weser J, Gilmore EB. Benign intracranial hypertension in an adult after tetracycline therapy. *JAMA*. 1967;200:345–347.
233. Chiu AM, Chuenkongkaew WL, Cornblath WT, et al. Minocycline treatment and pseudotumor cerebri syndrome. *Am J Ophthalmol*. 1998;126:116–121.
234. Kesler A, Goldhammer Y, Hadayer A, et al. The outcome of pseudotumor cerebri induced by tetracycline therapy. *Acta Neurol Scand*. 2004;110:408–411.
235. Lochhead J, Elston JS. Doxycycline induced intracranial hypertension. *BMJ*. 2003;326:641–642.

236. Knowles SR, Shapiro L, Shear NH. Serious adverse reactions induced by minocycline. Report of 13 patients and review of the literature. *Arch Dermatol*. 1996;132:934–939.
237. Fellner MJ, Baer RL. Anaphylactic reaction to tetracycline in a penicillin-allergic patient: immunologic studies. *JAMA*. 1965;192:997–998.
238. Cac NN, Messingham MJ, Sniezek PJ, et al. Stevens-Johnson syndrome induced by doxycycline. *Cutis*. 2007;79:119–122.
239. Czeizel AE, Rockenbauer M. Teratogenic study of doxycycline. *Obstet Gynecol*. 1997;89:524–528.
240. Rosa F. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. Philadelphia (PA): Lippincott Williams & Wilkins; 2002.
241. Ellis-Grosse EJ, Babinchak T, Dartois N, et al. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. *Clin Infect Dis*. 2005;41(suppl 5):S341–S353.
242. Babinchak T, Ellis-Grosse E, Dartois N, et al. The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: analysis of pooled clinical trial data. *Clin Infect Dis*. 2005;41(suppl 5):S354–S367.
243. Tanaseanu C, Bergallo C, Teglia O, et al. Integrated results of 2 phase 3 studies comparing tigecycline and levofloxacin in community-acquired pneumonia. *Diagn Microbiol Infect Dis*. 2008;61:329–338.
244. Dartois N, Castaing N, Gandjini H, et al. Tigecycline versus levofloxacin for the treatment of community-acquired pneumonia: European experience. *J Chemother*. 2008;20(suppl 1):28–35.
245. FDA. FDA Drug Safety Communication: Increased risk of death with Tygacil (tigecycline) compared to other antibiotics used to treat similar infections; September 1, 2010. http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm. Accessed December 9, 2012.
246. FDA. FDA Drug Safety Communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new boxed warning; September 27, 2013. http://www.fda.gov/Drugs/DrugSafety/ucm369580.htm. Accessed January 26, 2014.
247. McGovern PC, Wible M, El-Tahtawy A, et al. All-cause mortality imbalance in the tigecycline phase 3 and 4 clinical trials. *Int J Antimicrob Agents*. 2013;41:463–467.
248. Sum PE, Lee VJ, Testa RT, et al. Glycylcyclines. 1. A new generation of potent antibacterial agents through modification of 9-aminotetracyclines. *J Med Chem*. 1994;37:184–188.
249. Bauer G, Berens C, Projan SJ, et al. Comparison of tetracycline and tigecycline binding to ribosomes mapped by dimethylsulphate and drug-directed fe2+ cleavage of 16s rRNA. *J Antimicrob Chemother*. 2004;53:592–599.
250. Olson MW, Ruzin A, Feyfant E, et al. Functional, biophysical, and structural bases for antibacterial activity of tigecycline. *Antimicrob Agents Chemother*. 2006;50:2156–2166.
251. Bergeron J, Ammirati M, Danley D, et al. Glycylcyclines bind to the high-affinity tetracycline ribosomal binding site and evade tet(M)- and tet(O)-mediated ribosomal protection. *Antimicrob Agents Chemother*. 1996;40:2226–2228.
252. Zhanel GG, Homenuik K, Nichol K, et al. The glycylcyclines: a comparative review with the tetracyclines. *Drugs*. 2004;64:63–88.
253. Wyeth. Tygacil (tigecycline) package insert. In: *Wyeth Pharmaceuticals I, ed.* Philadelphia: 2011.
254. Troy S, Muralidharan G, Micalizzi M, et al The effects of renal disease on the pharmacokinetics of tigecycline (GAR-936) (Abstract A-43). Proceedings of the 43rd Annual Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy; 2003; Chicago, IL.
255. Frampton JE, Curran MP. Tigecycline. *Drugs*. 2005;65:2623–2635, discussion 2636–2627.
256. Muralidharan G, Fruncillo RJ, Micalizzi M, et al. Effects of age and sex on single-dose pharmacokinetics of tigecycline in healthy subjects. *Antimicrob Agents Chemother*. 2005;49:1656–1659.
257. Muralidharan G, Micalizzi M, Speth J, et al. Pharmacokinetics of tigecycline after single and multiple doses in healthy subjects. *Antimicrob Agents Chemother*. 2005;49:220–229.
258. Rodvold KA, Gotfried MH, Cwik M, et al. Serum, tissue and body fluid concentrations of tigecycline after a single 100 mg dose. *J Antimicrob Chemother*. 2006;58:1221–1229.
259. Bhattacharya I, Gotfried MH, Ji AJ, et al. Reassessment of tigecycline bone concentrations in volunteers undergoing elective orthopedic procedures. *J Clin Pharmacol*. 2014;54:70–74.
260. Cunha BA. Pharmacokinetic considerations regarding tigecycline for multidrug-resistant (MDR) *Klebsiella pneumoniae* or MDR *Acinetobacter baumannii* urosepsis. *J Clin Microbiol*. 2009;47:1613.
261. Livermore DM. Tigecycline: what is it, and where should it be used? *J Antimicrob Chemother*. 2005;56:611–614.
262. Barbour A, Scaglione F, Derendorf H. Class-dependent relevance of tissue distribution in the interpretation of anti-infective pharmacokinetic/pharmacodynamic indices. *Int J Antimicrob Agents*. 2010;35:431–438.
263. Hoffmann M, DeMaio W, Jordan RA, et al. Metabolism, excretion, and pharmacokinetics of [14c]tigecycline, a first-in-class glycylcycline antibiotic, after intravenous infusion to healthy male subjects. *Drug Metab Dispos*. 2007;35:1543–1553.
264. Low DE, Kreiswirth BN, Weiss K, et al. Activity of GAR-936 and other antimicrobial agents against north American isolates of *Staphylococcus aureus*. *Int J Antimicrob Agents*. 2002;20:220–222.
265. Goff DA, Dowzicky MJ. Prevalence and regional variation in meticillin-resistant *Staphylococcus aureus* (MRSA) in the USA and comparative in vitro activity of tigecycline, a glycylcycline antimicrobial. *J Med Microbiol*. 2007;56(Pt 9):1189–1193.
266. Gales AC, Sader HS, Fritsche TR. Tigecycline activity tested against 11808 bacterial pathogens recently collected from US medical centers. *Diagn Microbiol Infect Dis*. 2008;60:421–427.
267. Mendes RE, Sader HS, Deshpande L, et al. Antimicrobial activity of tigecycline against community-acquired methicillin-resistant *Staphylococcus aureus* isolates recovered from north American medical centers. *Diagn Microbiol Infect Dis*. 2008;60:433–436.
268. Namdari H, Tan TY, Dowzicky MJ. Activity of tigecycline and comparators against skin and skin structure pathogens: global results of the tigecycline evaluation and surveillance trial, 2004-2009. *Int J Infect Dis*. 2012;16:e60–e66.
269. Borbone S, Lupo A, Mezzatesta ML, et al. Evaluation of the in vitro activity of tigecycline against multiresistant Gram-positive cocci containing tetracycline resistance determinants. *Int J Antimicrob Agents*. 2008;31:209–215.
270. Cercenado E, Cercenado S, Gomez JA, et al. In vitro activity of tigecycline (GAR-936), a novel glycylcycline, against vancomycin-resistant enterococci and staphylococci with diminished susceptibility to glycopeptides. *J Antimicrob Chemother*. 2003;52:138–139.
271. Aznar J, Lepe JA, Dowzicky MJ. Antimicrobial susceptibility among *E. faecalis* and *E. faecium* from France, Germany, Italy, Spain and the UK (T.E.S.T. Surveillance Study, 2004-2009). *J Chemother*. 2012;24:74–80.
272. Lee do K, Kim Y, Park KS, et al. Antimicrobial activity of mupirocin, daptomycin, linezolid, quinupristin/dalfopristin and tigecycline against vancomycin-resistant enterococci (VRE) from clinical isolates in Korea (1998 and 2005). *J Biochem Mol Biol*. 2007;40:881–887.
273. Moet GJ, Dowzicky MJ, Jones RN. Tigecycline (GAR-936) activity against *Streptococcus gallolyticus (bovis)* and viridans group streptococci. *Diagn Microbiol Infect Dis*. 2007;57:333–336.
274. Fritsche TR, Sader HS, Stilwell MG, et al. Potency and spectrum of tigecycline tested against an international collection of bacterial pathogens associated with skin and soft tissue infections (2000-2004). *Diagn Microbiol Infect Dis*. 2005;52:195–201.
275. Hoban DJ, Bouchillon SK, Johnson BM, et al. In vitro activity of tigecycline against 6792 Gram-negative and Gram-positive clinical isolates from the global tigecycline evaluation and surveillance trial (TEST program, 2004). *Diagn Microbiol Infect Dis*. 2005;52:215–227.
276. Hoellman DB, Pankuch GA, Jacobs MR, et al. Antipneumococcal activities of GAR-936 (a new glycylcycline) compared to those of nine other agents against penicillin-susceptible and -resistant pneumococci. *Antimicrob Agents Chemother*. 2000;44:1085–1088.
277. Salas C, Calvo J, Martinez-Martinez L. Activity of tigecycline against coryneform bacteria of clinical interest and *Listeria monocytogenes*. *Antimicrob Agents Chemother*. 2008;52:1503–1505.
278. Milatovic D, Schmitz FJ, Verhoef J, et al. Activities of the glycylcycline tigecycline (GAR-936) against 1,924 recent European clinical bacterial isolates. *Antimicrob Agents Chemother*. 2003;47:400–404.
279. Garcia CP, Juliet LC, Fernandez VA, et al. Multicenter study on the monitoring of in vitro susceptibility to tigeeyeline in santiago, Chile. *Rev Chilena Infectol*. 2009;26:220–226.
280. Fritsche TR, Strabala PA, Sader HS, et al. Activity of tigecycline tested against a global collection of enterobacteriaceae, including tetracycline-resistant isolates. *Diagn Microbiol Infect Dis*. 2005;52:209–213.
281. Nabuurs-Franssen M, Mouton JW. Tigecycline. In: Grayson ML, ed. *Kucers' the Use of Antibiotics*. 6th ed. Boca Raton, FL: CRC Press; 2010:881–892.
282. Bouchillon SK, Hoban DJ, Johnson BM, et al. In vitro activity of tigecycline against 3989 gram-negative and gram-positive clinical isolates from the United States tigecycline evaluation and surveillance trial (TEST program; 2004). *Diagn Microbiol Infect Dis*. 2005;52:173–179.
283. Castanheira M, Sader HS, Deshpande LM, et al. Antimicrobial activities of tigecycline and other broad-spectrum antimicrobials tested against serine carbapenemase- and metallo-beta-lactamase-producing enterobacteriaceae: report from the SENTRY antimicrobial surveillance program. *Antimicrob Agents Chemother*. 2008;52:570–573.
284. Zhanel GG, Karlowsky JA, Rubinstein E, et al. Tigecycline: a novel glycylcycline antibiotic. *Expert Rev Anti Infect Ther*. 2006;4:9–25.
285. Dowzicky MJ, Park CH. Update on antimicrobial susceptibility rates among gram-negative and gram-positive organisms in the United States: results from the tigecycline evaluation and surveillance trial (TEST) 2005 to 2007. *Clin Ther*. 2008;30:2040–2050.
286. Navon-Venezia S, Leavitt A, Carmeli Y. High tigecycline resistance in multidrug-resistant *Acinetobacter baumannii*. *J Antimicrob Chemother*. 2007;59:772–774.
287. Farrell DJ, Sader HS, Jones RN. Antimicrobial susceptibilities of a worldwide collection of *Stenotrophomonas maltophilia* isolates tested against tigecycline and agents commonly used for *S. maltophilia* infections. *Antimicrob Agents Chemother*. 2010;54:2735–2737.
288. Fritsche TR, Kirby JT, Jones RN. In vitro activity of tigecycline (GAR-936) tested against 11,859 recent clinical isolates associated with community-acquired respiratory tract and gram-positive cutaneous infections. *Diagn Microbiol Infect Dis*. 2004;49:201–209.
289. Dizbay M, Kilic S, Hizel K, et al. Tigecycline: its potential for treatment of brucellosis. *Scand J Infect Dis*. 2007;39:432–434.
290. Turan H, Arslan H, Azap OK, et al. In vitro antibacterial activity of tigecycline in comparison with doxycycline, ciprofloxacin and rifampicin against *Brucella* spp. *Int J Antimicrob Agents*. 2007;30:186–187.
291. Pappas G, Papadimitriou P, Christou L, et al. Future trends in human brucellosis treatment. *Expert Opin Investig Drugs*. 2006;15:1141–1149.
292. Jacobus NV, McDermott LA, Ruthazer R, et al. In vitro activities of tigecycline against the *Bacteroides fragilis* group. *Antimicrob Agents Chemother*. 2004;48:1034–1036.
293. Nagy E, Dowzicky MJ. In vitro activity of tigecycline and comparators against a European compilation of anaerobes collected as part of the tigecycline evaluation and surveillance trial (TEST). *Scand J Infect Dis*. 2010;42:33–38.
294. Kenny GE, Cartwright FD. Susceptibilities of *Mycoplasma hominis, M. pneumoniae,* and *Ureaplasma urealyticum* to GAR-936, dalfopristin, dirithromycin, evernimicin, gatifloxacin, linezolid, moxifloxacin, quinupristin-dalfopristin, and telithromycin compared to their susceptibilities to reference macrolides, tetracyclines, and quinolones. *Antimicrob Agents Chemother*. 2001;45:2604–2608.
295. Edelstein PH, Weiss WJ, Edelstein MA. Activities of tigecycline (GAR-936) against *Legionella pneumophila* in vitro and in Guinea pigs with *L. pneumophila* pneumonia. *Antimicrob Agents Chemother*. 2003;47:533–540.
296. Fernandez-Roblas R, Martin-de-Hijas NZ, Fernandez-Martinez AI, et al. In vitro activities of tigecycline and 10 other antimicrobials against nonpigmented rapidly growing mycobacteria. *Antimicrob Agents Chemother*. 2008;52:4184–4186.
297. Coban AY, Deveci A, Cayci YT, et al. In vitro effect of tigecycline against *Mycobacterium tuberculosis* and a review of the available drugs for tuberculosis. *Afr J Microbiol Res*. 2011;5:311–315.
298. Breedt J, Teras J, Gardovskis J, et al. Safety and efficacy of tigecycline in treatment of skin and skin structure infections: results of a double-blind phase 3 comparison study with vancomycin-aztreonam. *Antimicrob Agents Chemother*. 2005;49:4658–4666.
299. Sacchidanand S, Penn RL, Embil JM, et al. Efficacy and safety of tigecycline monotherapy compared with vancomycin plus aztreonam in patients with complicated skin and skin structure infections: results from a phase 3, randomized, double-blind trial. *Int J Infect Dis*. 2005;9:251–261.
300. Teras J, Gardovskis J, Vaasna T, et al. Overview of tigecycline efficacy and safety in the treatment of complicated skin and skin structure infections - a European perspective. *J Chemother*. 2008;20(suppl 1):20–27.
301. Chuang YC, Chang CM, Aradhya S, et al. Efficacy and safety of tigecycline monotherapy compared with

vancomycin-aztreonam in the treatment of complicated skin and skin structure infections in patients from India and Taiwan. *J Microbiol Immunol Infect*. 2011;44:116–124.

302. Lauf L, Ozsvar Z, Mitha I, et al. Phase 3 study comparing tigecycline and ertapenem in patients with diabetic foot infections with and without osteomyelitis. *Diagn Microbiol Infect Dis*. 2014;78:469–480.
303. Oliva ME, Rekha A, Yellin A, et al. A multicenter trial of the efficacy and safety of tigecycline versus imipenem/cilastatin in patients with complicated intra-abdominal infections [study ID numbers: 3074a1-301-WW; ClinicalTrials.gov identifier: NCT00081744]. *BMC Infect Dis*. 2005;5:88.
304. Chen Z, Wu J, Zhang Y, et al. Efficacy and safety of tigecycline monotherapy vs. imipenem/cilastatin in Chinese patients with complicated intra-abdominal infections: a randomized controlled trial. *BMC Infect Dis*. 2010;10:217.
305. Towfigh S, Pasternak J, Poirier A, et al. A multicentre, open-label, randomized comparative study of tigecycline versus ceftriaxone sodium plus metronidazole for the treatment of hospitalized subjects with complicated intra-abdominal infections. *Clin Microbiol Infect*. 2010;16:1274–1281.
306. Qvist N, Warren B, Leister-Tebbe H, et al. Efficacy of tigecycline versus ceftriaxone plus metronidazole for the treatment of complicated intra-abdominal infections: results from a randomized, controlled trial. *Surg Infect (Larchmt)*. 2012;13:102–109.
307. Tanaseanu C, Milutinovic S, Calistru PI, et al. Efficacy and safety of tigecycline versus levofloxacin for community-acquired pneumonia. *BMC Pulm Med*. 2009;9:44.
308. Bergallo C, Jasovich A, Teglia O, et al. Safety and efficacy of intravenous tigecycline in treatment of community-acquired pneumonia: results from a double-blind randomized phase 3 comparison study with levofloxacin. *Diagn Microbiol Infect Dis*. 2009;63:52–61.
309. Curcio D, Castagnino J, Vazquez W, et al. Tigecycline in the treatment of ventilator-associated pneumonia: experience from the latin American tigecycline use registry. *Infez Med*. 2010;18:27–34.
310. Freire AT, Melnyk V, Kim MJ, et al. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. *Diagn Microbiol Infect Dis*. 2010;68:140–151.
311. Ramirez J, Dartois N, Gandjini H, et al. Randomized phase 2 trial to evaluate the clinical efficacy of two high-dosage tigecycline regimens versus imipenem-cilastatin for treatment of hospital-acquired pneumonia. *Antimicrob Agents Chemother*. 2013;57:1756–1762.
312. Curcio D, Fernández F, Cané A, et al. Indications of a new antibiotic in clinical practice: results of the tigecycline initial use registry. *Braz J Infect Dis*. 2008;12:198–201.
313. Gardiner D, Dukart G, Cooper A, et al. Safety and efficacy of intravenous tigecycline in subjects with secondary bacteremia: pooled results from 8 phase III clinical trials. *Clin Infect Dis*. 2010;50:229–238.
314. Aslam S, Trautner BW, Ramanathan V, et al. Pilot trial of N-acetylcysteine and tigecycline as a catheter-lock solution for treatment of hemodialysis catheter-associated bacteremia. *Infect Control Hosp Epidemiol*. 2008;29:894–897.
315. Vasilev K, Reshedko G, Orasan R, et al. A phase 3, open-label, non-comparative study of tigecycline in the treatment of patients with selected serious infections due to resistant Gram-negative organisms including *Enterobacter* species, *Acinetobacter baumannii* and *Klebsiella pneumoniae*. *J Antimicrob Chemother*. 2008;62(suppl 1):i29–i40.
316. Florescu I, Beuran M, Dimov R, et al. Efficacy and safety of tigecycline compared with vancomycin or linezolid for treatment of serious infections with methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococci: a phase 3, multicentre, double-blind, randomized study. *J Antimicrob Chemother*. 2008;62(suppl 1):i17–i28.
317. Chemaly RF, Hanmod SS, Jiang Y, et al. Tigecycline use in cancer patients with serious infections: a report on 110 cases from a single institution. *Medicine (Baltimore)*. 2009;88:211–220.
318. Bucaneve G, Micozzi A, Picardi M, et al. Results of a multicenter, controlled, randomized clinical trial evaluating the combination of piperacillin/tazobactam and tigecycline in high-risk hematologic patients with cancer with febrile neutropenia. *J Clin Oncol*. 2014;32:1463–1471.
319. Cheng A, Chuang YC, Sun HY, et al. Excess mortality associated with colistin-tigecycline compared with colistin-carbapenem combination therapy for extensively drug-resistant *Acinetobacter baumannii* bacteremia: a multicenter prospective observational study. *Crit Care Med*. 2015;43:1194–1204.
320. Satlin M, Kubin C, Blumenthal J, et al. Comparative effectiveness of aminoglycosides, polymyxin B, and tigecycline for clearance of carbapenem-resistant *Klebsiella pneumoniae* from urine. *Antimicrob Agents Chemother*. 2011;55:5893–5899.
321. Larson KC, Belliveau PP, Spooner LM. Tigecycline for the treatment of severe *Clostridium difficile* infection. *Ann Pharmacother*. 2011;45:1005–1010.
322. Kopterides P, Papageorgiou C, Antoniadou A, et al. Failure of tigecycline to treat severe *Clostridium difficile* infection. *Anaesth Intensive Care*. 2010;38:755–758.
323. Navalkele BD, Lerner SA. Intravenous tigecycline facilitates cure of severe *Clostridium difficile* infection (CDI) after failure of standard therapy: a case report and literature review of tigecycline use in CDI. *Open Forum Infect Dis*. 2016;3:ofw094.
324. Thomas A, Khan F, Uddin N, et al. Tigecycline for severe *Clostridium difficile* infection. *Int J Infect Dis*. 2014;26:171–172.
325. Seyman D, Berk H, Sepin-Ozen N, et al. Successful use of tigecycline for treatment of culture-negative pyogenic vertebral osteomyelitis. *Infect Dis (Lond)*. 2015;47:783–788.
326. Griffin AT, Harting JA, Christensen DM. Tigecycline in the management of osteomyelitis: a case series from the bone and joint infection (BAJIO) database. *Diagn Microbiol Infect Dis*. 2013;77:273–277.
327. Wallace RJ Jr, Dukart G, Brown-Elliott BA, et al. Clinical experience in 52 patients with tigecycline-containing regimens for salvage treatment of *Mycobacterium abscessus* and *Mycobacterium chelonae* infections. *J Antimicrob Chemother*. 2014;69:1945–1953.
328. Someya Y, Yamaguchi A, Sawai T. A novel glycylcycline, 9-(N,N-dimethylglycylamido)-6-demethyl-6-deoxytetracycline, is neither transported nor recognized by the transposon Tn10-encoded metal-tetracycline/H+ antiporter. *Antimicrob Agents Chemother*. 1995;39:247–249.
329. Projan SJ. Preclinical pharmacology of GAR-936, a novel glycylcycline antibacterial agent. *Pharmacotherapy*. 2000;20(9 Pt 2):219S–223S, discussion 224S–228S.
330. Visalli MA, Murphy E, Projan SJ, et al. AcrAB multidrug efflux pump is associated with reduced levels of susceptibility to tigecycline (GAR-936) in *Proteus mirabilis*. *Antimicrob Agents Chemother*. 2003;47:665–669.
331. Ruzin A, Keeney D, Bradford PA. AcrAB efflux pump plays a role in decreased susceptibility to tigecycline in *Morganella morganii*. *Antimicrob Agents Chemother*. 2005;49:791–793.
332. Dean CR, Visalli MA, Projan SJ, et al. Efflux-mediated resistance to tigecycline (GAR-936) in *Pseudomonas aeruginosa* PAO1. *Antimicrob Agents Chemother*. 2003;47:972–978.
333. McAleese F, Petersen P, Ruzin A, et al. A novel MATE family efflux pump contributes to the reduced susceptibility of laboratory-derived *Staphylococcus aureus* mutants to tigecycline. *Antimicrob Agents Chemother*. 2005;49:1865–1871.
334. Fomin P, Beuran M, Gradauskas A, et al. Tigecycline is efficacious in the treatment of complicated intra-abdominal infections. *Int J Surg*. 2005;3:35–47.
335. Postier RG, Green SL, Klein SR, et al. Results of a multicenter, randomized, open-label efficacy and safety study of two doses of tigecycline for complicated skin and skin-structure infections in hospitalized patients. *Clin Ther*. 2004;26:704–714.
336. Marot JC, Jonckheere S, Munyentwali H, et al. Tigecycline-induced acute pancreatitis: about two cases and review of the literature. *Acta Clin Belg*. 2012;67:229–232.
337. Cai Y, Wang R, Liang B, et al. Systematic review and meta-analysis of the effectiveness and safety of tigecycline for treatment of infectious disease. *Antimicrob Agents Chemother*. 2011;55:1162–1172.
338. Yahav D, Lador A, Paul M, et al. Efficacy and safety of tigecycline: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2011;66:1963–1971.
339. Tasina E, Haidich AB, Kokkali S, et al. Efficacy and safety of tigecycline for the treatment of infectious diseases: a meta-analysis. *Lancet Infect Dis*. 2011;11:834–844.
340. Stein GE, Craig WA. Tigecycline: a critical analysis. *Clin Infect Dis*. 2006;43:518–524.
341. Zimmerman JJ, Harper DM, Matschke K, et al. Absence of an interaction between tigecycline and digoxin in healthy men. *Pharmacotherapy*. 2007;27:835–844.

341a. US Food and Drug Administration. Xerava: highlights of prescribing information; revised 8/2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211109lbl.pdf. Accessed November 3, 2018.

341b. US Food and Drug Administration. FDA briefing document: omadacycline injection and oral tablets; August 8, 2018. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM615848.pdf. Accessed November 3, 2018.

341c. US Food and Drug Administration. Antimicrobial resistance information from FDA; page last updated 11/5/18. https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm620149.htm. Accessed November 9, 2018.

342. Ehrlich J, Bartz QR, Smith RM, et al. Chloromycetin, a new antibiotic from a soil actinomycete. *Science*. 1947;106:417.
343. Rich ML, Ritterhoff RJ, Hoffmann RJ. A fatal case of aplastic anemia following chloramphenicol (chloromycetin) therapy. *Ann Intern Med*. 1950;33:1459–1467.
344. MacLaren G, Shann F. Chloramphenicol and thiamphenicol. In: Grayson ML, ed. *Kucers' the Use of Antibiotics*. 6th ed. Boca Raton, FL: CRC Press; 2010:1008–1029.
345. Vince R, Almquist RG, Ritter CL, et al. Chloramphenicol binding site with analogues of chloramphenicol and puromycin. *Antimicrob Agents Chemother*. 1975;8:439–443.
346. Pestka S. Inhibitors of ribosome functions. *Annu Rev Microbiol*. 1971;25:487–562.
347. Green CE, Cameron HJ, Julian GR. Recovery of polysome function of T4-infected *Escherichia coli* after brief treatment with chloramphenicol and rifampin. *Antimicrob Agents Chemother*. 1975;7:549–554.
348. Rahal JJ Jr, Simberkoff MS. Bactericidal and bacteriostatic action of chloramphenicol against memingeal pathogens. *Antimicrob Agents Chemother*. 1979;16:13–18.
349. Manyan DR, Arimura GK, Yunis AA. Chloramphenicol-induced erythroid suppression and bone marrow ferrochelatase activity in dogs. *J Lab Clin Med*. 1972;79:137–144.
350. Kauffman RE, Miceli JN, Strebel L, et al. Pharmacokinetics of chloramphenicol and chloramphenicol succinate in infants and children. *J Pediatr*. 1981;98:315–320.
351. Yogev R, Kolling WM, Williams T. Pharmacokinetic comparison of intravenous and oral chloramphenicol in patients with *Haemophilus influenzae* meningitis. *Pediatrics*. 1981;67:656–660.
352. Hammett-Stabler CA, Johns T. Laboratory guidelines for monitoring of antimicrobial drugs. National academy of clinical biochemistry. *Clin Chem*. 1998;44:1129–1140.
353. Smith AL, Weber A. Pharmacology of chloramphenicol. *Pediatr Clin North Am*. 1983;30:209–236.
354. Slaughter RL, Cerra FB, Koup JR. Effect of hemodialysis on total body clearance of chloramphenicol. *Am J Hosp Pharm*. 1980;37:1083–1086.
355. Greenberg PA, Sanford JP. Removal and absorption of antibiotics in patients with renal failure undergoing peritoneal dialysis. Tetracycline, chloramphenicol, kanamycin, and colistimethate. *Ann Intern Med*. 1967;66:465–470.
356. Koup JR, Lau AH, Brodsky B, et al. Chloramphenicol pharmacokinetics in hospitalized patients. *Antimicrob Agents Chemother*. 1979;15:651–657.
357. DuPont HL, Hornick RB, Weiss CF, et al. Evaluation of chloramphenicol acid succinate therapy of induced typhoid fever and rocky mountain spotted fever. *N Engl J Med*. 1970;282:53–57.
358. Kunin CM, Glazko AJ, Finland M. Persistence of antibiotics in blood of patients with acute renal failure. II. Chloramphenicol and its metabolic products in the blood of patients with severe renal disease or hepatic cirrhosis. *J Clin Invest*. 1959;38:1498–1508.
359. Shah PN, D'Souza J, Dattani KK. Absorption of chloramphenicol by various routes of administration. *Indian J Med Res*. 1977;65:549–553.
360. Gerding DN, Hall WH, Schierl EA. Antibiotic concentrations in ascitic fluid of patients with ascites and bacterial peritonitis. *Ann Intern Med*. 1977;86:708–713.
361. Rapp GF, Griffith RS, Hebble WM. The permeability of traumatically inflamed synovial membrane to commonly used antibiotics. *J Bone Joint Surg Am*. 1966;48:1534–1540.
362. Balbi HJ. Chloramphenicol: a review. *Pediatr Rev*. 2004;25:284–288.
363. Mayers M, Rush D, Madu A, et al. Pharmacokinetics of amikacin and chloramphenicol in the aqueous humor of rabbits. *Antimicrob Agents Chemother*. 1991;35:1791–1798.
364. Hand WL, King-Thompson NL, Steinberg TH. Interactions of antibiotics and phagocytes. *J Antimicrob Chemother*. 1983;12 Suppl C:1–11.

365. Neuhauser M, Pendland S. Chloramphenicol. In: Yu VL, Edwards G, McKinnon PS, et al, eds. *Antimicrobial Therapy and Vaccines*. Vol. II: Antimicrobial Agents. 2nd ed. Pittsburgh: ESun Technologies LLC; 2005:121–129.
366. Bell JM, Turnidge JD, Jones RN. Antimicrobial resistance trends in community-acquired respiratory tract pathogens in the western pacific region and South Africa: report from the SENTRY antimicrobial surveillance program, (1998-1999) including an in vitro evaluation of BMS284756. *Int J Antimicrob Agents*. 2002;19:125–132.
367. Deshpande LM, Jones RN, Pfaller MA. Accuracy of broth microdilution and E test methods for detecting chloramphenicol acetyl transferase mediated resistance in *Streptococcus pneumoniae*: geographic variations in the prevalence of resistance in the SENTRY antimicrobial surveillance program (1999). *Diagn Microbiol Infect Dis*. 2001;39:267–269.
368. Hoban DJ, Biedenbach DJ, Mutnick AH, et al. Pathogen of occurrence and susceptibility patterns associated with pneumonia in hospitalized patients in north America: results of the SENTRY antimicrobial surveillance study (2000). *Diagn Microbiol Infect Dis*. 2003;45:279–285.
369. Jones RN, Ballow CH, Biedenbach DJ, et al. Antimicrobial activity of quinupristin-dalfopristin (RP 59500, Synercid) tested against over 28,000 recent clinical isolates from 200 medical centers in the United States and Canada. *Diagn Microbiol Infect Dis*. 1998;31:437–451.
370. Marchese A, Debbia EA, Tonoli E, et al. In vitro activity of thiamphenicol against multiresistant *Streptococcus pneumoniae, Haemophilus influenzae* and *Staphylococcus aureus* in Italy. *J Chemother*. 2002;14:554–561.
371. Weigel LM, Donlan RM, Shin DH, et al. High-level vancomycin-resistant *Staphylococcus aureus* isolates associated with a polymicrobial biofilm. *Antimicrob Agents Chemother*. 2007;51:231–238.
372. Mutnick AH, Biedenbach DJ, Jones RN. Geographic variations and trends in antimicrobial resistance among *Enterococcus faecalis* and *Enterococcus faecium* in the SENTRY antimicrobial surveillance program (1997-2000). *Diagn Microbiol Infect Dis*. 2003;46:63–68.
373. Deshpande LM, Fritsche TR, Moet GJ, et al. Antimicrobial resistance and molecular epidemiology of vancomycin-resistant enterococci from North America and Europe: a report from the SENTRY antimicrobial surveillance program. *Diagn Microbiol Infect Dis*. 2007;58:163–170.
374. Gill VJ, Manning C, Lamson M, et al. Antibiotic-resistant group JK bacteria in hospitals. *J Clin Microbiol*. 1981;13:472–477.
375. Gutmann L, Goldstein FW, Kitzis MD, et al. Susceptibility of *Nocardia asteroides* to 46 antibiotics, including 22 beta-lactams. *Antimicrob Agents Chemother*. 1983;23:248–251.
376. Blondeau JM, Yaschuk Y. In vitro activities of ciprofloxacin, cefotaxime, ceftriaxone, chloramphenicol, and rifampin against fully susceptible and moderately penicillin-resistant *Neisseria meningitidis*. *Antimicrob Agents Chemother*. 1995;39:2577–2579.
377. Meless H, Abegaze B. Drug susceptibility of *Neisseria* isolates from patients attending clinics for sexually transmitted diseases in addis ababa. *East Afr Med J*. 1997;74:447–449.
378. Nys S, Okeke IN, Kariuki S, et al. Antibiotic resistance of faecal *Escherichia coli* from healthy volunteers from eight developing countries. *J Antimicrob Chemother*. 2004;54:952–955.
379. Bean DC, Livermore DM, Papa I, et al. Resistance among *Escherichia coli* to sulphonamides and other antimicrobials now little used in man. *J Antimicrob Chemother*. 2005;56:962–964.
380. Finland M, Garner C, Wilcox C, et al. Susceptibility of "enterobacteria" to aminoglycoside antibiotics: comparisons with tetracyclines, polymyxins, chloramphenicol, and spectinomycin. *J Infect Dis*. 1976;134(suppl):S57–S74.
381. Rubinstein E, Shainberg B. In vitro activity of cinoxacin, ampicillin, and chloramphenicol against *Shigella* and nontyphoid *Salmonella*. *Antimicrob Agents Chemother*. 1977;11:577–579.
382. Fontana R, Lo Cascio G, Ligozzi M, et al. Antimicrobial susceptibility of respiratory isolates of enterobacteriaceae and *Staphylococcus aureus* in Italy: incidence and trends over the period 1997-1999. *Eur J Clin Microbiol Infect Dis*. 2001;20:854–863.
383. Preston MA, Brown S, Borczyk AA, et al. Antimicrobial susceptibility of pathogenic *Yersinia enterocolitica* isolated in Canada from 1972 to 1990. *Antimicrob Agents Chemother*. 1994;38:2121–2124.
384. Abdul Rahim N, Cheah SE, Johnson MD, et al. Synergistic killing of NDM-producing MDR *Klebsiella pneumoniae* by two 'old' antibiotics-polymyxin B and chloramphenicol. *J Antimicrob Chemother*. 2015;70:2589–2597.
385. Li XZ, Ma D, Livermore DM, et al. Role of efflux pump(s) in intrinsic resistance of *Pseudomonas aeruginosa*: active efflux as a contributing factor to beta-lactam resistance. *Antimicrob Agents Chemother*. 1994;38:1742–1752.
386. Shakibaie MR, Adeli S, Salehi MH. Antibiotic resistance patterns and extended-spectrum beta-lactamase production among *Acinetobacter* spp. isolated from an intensive care unit of a hospital in kerman, Iran. *Antimicrob Resist Infect Control*. 2012;1:1.
387. Friedman ND, Korman TM, Fairley CK, et al. Bacteraemia due to *Stenotrophomonas maltophilia*: an analysis of 45 episodes. *J Infect*. 2002;45:47–53.
388. Eickhoff TC, Bennett JV, Hayes PS, et al. *Pseudomonas pseudomallei*: susceptibility to chemotherapeutic agents. *J Infect Dis*. 1970;121:95–102.
389. Burns JL, Hedin LA, Lien DM. Chloramphenicol resistance in *Pseudomonas cepacia* because of decreased permeability. *Antimicrob Agents Chemother*. 1989;33:136–141.
390. Sutter VL, Finegold SM. Susceptibility of anaerobic bacteria to 23 antimicrobial agents. *Antimicrob Agents Chemother*. 1976;10:736–752.
391. Rood JI, Jefferson S, Bannam TL, et al. Hybridization analysis of three chloramphenicol resistance determinants from *Clostridium perfringens* and *Clostridium difficile*. *Antimicrob Agents Chemother*. 1989;33:1569–1574.
392. Delmee M, Avesani V. Correlation between serogroup and susceptibility to chloramphenicol, clindamycin, erythromycin, rifampicin and tetracycline among 308 isolates of *Clostridium difficile*. *J Antimicrob Chemother*. 1988;22:325–331.
393. Snydman DR, Jacobus NV, McDermott LA, et al. National survey on the susceptibility of *Bacteroides fragilis* group: report and analysis of trends in the United States from 1997 to 2004. *Antimicrob Agents Chemother*. 2007;51:1649–1655.
394. Cevenini R, Donati M, Sambri V, et al. Enzyme-linked immunosorbent assay for the in-vitro detection of sensitivity of *Chlamydia trachomatis* to antimicrobial drugs. *J Antimicrob Chemother*. 1987;20:677–684.
395. Denny FW, Clyde WA Jr, Glezen WP. *Mycoplasma pneumoniae* disease: clinical spectrum, pathophysiology, epidemiology, and control. *J Infect Dis*. 1971;123:74–92.
396. Harrell GT. Treatment of rocky mountain spotted fever with antibiotics. *Ann N Y Acad Sci*. 1952;55:1027–1042.
397. Hussein AA, Abdel Rahman SI. Meningococcal meningitis epidemic. A new role for single-dose oily chloramphenicol. *Saudi Med J*. 2002;23:797–801.
398. Prasad K, Singhal T, Jain N, et al. Third generation cephalosporins versus conventional antibiotics for treating acute bacterial meningitis. *Cochrane Database Syst Rev*. 2004;(2):CD001832.
399. Akpede GO, Dawodu SO, Umoffia ME. Response to antimicrobial therapy in childhood bacterial meningitis in tropical Africa: report of a bi-centre experience in Nigeria, 1993-1998. *Ann Trop Paediatr*. 1999;19:237–243.
400. Nathan N, Borel T, Djibo A, et al. Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics: a randomised non-inferiority study. *Lancet*. 2005;366:308–313.
401. Duke T, Michael A, Mokela D, et al. Chloramphenicol or ceftriaxone, or both, as treatment for meningitis in developing countries? *Arch Dis Child*. 2003;88:536–539.
402. Friedland IR, Klugman KP. Failure of chloramphenicol therapy in penicillin-resistant pneumococcal meningitis. *Lancet*. 1992;339:405–408.
403. Laferriere CI, Marks MI. Chloramphenicol: properties and clinical use. *Pediatr Infect Dis*. 1982;1:257–264.
404. Rehman AU, Rehman T, Ali R. Multi-antibiotic resistant brain abscess sensitive only to chloramphenicol: a case report. *Cases J*. 2009;2:6352.
405. Robertson RP, Wahab MF, Raasch FO. Evaluation of chloramphenicol and ampicillin in salmonella enteric fever. *N Engl J Med*. 1968;278:171–176.
406. Akalin HE. Quinolones in the treatment of typhoid fever. *Drugs*. 1999;58(suppl 2):52–54.
407. Liberti A, Loiacono L. Ciprofloxacin versus chloramphenicol in the treatment of salmonella infection. *Int J Antimicrob Agents*. 2000;16:347–348.
408. Tatli MM, Aktas G, Kosecik M, et al. Treatment of typhoid fever in children with a flexible-duration of ceftriaxone, compared with 14-day treatment with chloramphenicol. *Int J Antimicrob Agents*. 2003;21:350–353.
409. Sood S, Kapil A, Das B, et al. Re-emergence of chloramphenicol-sensitive *Salmonella typhi*. *Lancet*. 1999;353:1241–1242.
410. Snyder MJ, Gonzalez O, Palomino C, et al. Comparative efficacy of chloramphenicol, ampicillin, and co-trimoxazole in the treatment of typhoid fever. *Lancet*. 1976;2:1155–1157.
411. Parry CM, Hien TT, Dougan G, et al. Typhoid fever. *N Engl J Med*. 2002;347:1770–1782.
412. Aserkoff B, Bennett JV. Effect of antibiotic therapy in acute salmonellosis on the fecal excretion of salmonellae. *N Engl J Med*. 1969;281:636–640.
413. Sirinavin S, Garner P. Antibiotics for treating salmonella gut infections. *Cochrane Database Syst Rev*. 2000;(2):CD001167.
414. Chiu CH, Chuang CH, Chiu S, et al. *Salmonella enterica* serotype choleraesuis infections in pediatric patients. *Pediatrics*. 2006;117:e1193–e1196.
415. Walker DH. Rocky mountain spotted fever: a seasonal alert. *Clin Infect Dis*. 1995;20:1111–1117.
416. Holman RC, Paddock CD, Curns AT, et al. Analysis of risk factors for fatal rocky mountain spotted fever: evidence for superiority of tetracyclines for therapy. *J Infect Dis*. 2001;184:1437–1444.
417. Norris AH, Reilly JP, Edelstein PH, et al. Chloramphenicol for the treatment of vancomycin-resistant enterococcal infections. *Clin Infect Dis*. 1995;20:1137–1144.
418. Ricaurte JC, Boucher HW, Turett GS, et al. Kislak JW. Chloramphenicol treatment for vancomycin-resistant *Enterococcus faecium* bacteremia. *Clin Microbiol Infect*. 2001;7:17–21.
419. Mehta NJ, Khan IA, Mehta RN, et al. *Stenotrophomonas maltophilia* endocarditis of prosthetic aortic valve: report of a case and review of literature. *Heart Lung*. 2000;29:351–355.
420. Lam RF, Lai JS, Ng JS, et al. Topical chloramphenicol for eye infections. *Hong Kong Med J*. 2002;8:44–47.
421. Ramirez-Ortiz MA, Rodriguez-Almaraz M, Ochoa-Diazlopez H, et al. Randomised equivalency trial comparing 2.5% povidone-iodine eye drops and ophthalmic chloramphenicol for preventing neonatal conjunctivitis in a trachoma endemic area in southern Mexico. *Br J Ophthalmol*. 2007;91:1430–1434.
422. Rose PW, Harnden A, Brueggemann AB, et al. Chloramphenicol treatment for acute infective conjunctivitis in children in primary care: a randomised double-blind placebo-controlled trial. *Lancet*. 2005;366:37–43.
423. Everitt HA, Little PS, Smith PW. A randomised controlled trial of management strategies for acute infective conjunctivitis in general practice. *BMJ*. 2006;333:321.
424. Dennis DT, Inglesby TV, Henderson DA, et al. Tularemia as a biological weapon: medical and public health management. *JAMA*. 2001;285:2763–2773.
425. Inglesby TV, Dennis DT, Henderson DA, et al. Plague as a biological weapon: medical and public health management. Working group on civilian biodefense. *JAMA*. 2000;283:2281–2290.
426. Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon, 2002: updated recommendations for management. *JAMA*. 2002;287:2236–2252.
427. Miyamura S, Ochiai H, Nitahara Y, et al. Resistance mechanism of chloramphenicol in *Streptococcus haemolyticus, Streptococcus pneumoniae* and *Streptococcus faecalis*. *Microbiol Immunol*. 1977;21:69–76.
428. Goldstein FW, Chumpitaz JC, Guevara JM, et al. Plasmid-mediated resistance to multiple antibiotics in *Salmonella typhi*. *J Infect Dis*. 1986;153:261–266.
429. Datta N, Richards H, Datta C. *Salmonella typhi* in vivo acquires resistance to both chloramphenicol and co-trimoxazole. *Lancet*. 1981;1:1181–1183.
430. Rowe B, Ward LR, Threlfall EJ. Multidrug-resistant *Salmonella typhi*: a worldwide epidemic. *Clin Infect Dis*. 1997;24(suppl 1):S106–S109.
431. Alonso A, Martinez JL. Multiple antibiotic resistance in *Stenotrophomonas maltophilia*. *Antimicrob Agents Chemother*. 1997;41:1140–1142.
432. Burns JL, Rubens CE, Mendelman PM, et al. Cloning and expression in *Escherichia coli* of a gene encoding nonenzymatic chloramphenicol resistance from *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 1986;29:445–450.
433. Burns JL, Mendelman PM, Levy J, et al. A permeability barrier as a mechanism of chloramphenicol resistance in *Haemophilus influenzae*. *Antimicrob Agents Chemother*. 1985;27:46–54.
434. Butaye P, Cloeckaert A, Schwarz S. Mobile genes coding for efflux-mediated antimicrobial resistance in Gram-positive and Gram-negative bacteria. *Int J Antimicrob Agents*. 2003;22:205–210.
435. McMurry LM, George AM, Levy SB. Active efflux of chloramphenicol in susceptible *Escherichia coli* strains and in multiple-antibiotic-resistant (Mar) mutants. *Antimicrob Agents Chemother*. 1994;38:542–546.
436. Osawa S, Takata R, Tanaka K, et al. Chloramphenicol resistant mutants of *Bacillus subtilis*. *Mol Gen Genet*. 1973;127:163–173.
437. Yunis AA. Chloramphenicol-induced bone marrow suppression. *Semin Hematol*. 1973;10:225–234.

438. Scott JL, Finegold SM, Belkin GA, et al. A controlled double-blind study of the hematologic toxicity of chloramphenicol. *N Engl J Med*. 1965;272:1137–1142.
439. McCaffrey RP, Halsted CH, Wahab MF, et al. Chloramphenicol-induced hemolysis in caucasian glucose-6-phosphate dehydrogenase deficiency. *Ann Intern Med*. 1971;74:722–726.
440. Wallerstein RO, Condit PK, Kasper CK, et al. Statewide study of chloramphenicol therapy and fatal aplastic anemia. *JAMA*. 1969;208:2045–2050.
441. Davis S, Rubin AD. Treatment and prognosis in aplastic anaemia. *Lancet*. 1972;1:871–873.
442. Murray T, Downey KM, Yunis AA. Degradation of isolated deoxyribonucleic acid mediated by nitroso-chloramphenicol. Possible role in chloramphenicol-induced aplastic anemia. *Biochem Pharmacol*. 1982;31:2291–2296.
443. Jimenez JJ, Arimura GK, Abou-Khalil WH, et al. Chloramphenicol-induced bone marrow injury: possible role of bacterial metabolites of chloramphenicol. *Blood*. 1987;70:1180–1185.
444. Yunis AA, Arimura GK, Isildar M. DNA damage induced by chloramphenicol and its nitroso derivative: damage in intact cells. *Am J Hematol*. 1987;24:77–84.
445. Nagao T, Mauer AM. Concordance for drug-induced aplastic anemia in identical twins. *N Engl J Med*. 1969;281:7–11.
446. Morley A, Trainor K, Remes J. Residual marrow damage: possible explanation for idiosyncrasy to chloramphenicol. *Br J Haematol*. 1976;32:525–531.
447. Holt R. The bacterial degradation of chloramphenicol. *Lancet*. 1967;1:1259–1260.
448. Daum RS, Cohen DL, Smith AL. Fatal aplastic anemia following apparent "dose-related" chloramphenicol toxicity. *J Pediatr*. 1979;94:403–406.
449. Plaut ME, Best WR. Aplastic anemia after parenteral chloramphenicol: warning renewed. *N Engl J Med*. 1982;306:1486.
450. Alavi JB. Aplastic anemia associated with intravenous chloramphenicol. *Am J Hematol*. 1983;15:375–379.
451. West BC, DeVault GA Jr, Clement JC, et al. Aplastic anemia associated with parenteral chloramphenicol: review of 10 cases, including the second case of possible increased risk with cimetidine. *Rev Infect Dis*. 1988;10:1048–1051.
452. Lancaster T, Swart AM, Jick H. Risk of serious haematological toxicity with use of chloramphenicol eye drops in a British general practice database. *BMJ*. 1998;316:667.
453. Laporte JR, Vidal X, Ballarin E, et al. Possible association between ocular chloramphenicol and aplastic anaemia–the absolute risk is very low. *Br J Clin Pharmacol*. 1998;46:181–184.
454. Wiholm BE, Kelly JP, Kaufman D, et al. Relation of aplastic anaemia to use of chloramphenicol eye drops in two international case-control studies. *BMJ*. 1998;316:666.
455. Shu XO, Gao YT, Linet MS, et al. Chloramphenicol use and childhood leukaemia in shanghai. *Lancet*. 1987;2:934–937.
456. Zheng W, Linet MS, Shu XO, et al. Prior medical conditions and the risk of adult leukemia in shanghai, People's Republic of China. *Cancer Causes Control*. 1993;4:361–368.
457. Doody MM, Linet MS, Glass AG, et al. Risks of non-hodgkin's lymphoma, multiple myeloma, and leukemia associated with common medications. *Epidemiology*. 1996;7:131–139.
458. Sutherland JM. Fatal cardiovascular collapse of infants receiving large amounts of chloramphenicol. *AMA J Dis Child*. 1959;97:761–767.
459. Werner JC, Whitman V, Schuler HG, et al. Acute myocardial effects of chloramphenicol in newborn pigs: a possible insight into the gray baby syndrome. *J Infect Dis*. 1985;152:344–350.
460. Suarez CR, Ow EP. Chloramphenicol toxicity associated with severe cardiac dysfunction. *Pediatr Cardiol*. 1992;13:48–51.
461. Thompson WL, Anderson SE, Lipsky JJ, et al. Letter: overdoses of chloramphenicol. *JAMA*. 1975;234:149–150.
462. Evans LS, Kleiman MB. Acidosis as a presenting feature of chloramphenicol toxicity. *J Pediatr*. 1986;108:475–477.
463. Stevens DC, Kleiman MB, Lietman PS, et al. Exchange transfusion in acute chloramphenicol toxicity. *J Pediatr*. 1981;99:651–653.
464. Freundlich M, Cynamon H, Tamer A, et al. Management of chloramphenicol intoxication in infancy by charcoal hemoperfusion. *J Pediatr*. 1983;103:485–487.
465. Woolf DL. Chloramphenicol blindness. *Br Med J*. 1965;1:1511.
466. Fung AT, Hudson B, Billson FA. Chloramphenicol—not so innocuous: a case of optic neuritis. *BMJ Case Rep*. 2011;2011.
467. Cahill KM. Chloramphenicol hypersensitivity, a severe haemorrhagic reaction. *Lancet*. 1962;2:277–278.
468. Van Brummelen R, Myburgh S, Bissbort SH. The influence of porphyrogenic drugs on the glyoxalase enzymes. *Res Commun Chem Pathol Pharmacol*. 1993;82:339–349.
469. Ambrose CT, Coons AH. Studies on antibody production. VIII. The inhibitory effect of chloramphenicol on the synthesis of antibody in tissue culture. *J Exp Med*. 1963;117:1075–1088.
470. Christensen LK, Skovsted L. Inhibition of drug metabolism by chloramphenicol. *Lancet*. 1969;2:1397–1399.
471. Krasinski K, Kusmiesz H, Nelson JD. Pharmacologic interactions among chloramphenicol, phenytoin and phenobarbital. *Pediatr Infect Dis*. 1982;1:232–235.
472. Prober CG. Effect of rifampin on chloramphenicol levels. *N Engl J Med*. 1985;312:788–789.
473. Paisley JW, Washington JA 2nd. Susceptibility of *Escherichia coli* K1 to four combinations of antimicrobial agents potentially useful for treatment of neonatal meningitis. *J Infect Dis*. 1979;140:183–191.
474. Brown TH, Alford RH. Antagonism by chloramphenicol of broad-spectrum beta-lactam antibiotics against *Klebsiella pneumoniae*. *Antimicrob Agents Chemother*. 1984;25:405–407.
475. Gradelski E, Kolek B, Bonner DP, et al. Activity of gatifloxacin and ciprofloxacin in combination with other antimicrobial agents. *Int J Antimicrob Agents*. 2001;17:103–107.

27 Rifamycins

Melanie Jane Maslow and Cynthia Portal-Celhay

SHORT VIEW SUMMARY

OVERVIEW

- The rifamycin class of antibiotics acts through inhibition of RNA synthesis by high-affinity binding to the DNA-dependent RNA polymerase of prokaryotes. Spontaneous resistance limits use as monotherapy. The rifamycins differ in their pharmacokinetics and adverse reactions, but most have significant drug interactions, especially with CYP3A4. In addition to the traditional uses of rifamycins in mycobacterial and staphylococcal infections, there are both newer indications for rifampin and unique rifamycins, such as rifaximin, which are used to treat gastrointestinal infections and disorders. The indications and doses of the specific drugs are detailed as follows.

RIFAMPIN

- *Mycobacterium tuberculosis* infection: 600 mg daily (10 mg/kg)
- *Mycobacterium kansasii* and *Mycobacterium leprae* infection: 600 mg daily
- Staphylococcal prosthetic valve endocarditis: 300 mg three times daily
- Staphylococcal prosthetic joint infections: 300 to 450 mg twice daily or 600 mg daily
- Methicillin-resistant *Staphylococcus aureus* osteomyelitis in combination with TMP/SMX, doxycycline, minocycline, clindamycin of a fluoroquinolone based on susceptibilities: 600 to 900 mg daily (single dose or divided in two)
- Multidrug-resistant gram-negative bacilli: 10 mg/kg intravenously every 12 hours
- *Bartonella henselae* infection: 300 mg twice daily with doxycycline for complicated disease
- Brucellosis: 600 to 900 mg daily with doxycycline (second-line therapy)
- Chemoprophylaxis for *Neisseria meningitidis:* 600 mg twice daily for 2 days
- Chemoprophylaxis for infection with *Haemophilus influenzae* type b: 600 mg daily for 4 days

RIFABUTIN

- *Mycobacterium avium* complex infection: 300 mg daily; 450 mg daily when used with efavirenz and 150 mg daily when used with human immunodeficiency virus (HIV) protease inhibitors
- *M. avium* complex prophylaxis: 300 mg daily (azithromycin is preferred)
- *M. tuberculosis:* 300 mg daily; for HIV-infected patients on protease inhibitors: 150 mg daily; if on efavirenz, 450 mg daily; decrease dose to 150 mg daily for creatinine clearance less than 30 mL/min

RIFAPENTINE

- Tuberculosis (active): 600 mg (10 mg/kg) twice weekly for induction phase and once weekly for maintenance; for latent disease: 900 mg weekly with isoniazid for 12 weeks

RIFAXIMIN

- Hepatic encephalopathy: 400 mg every 8 hours; prevention: 550 mg twice daily
- Recurrent *Clostridioides difficile* (formerly *Clostridium difficile*) infection: 400 mg twice daily
- Traveler's diarrhea: 200 mg three times daily for 3 days
- Irritable bowel syndrome: 550 mg three times daily for 14 days

The rifamycins were isolated by Sensi and colleagues at the Dow-Lepetit Research Laboratories in Milan in 1959 as a mixture of five substances from fermentation cultures of the organism now classified as *Amycolatopsis mediterranei,* in the Actinomycetaceae family. The nickname for the drug, "Rififi," was taken from the title of a French crime movie popular at that time and became the root of the name given to this class, the rifamycins.[1] Rifamycin SV, the first rifamycin used clinically in 1963, was replaced by rifampicin (rifampin) in 1968 due to its improved bioavailability and greater activity against gram-positive and gram-negative bacteria and, especially, *Mycobacterium tuberculosis*. Rifampin is increasingly used as an adjunct for foreign-body infections associated with biofilm production, in combination with other antibiotics for infections due to multidrug-resistant (MDR) gram-negative bacilli and for infections caused by intracellular pathogens.[2] The newer rifamycins have fewer drug interactions and improved pharmacokinetics, resulting in shorter treatment courses for tuberculosis (TB). Some of the newer rifamycins have an expanded spectrum of activity and unique pharmacokinetics, and are used to treat *Clostridioides difficile* (formerly *Clostridium difficile*) infection, hepatic encephalopathy, traveler's diarrhea, and inflammatory bowel diseases. Novel investigational rifamycins and new delivery systems are in development.

STRUCTURE AND MECHANISM OF ACTION

The rifamycins belong to the ansamycin family (from the Latin *ansa,* meaning "handle") of antimicrobial agents because of their basket-like structure containing an aliphatic chain connecting two ends of a naphthoquinone core. Rifampin is the 3-(4-methyl-1-piperazinyl)-iminomethyl derivative of rifamycin SV. The structures of the four rifamycins currently approved in the United States—rifampin, rifabutin, rifapentine, and rifaximin—are shown in Fig. 27.1.

The antibacterial action of the rifamycins results from high-affinity binding to the DNA-dependent RNA polymerase of prokaryotes (RNAP) and inhibition of RNA synthesis. RNAP is a complex enzyme with an $\alpha_2\beta\beta'\omega$-subunit structure. The structure of the *Thermus aquaticus* core RNAP in complex with rifampin, determined at 3.3-Å resolution, showed that rifampin binds to a site on the β-subunit deep within the DNA/RNA channel, in a position that physically hinders the growing oligonucleotide chain after the first- or second-chain elongation step.[3] The structure, combined with biochemical results, led to a mechanistic model for inhibition of RNAP in which rifamycins sterically block synthesis of an RNA product longer than three nucleotides ("steric-occlusion model"). Artsimovich and associates[4] proposed a different mechanism for inhibition of RNAP by rifamycins that operates in addition to, or instead of, the steric-occlusion mechanism. Their model proposes that rifamycins also inhibit transcription at earlier steps through an allosteric signal that disfavors binding of Mg^{2+} ion in the active site, slowing down catalysis and facilitating dissociation of short RNA transcripts. The allosteric model remains controversial because others have shown that rifamycins do not affect the affinity of binding of Mg^{3+} to the RNAP active center.[5]

MECHANISMS OF RESISTANCE

Rifampin possesses highly effective bactericidal action against *M. tuberculosis* and is used as a first-line regimen against this agent. However, many exposed bacteria develop resistance to rifampin at a rate of 10^{-8} to 10^{-9} per bacterium per cell division, which is a potential source of transmissible resistance that selects for resistance in the microbiome.

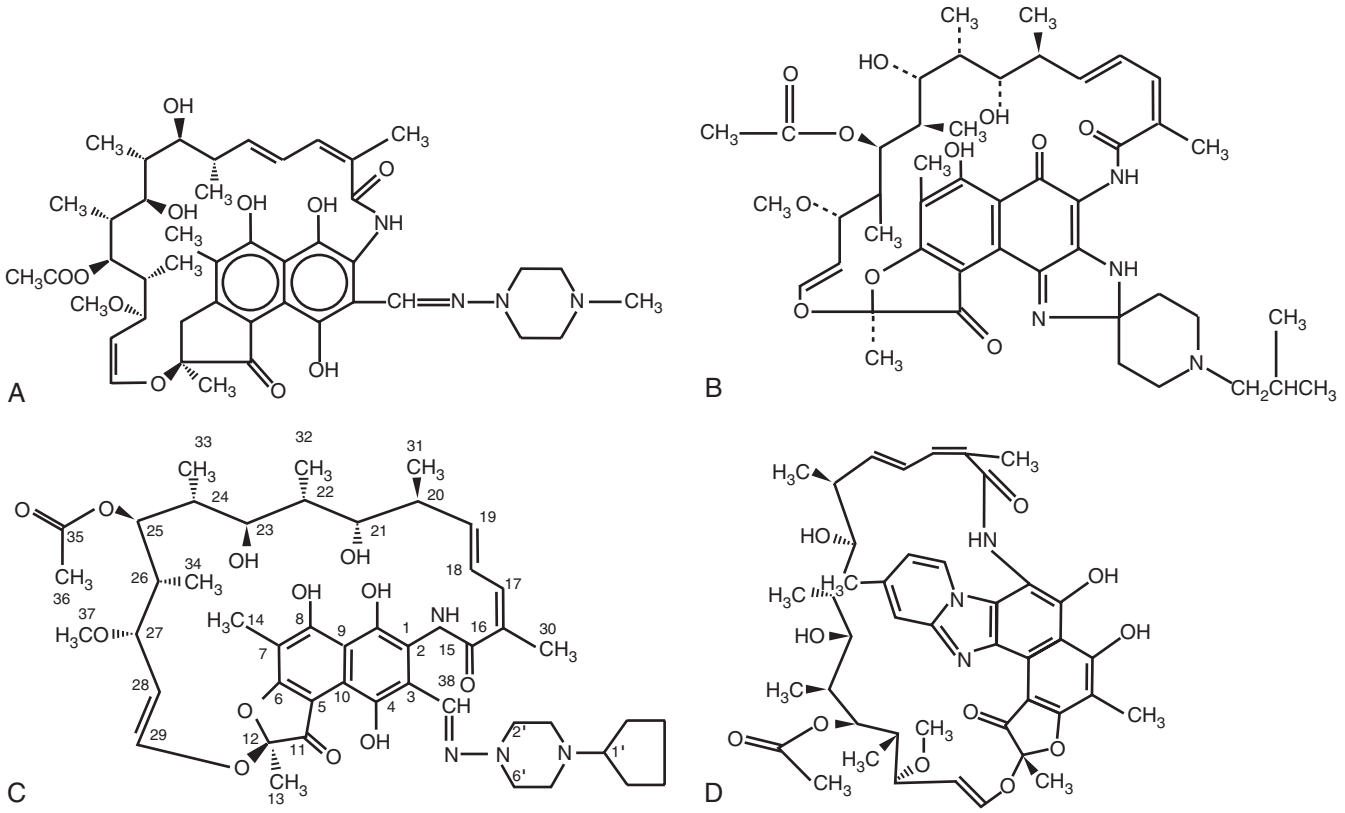

FIG. 27.1 Structures of the four major rifamycins. (A) Rifampin. (B) Rifabutin. (C) Rifapentine. (D) Rifaximin.

Mutations conferring rifampin resistance are confined almost exclusively to the *rpoB* gene in most organisms and result in a decreased affinity of the RNAP to the antibiotic. Greater than 95% of *M. tuberculosis* clinical strains resistant to rifampin harbor a mutation in an 81–base pair region of the *rpoB* gene known as the rifampin resistance determining region (RRDR), which includes codons 507 to 533 and encodes 27 amino acids.[6] Of importance, most of the strains have alterations at codon 526 that result in amino-acid replacements or have missense mutations in codon 531. Studies with patient isolates have confirmed and extended these findings.[7,8] Studies designed to determine the relationship between *rpoB* structural changes and rifampin minimal inhibitory concentrations (MICs) have found a strong correlation. In particular, amino-acid substitutions at positions 526 and 531 conferred high-level resistance to rifampin, rifabutin, and rifapentine.[9] The molecular mechanism in the 4% of the rifampin-resistant *M. tuberculosis* isolates that lack RRDR changes is unknown.

Alternative mechanisms of rifampin resistance also have been observed. *Pseudomonas fluorescens* has impaired cellular uptake of rifampin. Antibiotic modification occurs in strains of *Mycobacterium smegmatis* that carry the *arr* gene, causing ribosylation of rifampin and decreased susceptibility. An *arr2* gene, similar to that in *M. smegmatis,* has been identified on a plasmid in clinical isolates of *Klebsiella pneumoniae, Pseudomonas aeruginosa,* and Enterobacteriaceae. Finally, the enzyme from some species, such as *Nocardia,* is intrinsically less susceptible to rifampin inhibition because of metabolic changes at the critical hydrogen-binding sites.[10]

Delineation of the molecular mechanisms of rifamycin resistance has resulted in the development and application of several polymerase chain reaction (PCR)-based strategies designed to rapidly detect mutations associated with rifampin resistance. One of the latest assays, Xpert MTB/RIF (Cepheid; Sunnyvale, CA), a heminested PCR, detects *M. tuberculosis* and rifampin resistance by amplifying five overlapping probes complementary to the RRDR of the *rpoB* gene and subsequently probes this region for mutations associated with rifampin resistance.[11,12] Compared with conventional diagnosis methods, the Xpert MTB/RIF assay can detect *M. tuberculosis* and rifampin resistance in one sputum sample within 2 hours, is nearly fully automated, and requires minimal biosafety measures. The Xpert MTB/RIF assay has been validated by several studies as a highly sensitive and specific detection test for the diagnosis of pulmonary tuberculosis and rifampin resistance.[13] Recent evidence supports the use of this assay in nonrespiratory clinical samples as well,[14] and the Xpert MTB/RIF assay is now recommended by World Health Organization (WHO) for the diagnosis of extrapulmonary tuberculosis and rifampin resistance.[15]

Other molecular assays to detect rifampin resistance are commercially available. The Genotype MTBDRplus assay (Hain Lifescience; Nehren, Germany)[16] and the INNO-LiPA Rif assay (Innogenetics; Gent, Belgium) have been validated and are currently in use in several countries.[17] In a systematic review, all three commercial tests performed well when detecting drug resistance in clinical samples, although the Xpert MTB/RIF assay had the highest sensitivity and specificity and appeared to be most cost-effective.[18]

Although presence of mutations in the RRDR is highly associated with rifampin resistance, false rifampin resistance detected by Xpert MTB/RIF has been reported.[19] Therefore the package insert of the Xpert MTB/RIF assay states that detection of rifampin resistance must have results confirmed by a reference laboratory. Given that the prevalence of rifampin resistance is low in the United States, the Centers for Disease Control and Prevention (CDC) recommends that a positive result indicating a mutation in the *rpoB* gene should be confirmed by rapid DNA sequencing and growth-based drug susceptibility testing.[20] Cases with discrepant genotypic (resistant) and phenotypic (susceptible) rifampin susceptibility results account for at least 10% of all rifampin-resistant diagnoses obtained with molecular tests. Some of the discrepant strains harbor "low-level" *rpoB* mutations that confer MICs above the level determined for fully susceptible strains but below the critical concentration of 1 μg/mL currently used in standardized culture-based susceptibility tests.[21] The complexity of distinguishing false-positive from true-positive rifampin-resistant results underscores the need for new guidelines to inform therapeutic decision making.

More novel diagnostic tests, such as TB intradermal reaction,[22] pyrosequencing assays,[23] whole-genome sequencing,[24] and next-generation

TABLE 27.1 Comparative Pharmacokinetics of the Rifamycins in Healthy Adults

DRUG	BIOAVAILABILITY (%)	t_{max} (hr)	C_{max} (μg/mL)	$t_{1/2}$ (hr)	PROTEIN BINDING (%)
Rifampin	68	1.5–2	8–20	2–5	80
Rifabutin	20	2.5–4	0.2–0.9	32–67	72–85[a]
Rifapentine	70 with food	4.8–6.6	8–30	14–18	98
Rifaximin	<0.4	0.8–1	3.4 ± 1.6 ng/mL	1.8–4.8	62–67.5

[a]From Blaschke TF, Skinner MH. The clinical pharmacokinetics of rifabutin. *Clin Infect Dis.* 1996;22(suppl 1):S15–S21.
C_{max}, Peak serum concentration; *ng*, nanograms; t_{max}, time to C_{max}; $t_{1/2}$, serum half-life.
Modified from Burman WJ, Gallicano K, Peloquin C. Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. Clin Pharmacokinet. *2001;40:327–341.*

sequencing[25,26] are being configured in a low-cost test platform to provide rapid diagnosis and drug susceptibility information for tuberculosis in the developing world and in countries dealing with a dual burden of human immunodeficiency virus (HIV) infection and MDR tuberculosis, where the need is acute.

SHARED PROPERTIES OF THE RIFAMYCINS

The rifamycins are highly lipophilic compounds that share a common chemical structure but differ in their pharmacokinetic properties,[27] summarized in Table 27.1. The systemic rifamycins—rifampin, rifabutin, and rifapentine—have long postantibiotic effects against *M. tuberculosis* of 68 to75 hours.[28] These drugs are metabolized in hepatocytes and intestinal microsomes to deacetylated, hydroxylated, and formyl derivatives.[27] The parent drug and the active 25-*O*-deacetyl metabolite are found in serum, excreted in bile, and eliminated in feces. Repeated administration of rifampin and rifabutin results in autoinduction by gut or hepatic metabolism and increasing biliary secretion, resulting in a decrease in the area under the concentration-time curve (AUC) of both drugs and a decrease in the half-life of rifampin.

The major rifamycin adverse reactions are divided by daily versus intermittent administration. The rifamycins have similar side-effect profiles, except for rifabutin, which is discussed later. Despite the adverse reactions, the overall incidence of drug discontinuation was 1.9% in a large retrospective study, with discontinuation in over half the cases judged to be unnecessary.[29]

Drug-drug interactions are common with the rifamycins. The HIV integrase inhibitors and the direct-acting antivirals (DAAs) for treatment of hepatitis C (HCV) are recent additions to the interaction list. Coadministration of the rifamycins may lead to a decrease in the plasma concentrations of the integrase inhibitor and HCV DAAs. An excellent review of rifamycin drug interactions and dosing recommendations was done by Baciewicz and colleagues.[30] The 2016 antiretroviral interactions can be found in the latest US Department of Health and Human Services Guidelines.[31]

Gastrointestinal (GI) symptoms from the rifamycins are nausea, vomiting, diarrhea, and abdominal pain. Headache, fever, and pruritus can be seen. Rash may occur early and resolve without discontinuation of the drug. More severe reactions include urticarial and diffuse rash, which may be accompanied by systemic symptoms. A lupus-like syndrome with detection of antinuclear antibodies has been reported with rifampin and rifabutin, often attributed to cytochrome P (CYP) drug interactions, and usually resolves after discontinuation of the drug.[32]

RIFAMPIN

Pharmacokinetics

Rifampin is dosed daily as 600 mg in adults and 10 to 20 mg/kg in children. The drug undergoes rapid and complete absorption, improved if taken on an empty stomach. Rifampin is the only rifamycin available in an intravenous formulation. It is widely distributed to most body tissues and fluids, including the cerebrospinal fluid (CSF), where doses of 20 mg/kg in children achieve mean CSF levels of 2 μg/mL.[33] Concentrations in bone are similar to or exceed serum concentrations,[34] and the drug crosses the placenta and enters breast milk. Rifampin undergoes an enterohepatic circulation and deacetylation with rapid elimination in bile. Urinary excretion is 13% to 24% with no dose adjustment necessary in renal insufficiency. Dose adjustment is recommended with severe hepatic insufficiency. The rifampin substrate is red, and the high lipophilic properties and wide distribution often turn body fluids, such as urine, tears, sweat, and feces, and contact lenses per se, red-orange.

Rifampin has the greatest effect on induction of hepatic and intestinal enzymes, especially CYP3A. Induction is responsible for the majority of rifampin drug interactions. The maximal effect occurs approximately 1 week after initiation of therapy. The serum concentration of rifampin is rarely affected because the metabolism is not mediated by CYP. Most drug interactions result from induction of metabolic enzymes, especially CYP3A4, in the liver and small intestine. Rifampin and the other rifamycins have numerous interactions, outlined in Table 27.2, that usually result in a decrease in the AUC or maximum drug concentration (C_{max}) of the concomitant drug, requiring dose adjustments. Rifampin also induces CYP1A2, CYP2C, and CYP2D6 and some drug transporter proteins, including P-glycoprotein, a transmembrane protein that acts as a cellular efflux pump. The HIV protease inhibitors are especially problematic when used with rifampin, with significant decreases in AUC.

Adverse Reactions

Allergic reactions to rifampin range from 0.01% to 0.26% and often occur in patients previously treated or with intermittent dosing. Type I hypersensitivity reactions, mediated by immunoglobulin (Ig)E antibodies, can occur with symptoms ranging from angioedema, bronchospasm, and urticaria to shock. Anaphylaxis can occur within minutes of the dose or be associated with prodromes, such as rash, from prior or intermittent dosing. Patients with HIV infection had poorer outcomes, and antirifampin serum IgE antibodies were detected.[35]

The rifampin-associated flulike syndrome consists of fever, chills, malaise, myalgias, and headache several hours after dosing and usually resolves within several hours. Flulike symptoms are most commonly seen with intermittent regimens, although HIV-infected patients experience a higher incidence of flulike symptoms with higher daily dosages, which may be due to a direct toxic effect of the drug in this population.[35] The incidence of flulike syndrome escalates with higher doses (900–1200 mg) given weekly and can be as high as 54%.[35] The flulike syndrome usually develops after 3 months of therapy and is rarely associated with thrombocytopenia, hemolysis, and renal failure. The etiology is believed due to circulating IgG or IgM immune complexes that fix complement on endothelial cells or bind on the surface of cytokine-producing cells.[35] After a change to weekly dosing or intermittent therapy, a more robust immune response may be seen on rechallenge. Switching to daily rifampin therapy usually results in disappearance of all symptoms. Thrombocytopenia and hemolysis are also likely immune mediated with formation of antigen-antibody complexes that bind to erythrocytes and platelets. Recent reports highlight newly observed adverse reactions, including recurrent disseminated intravascular coagulation, with intermittent and continuous dosing.[36] Acute renal failure from rifampin usually occurs with intermittent dosing and presents as acute interstitial nephritis with tubular necrosis. Less common presentations are rapidly progressive glomerulonephritis and light-chain proteinuria with polyclonal κ and λ chains. Most cases are secondary to adhesion of antirifampin antibodies to the renal tubular epithelium with subsequent complement binding. Recovery is usually complete after stopping the drug.[37] Hemolysis and thrombocytopenia may occur in conjunction with renal toxicity.

TABLE 27.2 Major Rifamycin Drug Interactions

Anticoagulants
Warfarin
Clopidogrel
Dabigatran
Rivaroxaban
Apixaban

Antimicrobial Agents
Atovaquone
Azoles
Caspofungin
CCR5 antagonists[a]
Chloramphenicol
Clarithromycin
Cobicistat
Dapsone
Doxycycline
HCV direct-acting antivirals[d]
HIV integrase inhibitors[a]
HIV NNRTIs[b]
HIV protease inhibitors[c]
Linezolid
Maraviroc
Mefloquine
Moxifloxacin
Praziquantel
Tenofovir alafenamide

Cardiovascular Drugs
β-Blockers
Calcium channel blockers
Digoxin
Disopyramide
Endothelin receptor antagonists and agonists[f]
Losartan
Quinidine
Tocainide

Immunosuppressive Agents
Cyclosporine
Mycophenolate mofetil
Sirolimus
Tacrolimus

Endocrine Agents
Biguanide
Glucocorticoids
HMG-CoA reductase inhibitors
Levothyroxine
Oral contraceptives
Sulfonylureas
Tamoxifen

Neuropsychiatric and Neurologic Agents
Benzodiazepines
Bupropion
Citalopram
Clozapine
Haloperidol
Lamotrigine
Nortriptyline
Phenytoin
Risperidone

Opiates/Analgesics
Buprenorphine[e]
Cyclooxygenase inhibitors
Fentanyl transdermal
Ketamine
Methadone
Oxycodone
Propofol

Other Drugs
Cabozantinib
Cediranib
Deferasirox
Imatinib
Mirodenafil
Omeprazole
Roflumilast
Theophylline
Vandetanib

[a]Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services; 2016. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf (tables 18, 19a, 19b, 19d, and 19e).
[b]Efavirenz, nevirapine, etravirine, rilpivirine.
[c]Rifabutin preferred for use with HIV protease inhibitors in decreased doses.
[d]Includes N53/4A protease inhibitors, nucleoside and nucleotide NS5B inhibitors, N5SA inhibitors, and nonnucleoside NS5B polymerase inhibitors.
[e]Reported with rifampin only.
[f]Includes bosentan, ambrisentan, and atrasentan.
HCV, Hepatitis C virus; *HIV,* human immunodeficiency virus; *HMG-CoA,* 3-hydroxy-3-methylglutaryl coenzyme A; *NNRTIs,* nonnucleoside reverse-transcriptase inhibitors.
Modified with permission from Baciewicz AM, Chrisman CR, Finch CK, et al. Update on rifampin, rifabutin, and rifapentine drug interactions. Curr Med Res Opin. *2013;29:1–12.*

Rifampin can cause changes in liver function, but serious injury is usually confined to patients with underlying liver disease due to alcohol, viral hepatitis, and other hepatotoxins, such as isoniazid, which often is coprescribed. Long-term therapy is associated with minor, transient elevations in serum aminotransferase levels in 10% of patients. Liver injury from rifampin is primarily cholestatic. In most patients serum bilirubin levels increase during the first few days of therapy and normalize spontaneously. Within several weeks of starting rifampin in patients with underlying liver disease, there may be a significant increase in direct and total bilirubin without evidence of liver injury. The bilirubin elevation is attributed to inhibition of bilirubin excretion and may be related to genetic defects in multidrug-resistance protein 2 (MRP2), the major bilirubin glucuronide transporter in hepatocytes. There are many reports of hepatitis and jaundice in patients with tuberculosis treated with rifampin, isoniazid, and pyrazinamide. However, the actual incidence of hepatotoxicity from rifampin is 1.1%.[38] When rifampin is combined with isoniazid, there is an increased incidence of hepatotoxicity. One explanation is an additive hepatotoxic effect; however, a synergistic effect is favored. The induction of isoniazid hydrolase by rifampin is believed to lead to increased production of hydrazine, which can be activated by rifampin-induced CYP to hepatotoxins. This is seen more frequently in slow acetylators with the *N*-acetyltransferase 2 genotype.[39] The recommendation is to discontinue all antituberculous medications if hepatotoxicity occurs. If the patient is severely ill, an option is to start three new medications (often a fluoroquinolone, streptomycin, and ethambutol) until liver function normalizes, at which time the original drugs are introduced one at a time, usually starting with rifampin.[40]

Severe hepatitis has been reported in 1.2% to 13% of patients treated with rifampin and pyrazinamide for latent tuberculosis infection, leading to updated recommendations regarding use and monitoring of this combination.[41] A single nucleotide polymorphism in the gene encoding the organic anion transporting polypeptide 1B1, which plays a role in transporting bile acids and rifampin, has recently been identified with the *15 haplotype, a predisposing factor to rifampin-induced liver injury.[42]

Antimicrobial Activity

Although commonly associated with treatment of tuberculosis, the rifamycins exhibit broad antibacterial activity. Rifampin is most potent against gram-positive bacteria, including *Staphylococcus aureus,* coagulase-negative staphylococci, *Streptococcus pyogenes, Streptococcus pneumoniae, Streptococcus viridans, C. difficile,* and *Listeria monocytogenes.* Gram-negative bacterial coverage includes *Haemophilus influenzae, Neisseria meningitidis,* and *Helicobacter pylori.*[43] Rifampin has synergistic activity with other agents against MDR bacteria, especially *P. aeruginosa* and *Acinetobacter baumannii.* In addition to potent activity against *M. tuberculosis,* rifamycins have activity against nontuberculous mycobacteria, including *M. avium-intracellulare* complex (MAC), *M. kansasii,* and *M. marinum.*[44] Rifampin has activity against intracellular pathogens, including *Chlamydia, Legionella, Brucella,* and *Bartonella* spp.[45,46] The MICs of rifampin for representative organisms are shown in Table 27.3.

RIFABUTIN

Pharmacokinetics

Rifabutin is a spiropiperidyl rifamycin analogue with a slower and larger volume of distribution compared with rifampin and a long terminal half-life, permitting once-daily dosing. Food does not affect the AUC but increases the peak concentration. Rifabutin is more lipid soluble than rifampin and extensively distributed throughout the body, with a CSF concentration one half that of serum after a 450-mg dose.[47] The extensive redistribution of rifabutin in tissues leads to minimum plasma concentrations of 10% to 15% of the peak 24 hours after an oral dose. The two active metabolites are 25-*O*-desacetyl rifabutin and 31-OH-rifabutin. Fifty-three percent is excreted in urine as the primary active C-25 desacetyl metabolite, and dose reduction is recommended for a creatinine clearance less than 30 mL/min.[48] Rifabutin should be administered with caution in patients with severe hepatic disease. The ability to induce metabolic enzymes, especially CYP3A4, is least with rifabutin,[27] and cytochrome P450 (CYP) 3A is the major isozyme involved in the hydroxylation of rifabutin.[27] When used with HIV protease inhibitors, this leads to an increase in the rifabutin level, and decreased doses are required.[27] Rifabutin concentrations can be significantly increased, with the potential for complex bidirectional interactions with concomitant administration of other medications, particularly in patients taking antiretrovirals. Major interactions are seen with fluconazole, ketoconazole, clarithromycin, and the HIV protease and integrase inhibitors.[31]

Adverse Reactions

Rifabutin has a unique toxicity profile, including uveitis, leukopenia, and polyarthralgias. In a study of elderly patients with pulmonary MAC treated with 600 mg of rifabutin with ethambutol, streptomycin, and a macrolide, adverse events were seen in 77%, requiring dose adjustment in over half.[49] The most common event was leukopenia, followed by GI symptoms, abnormal liver enzymes, a diffuse polyarthralgia syndrome in 19%, and anterior uveitis in 8%. Uveitis was seen in patients receiving clarithromycin and is likely secondary to a drug interaction that raises rifabutin serum concentrations. Uveitis may mimic an infectious endophthalmitis with the presence of a hypopyon and has been reported in both HIV-infected and noninfected patients with pulmonary MAC infection with the 600-mg dose. Cases typically occur after several months of therapy, predominantly involve the anterior chamber, and

TABLE 27.3 Antimicrobial Activity of Rifampin

SPECIES	MIC[a] RANGE (μg/mL)	MIC_{90} (μg/mL)	MIC_{50} (μg/mL)
Staphylococcus aureus	0.008–0.015	0.015	0.015
Staphylococcus epidermidis	0.004–0.015	0.015	0.015
Group A streptococci	0.03–0.12	0.12	0.12
Group B streptococci	0.25–1	1	1
Streptococcus pneumoniae	0.06–32	0.12	0.12
Streptococcus viridans	0.03–8	0.06	0.12
Enterococcus faecalis	1–8	2	8
Haemophilus influenzae	0.5–64	1	1
Neisseria meningitidis	0.015–1	0.03	0.5
Listeria monocytogenes	≤0.12–0.25	≤0.12	0.25
Escherichia coli	8–16	8	16
Klebsiella pneumoniae	16–32	32	32
Proteus mirabilis	4–8	4	8
Enterobacter cloacae	16–64	64	64
Acinetobacter spp.	4–16	8	8
Clostridioides difficile (formerly *Clostridium difficile*)	0.10–>100	1.56	>100
Pseudomonas aeruginosa	32–>64	32	64
Mycobacterium tuberculosis	0.06–0.25	0.25	0.25
Mycobacterium avium-intracellulare	0.78–>100	6.25	50
Mycobacterium kansasii	0.025–3.13	0.2	3.13
Mycobacterium marinum	0.1–0.39	0.2	0.39
Mycobacterium fortuitum	12.5–100	50	100
Mycobacterium scrofulaceum	0.1–6.25	0.78	6.25
Legionella spp.	0.001–0.5	≤0.25[b]	0.125
Bartonella spp.	0.03–0.06	0.12	0.25
Chlamydia spp.	0.0075–0.03	0.015	0.031
Brucella spp.	0.5–1	2	4
Helicobacter pylori	0.125–0.75	0.125	0.125

[a]MIC ≤2 μg/mL is considered susceptible.
[b]Geometric mean MIC.
MIC, Minimal inhibitory concentration; *MIC_{50},* minimal inhibitory concentration for 50% of isolates; *MIC_{90},* minimal inhibitory concentration for 90% of isolates.

respond to corticosteroids and cycloplegics. The etiology is believed to be an immunologic reaction to cell wall proteins of dead organisms, although a direct toxic effect of rifabutin has been suggested.[50] Uveitis has been seen in HIV-infected patients receiving 300-mg dosing for prophylaxis as late as 14 months after initiation,[51] often in combination with fluconazole or azithromycin or both. The flulike syndrome has been reported with intermittent therapy. Hepatitis is more likely from concomitant use of hepatotoxins.

Antimicrobial Activity

Rifabutin is active against *M. tuberculosis* and *M. avium complex*.

RIFAPENTINE

Pharmacokinetics

Rifapentine, a cyclopentyl rifamycin, is a more potent and longer-acting rifamycin.[52] Food increases the absorption, and a high-fat meal results in a 50% increase in serum concentration and is recommended to be taken with a meal. Rifapentine achieves high intracellular concentrations, exceeding that of rifampin. CSF concentrations are undetectable.[52] Less than 10% of rifapentine is excreted in urine unchanged.[27] Rifapentine does not induce its own metabolism. The primary route of metabolism, mediated by an esterase enzyme, is nonoxidative to the 25-desacetyl metabolite. Rifapentine also induces CYP3A4 and CYP2C and can interact with the same drugs as rifampin. The degree of interaction correlates with the dose and frequency of administration. Rifapentine is not recommended for use in combination with the HIV protease inhibitors and may be associated with decreased absorption.[27]

Adverse Effects

Rifapentine is better tolerated than rifampin, likely due to higher protein binding. Once-weekly dosing has a lower incidence of the flulike syndrome[52]; however, cases with hemolysis and renal failure have been reported. The incidence of hepatotoxicity is similar to rifampin. Hyperuricemia has been reported with rifapentine in up to 21.3% of patients.[52]

Antimicrobial Activity

Rifapentine is active against *M. tuberculosis* only.

RIFAXIMIN

Pharmacokinetics

Rifaximin has an additional ring linking the C-3 and C-4 positions. Absorption after an oral dose is minimal secondary to low intestinal permeability and water solubility. Less than 0.01% of the dose is detectable in plasma, and 97% is recovered unchanged in the stool. Fecal concentrations were 8000 μg/mL in one study.[53] The AUC increases 10 to 20 times, and the C_{max} increases 6 to 10 times in patients with cirrhosis.[54] Rifaximin can induce cytochrome P450 3A4 but has no significant drug interactions secondary to extremely low systemic concentrations. Although caution is recommended when using rifaximin in patients with Child-Pugh class C cirrhosis, no dosage adjustments are required.

Adverse Effects

Rifaximin is associated with few adverse effects. An unusual case of rifaximin-associated neutropenia was described in a patient receiving 1200 mg daily with severe ulcerative colitis and a transjugular intrahepatic portosystemic shunt, suggesting increased absorption and decreased metabolism.[55]

Antimicrobial Activity

Rifaximin is bactericidal against enterotoxigenic and enteroaggregative strains of *E. coli, Salmonella, Shigella,* and *Campylobacter* and *C. difficile*. Antiprotozoal activity includes *Cryptosporidium parvum* and *Blastocystis hominis*.[56] Use in inflammatory bowel diseases, hepatic encephalopathy, and effects on the microbiome are discussed as follows.

IMMUNE-MODULATING EFFECTS OF RIFAMPIN

In addition to bactericidal activity, rifampin has immune-modulating properties. An in vitro study showed inhibition of interleukin (IL)-1β and tumor necrosis factor-α (TNF-α), with increases in IL-6 and IL-10 when rifampin was added to stimulated human monocytes.[57] Incubation of rifampin with proinflammatory cytokines in alveolar cells and human epithelial liver cells (HepG2) led to increased production of nitric oxide and increases in IL-8, interferon-γ (IFN-γ), and IL-β1.[58] Cytoprotective effects of rifampin have also been observed. Pretreatment of human lung carcinoma cells with rifampin before infection with *A. baumannii* significantly decreased the rate of cell death by reducing oxidative stress and release of TNF-α and IL-6, in the absence of bactericidal activity.[59] Pretreatment with rifampin in animal models of *S. pneumoniae* meningitis decreased neuronal loss by decreasing inflammation and free-radical production in CSF.[60,61] Rifampin also decreased TNF-α production and inhibited macrophage apoptosis in *M. tuberculosis* infection.[62] In vivo, patients with tuberculosis who mounted a higher IFN-γ response after 2 months of therapy had higher $AUC_{0–8}$ values to rifampin, which predicted a disease-free outcome. It is unclear whether the higher rifampin concentrations led to a stronger IFN-γ response, but the authors suggest that IFN-γ may be a useful surrogate marker for predicting outcome in tuberculosis.[63]

RIFAMYCINS FOR THE TREATMENT OF TUBERCULOSIS

The treatment of active tuberculosis requires combination chemotherapy to avoid the selection of naturally occurring drug-resistant mutants.

Since the introduction of rifampin 4 decades ago, the rifamycins have been cornerstone agents in the treatment of tuberculosis, particularly when it was shown that rifampin in combination therapy reduced the overall treatment time from 18 to 9 months.[64] In addition, it has been shown that infections caused by rifampin-resistant strains of *M. tuberculosis* require a longer duration of treatment and are associated with higher rates of treatment failure than those caused by drug-susceptible strains.[64]

The current rifamycins used in the treatment of tuberculosis include rifampin, rifapentine, and rifabutin. Rifampin has better penetration into cavitary lung lesions, it has a long track record of safety, it is inexpensive and globally available, and thus it is currently the first-line rifamycin drug for treatment of tuberculosis.[65] Rifampin is bactericidal against *M. tuberculosis*, and among the first-line agents against tuberculosis has the most potent sterilizing activity, which is defined as the ability of a drug to kill persistent and/or metabolically dormant organisms. This may be in part due to its rapid onset of action.[66] International guidelines recommend a maximum daily dose of 600 mg (10 mg/kg) for daily and intermittent treatment. However, these recommendations were based on historical pharmacokinetic,[67,68] toxicity,[69,70] and cost arguments[71] and have largely been refuted by more recent scientific data.[72] Data from in vitro systems and animal models provide compelling evidence that rifampin's activity against *M. tuberculosis* is concentration dependent and correlates best with the quotient of the AUC and the MIC.[72] Using the mouse model, Jayaram and coworkers[73] found that the 10 mg/kg dose of rifampin used in humans falls at the low end of a steep and tall dose-response curve, indicating that increasing doses may produce log linear increases in bactericidal activity. These data are supported by small-scale studies that showed an early bactericidal activity using high doses (20 mg/kg) of rifampin.[74,75] However, studies of early bactericidal activity reflect bactericidal and not necessarily sterilizing activity. Therefore more studies are needed to evaluate the potential of a higher dose of rifampin to further reduce treatment duration to less than 6 months. Evidence of this potential is provided by the study of Kreis and associates,[76] who evaluated a 3-month regimen with daily rifampin (1200 mg), isoniazid (900 mg), and streptomycin (1 g) and achieved near-complete sputum culture negativity after 90 days, without additional toxicity. Unfortunately, this study had several limitations. First, without pyrazinamide, the recurrence rate was 11.4% during the first year after treatment. Second, there was no direct comparison of daily administration of the current standard dose (600 mg) against daily administration of higher doses. In a recent trial 2 weeks of rifampin up to 35 mg/kg were safe and well tolerated.[77] This observation was confirmed by another study showing that a dose of 35 mg/kg rifampin was safe, reduced the time to culture conversion, and could be a promising component of future, shorter regimens.[78]

The primary toxicities attributed to rifampin are discussed in detail in the section on adverse reactions and are usually associated with intermittent dosing and not expected to occur more frequently with increased daily dosing. Transaminitis and increased bilirubin levels after starting treatment do not appear dose related,[79] and hepatoxicity usually occurs with preexisting liver disease or with use of concomitant hepatotoxins.[80] Systemic side effects, such as the "flulike syndrome," are related to intermittent treatment rather than to the dose of rifampin.[81] Furthermore, rifampin has been used at higher doses for nonmycobacterial infections, such as brucellosis,[82] staphylococcal infections,[83] and cutaneous leishmaniasis,[84] without reports of increased adverse effects, supporting the idea that the majority of rifampin's adverse effects are idiosyncratic and not dose related.

A recent study has suggested that high-dose rifampin may play a role in infections caused by low-level resistant strains[85] and may help prevent the emergence of drug resistance.[86] Recent data also suggest that regimens containing higher doses of rifampin are safe and could be associated with a survival benefit in patients with severe disease.[87]

In summary, higher doses of rifampin may help reduce the duration of treatment of tuberculosis without a significant increase in adverse events. However, more extensive, dose-ranging, tolerability, and extended bactericidal activity studies of high doses of rifampin are still undergoing, and their results should be expected soon.

Rifapentine, with its more potent in vitro activity (MIC, 0.06 vs. 0.25 μg/mL)[88] and longer serum half-life (11–18 hours vs. 2–4 hours) than rifampin,[27,89] was developed with the goal to provide an option for once-weekly therapy for tuberculosis.[90] The approved US Food and Drug Administration (FDA) dose for the treatment of active tuberculosis is 600 mg administered once or twice weekly in combination with other antimycobacterial drugs. However, it has seen little clinical use because once-weekly rifapentine-isoniazid during the continuation phase of treatment was associated with greater drug-susceptible relapse among HIV-negative patients with lung cavitation[91] and a significant incidence of acquired rifamycin monoresistance among HIV-positive patients. Based on this study, rifapentine intermittent therapy should not be used for treatment of tuberculosis in HIV-infected patients[92] A recent randomized study compared standard continuation phase therapy with regimens containing rifapentine and moxifloxacin in place of isoniazid and found similar rates of efficacy and no acquired drug resistance; however, larger studies are needed to assess the risk of rifamycin resistance.[93]

Recent work using the mouse model of antituberculosis chemotherapy has shown that regimens containing rifapentine administered 5 days per week can achieve durable cure without relapse after 3 months. Their results also indicated that rifapentine is four times more potent than rifampin in the murine model.[94] These encouraging results prompted a randomized, multicenter, phase II clinical trial conducted by the Tuberculosis Trials Consortium (TBTC study 29) to determine the safety, tolerability, and antimicrobial activity of a regimen in which rifampin 10 mg/kg was replaced by rifapentine 10 mg/kg administered 5 days per week during the first 8 weeks (intensive phase) of combination treatment of pulmonary tuberculosis.[95] Their results showed that the rifapentine regimen was safe but not significantly more active than a standard rifampin regimen by the surrogate end point of culture status at completion of the intensive phase. However, one limitation of this study was administration without food, which has been shown to increase the C_{max} of rifampin[96] but decreases rifapentine bioavailability.[97]

The optimal rifapentine dose and schedule for treating tuberculosis in humans have not been established, but the mouse model suggests that the bactericidal and sterilizing activity of rifapentine increases virtually without plateau up to doses of 160 mg/kg and that daily dosing improves outcomes. Dooley and colleagues[98] conducted a rifapentine dose-escalation study in healthy adults and showed that daily rifapentine doses of up to 20 mg/kg administered with food were safe and produced rifapentine exposures exceeding those in mice receiving 10 mg/kg. Their results provided safety and tolerability data to support the need of future clinical trials of rifapentine at high daily doses for treatment of tuberculosis. A recent trial showed that high rifapentine exposures were associated with high levels of sputum sterilization at completion of intensive phase, suggesting that regimens that deliver high rifapentine exposures can shorten duration of treatment to less than 6 months.[99]

Rifabutin has a much longer half-life than rifampin (35 hours vs. 2–4 hours). In clinical trials, the efficacy of rifabutin administered daily or intermittently has been shown to be similar to that of rifampin.[100,101] Rifabutin's primary advantage in the treatment of tuberculosis is its reduced induction of hepatic metabolism (cytochrome P450 system)[102] and its usefulness in patients with tuberculosis and HIV coinfection who are also receiving antiretroviral therapy (ART). Rifampin markedly decreases serum concentrations of the HIV type 1 (HIV-1) protease inhibitors[103] and has substantial effects on concentrations of nonnucleoside reverse-transcriptase inhibitors (NNRTIs).[104] Therefore rifabutin-based therapy was recommended by the CDC as a way of avoiding serious drug-drug interactions and allowing use of rifamycins during treatment of tuberculosis in HIV-coinfected patients.[105] However, Benator and colleagues[91] raised the question of whether the use of rifabutin was a cause of acquired rifampin resistance in HIV-infected patients who had low $CD4^+$ T-lymphocyte counts. Additional studies suggest that low concentrations of the rifamycin component related to intermittent dosing, rather than the specific agent, determine the risk for acquired rifamycin resistance.[106] Recently, Naiker and colleagues[107] evaluated the pharmacokinetics of different doses of rifabutin in African HIV-infected patients with tuberculosis and on lopinavir/ritonavir-based ART regimen. They demonstrated that a daily dose of 150 mg of rifabutin in

combination with lopinavir/ritonavir safely maintained rifabutin plasma concentrations.[107]

The most recent guidelines for the treatment of active tuberculosis in HIV-coinfected patients recommend that, despite pharmacokinetic drug interactions, a rifamycin should be included in regimens for patients receiving antiretroviral agents, with dosage adjustment if necessary. If a protease inhibitor–based regimen is used, rifabutin is the preferred rifamycin, but the dose should be decreased from 300 mg daily to 150 mg daily if given with unboosted protease inhibitor or to 150 mg every other day if given with ritonavir. If efavirenz-based regimen is used, the rifabutin dose should be increased from 300 mg to 450 mg daily, and the dose of efavirenz should remain unchanged.[31] However, rifampin is the rifamycin of choice for patients taking efavirenz-based ART, because efavirenz reduces the concentration of coadministered rifabutin.

Recent data examined the tolerability of rifabutin when coadministered with other medications affected by rifampin's induction of cytochrome P450, such as methadone and coumadin, and in patients who previously had a rifampin-related adverse effect. Their results showed that rifabutin is well tolerated and has limited the need for dosing adjustments of other medications. Their results also suggest that rifabutin could be considered as an alternative agent in patients who develop rifampin-related liver injury but that rifabutin should be used with caution in patients with other types of underlying liver disease.[108] Data from tuberculosis-infected transplant patients receiving tacrolimus or cyclosporine also suggest that rifabutin should be used in this population, instead of rifampin, to avoid pharmacologic interactions and achieve a lower risk for acute graft rejection.[109]

RIFAMYCINS FOR TREATMENT OF LATENT TUBERCULOSIS INFECTION

The current standard regimen for the treatment of latent *M. tuberculosis* infection (LTBI) is 9 months of daily isoniazid. Shorter LTBI regimens based on other regimens are of growing interest, given concerns about isoniazid-related hepatoxicity, poor adherence attributed to long-duration isoniazid regimens, and the growing proportion of tuberculosis cases that are resistant to isoniazid in foreign-born persons.

Early experiments in a mouse model demonstrated the potential efficacy of three short-course regimens that included rifampin, with or without companion medications. The results suggested that 2 months of therapy with rifampin with pyrazinamide or 3 months of therapy with rifampin alone were more effective than 6 months of therapy with isoniazid alone.[110] This study prompted a number of clinical trials with three different rifampin-containing regimens. A 2-month regimen of rifampin and pyrazinamide was shown to be as effective as isoniazid.[111,112] Unfortunately, this regimen has been largely abandoned, owing to severe liver toxicity.[113] Results from several randomized trials evaluating the combination of isoniazid and rifampin given for 3 to 4 months have shown an equivalent completion rate, toxicity, and effectiveness as 6 to 9 months of isoniazid.[114,115] A 4-month daily rifampin regimen has been recommended by the American Thoracic Society (ATS) as an alternative regimen in the treatment of LTBI after few studies have consistently found significantly better completion rates and significantly lower serious adverse effects, particularly hepatotoxicity, when compared with 9 months of isoniazid.[116]

With the use of animal models, it was shown that once-weekly isoniazid plus rifapentine combination therapy for 18 weeks was an effective preventive regimen with sterilizing potency and bacillary load reduction comparable with daily isoniazid therapy for 18 weeks.[117,118] These promising results were followed by a large-scale randomized clinical trial that was recently completed and published. Sterling and colleagues[119] showed that directly observed, once-weekly therapy with rifapentine plus isoniazid for 3 months was as effective as self-administered daily isoniazid for 9 months, with higher completion rates and lower rates of severe adverse events. This regimen has now been recommended as an equal alternative to the 9-month isoniazid regimen for otherwise healthy patients aged 12 years or older with LTBI.[120] A recent systematic review compared the efficacy and completion rate of different LTBI drug regimens: INH plus rifapentine once weekly for 12 weeks, 3 to 4 months of daily INH and rifampin, 6 and 9 months of daily INH, and 4 months of rifampin alone. The review showed no significant difference between the different groups in efficacy, but regimens of 3 to 4 months duration were more likely to be completed than longer regimens.[121]

RIFAMYCINS FOR NONTUBERCULOUS MYCOBACTERIAL INFECTIONS

Mycobacterium leprae

Rifampin is rapidly bactericidal against *M. leprae,* with bacteriologic success within 3 weeks of starting therapy. Even a single high dose was efficacious in a mouse footpad model.[122] Rifampin should never be used as monotherapy because of rapid development of resistance. Although not FDA approved for leprosy, rifampin is recommended by WHO for every manifestation of disease. Recommendations are a combination therapy of rifampin with dapsone for paucibacillary disease or rifampin with dapsone and clofazimine for multibacillary disease. The recommended duration of therapy is 6 months for patients with paucibacillary disease and 12 months for those with multibacillary disease, although longer treatment might be required in some patients with a high bacterial burden at diagnosis to prevent relapse.[123] Of concern is the emergence of rifampin-resistant strains of *M. leprae* from northern and eastern India, discovered in new cases of leprosy. DNA sequencing showed mutations at previously reported sites in addition to new codon positions, including Ala411 and Gln442, in the *rpoB* gene. The latter mutation leads to upregulation in the messenger RNA expression of the *rpoB* gene, which may lead to overexpression of this gene and other associated genes.[124,125] There is an urgent need to continue monitoring for rifampin resistance in these areas and include new drugs in treatment regimens. The use of rifamycins as chemoprophylaxis against leprosy has been suggested. The overall incidence of leprosy among contacts of patients with newly diagnosed disease can be reduced by a single dose of rifampin. Whether to use this approach more widely is under discussion, and a longer observation time is necessary to show whether the effect of rifampin prophylaxis will be sustained over long periods of time.[126]

Mycobacterium avium-intracellulare Complex

A variety of compounds and their combinations have been reported to be effective against MAC, the rifamycins (particularly rifampin and rifabutin) among them.[127] Medical treatment of MAC pulmonary disease has yielded inconsistent results and limited cure rates. Major limitations for effective therapy include the lower bactericidal activity of the rifamycins against MAC than against *M. tuberculosis,*[88] the absence of correlation between in vitro susceptibility for rifampin, clinical response for MAC disease, and the markedly decreased immunologic status of the host.[128] The limited success of current treatment regimens is also caused by an incomplete understanding of the relationships between the doses of the drugs used, their pharmacokinetics, and the eventual in vivo treatment outcome. The interactions between rifamycins and macrolides are likely most important, because these drugs are cornerstones of recommended treatment regimens for MAC lung disease. The ATS and the Infectious Diseases Society of America (IDSA) currently recommend for most patients with nodular/bronchiectatic disease a three-times-weekly regimen of clarithromycin (1000 mg) or azithromycin (500 mg), rifampin (600 mg), and ethambutol (25 mg/kg). For patients with fibrocavitary MAC lung disease or severe nodular/bronchiectatic disease, a daily regimen of clarithromycin (500–1000 mg) or azithromycin (250 mg), rifampin (600 mg) or rifabutin (150–300 mg), and ethambutol (15 mg/kg), with consideration of three times per week amikacin or streptomycin early in therapy, is recommended.[129] A recent study showed that currently recommended regimens for MAC lung disease yield important pharmacologic interactions and low concentrations of key drugs.[130] Trials of new drugs and new strategies are needed.

Disseminated MAC infection occurs largely in patients with HIV infection, especially with $CD4^+$ cells at less than 50 cells/mm.[4] The role of rifamycins in the treatment of disseminated MAC disease is unclear. If a rifamycin is used as a second-line agent, most experts would use rifabutin, which is more potent than rifampin against MAC, has a postantibiotic effect of 26 hours at the MIC, and has activity against some strains that are resistant to rifampin. Rifabutin accumulates within

phagocytes to a greater extent compared with rifampin[131] and is easier to use with most antiretroviral agents, especially protease inhibitors. A study of 160 patients with the acquired immunodeficiency syndrome (AIDS) and MAC bacteremia compared triple therapy with rifabutin, clarithromycin, and ethambutol to double therapy with clarithromycin with rifabutin or ethambutol. After 12 weeks, the microbiologic response was the same, but patients in the triple-therapy group had increased survival and fewer relapses.[132] Based on this study, some experts recommend the addition of rifabutin as a third drug for disseminated MAC infection in AIDS, especially with a high mycobacterial burden, but with careful monitoring for drug-drug interactions.[133] There is no role for rifabutin therapy in the prophylaxis of MAC due to the added toxicity seen when added to a macrolide.

Mycobacterium kansasii

There have been no randomized trials of treatment of disease caused by *M. kansasii.* However, there are several retrospective and prospective studies of various treatment regimens. Strains of *M. kansasii* often are susceptible to rifampin. With rifampin-containing multidrug regimens, sputum conversion within the first 4 months of treatment was achieved in 100% of the cases, and treatment failures and long-term relapses occur in approximately 1% of the cases when treated for at least 12 months.[134,135] The ATS and IDSA currently recommend a regimen for treating pulmonary *M. kansasii* disease of rifampin (600 mg/day), isoniazid (300 mg/day), and ethambutol (15 mg/kg/day) for a duration that includes 12 months of negative sputum cultures.[129] However, in a recent study a 12-month course of treatment, although effective in most cases, did not cure all patients with *M. kansasii* pulmonary disease. For older patients with debilitating conditions, treatment for longer periods guided by periodic sputum cultures is advisable.[136]

Other Nontuberculous Mycobacteria

The rifamycins show in vitro activity against several other nontuberculous mycobacteria, including *M. marinum, M. xenopi, M. scrofulaceum, M. haemophilum, M. terrae* complex, *M. malmoense, M. szulgai,* and *M. gordonae.* Rifampin is included in the multidrug therapy for infections caused by these nontuberculous mycobacteria. Rapidly growing mycobacteria, such as *M. fortuitum* and *M. chelonae,* are naturally resistant to rifamycins.[43]

RIFAMYCINS FOR NONTUBERCULOUS MYCOBACTERIAL INFECTIONS

Staphylococcal Infections

Rifampin is a logical treatment choice for staphylococcal infections because of its potent bactericidal activity in vitro against both *S. aureus* and coagulase-negative staphylococci (CoNS). The ability of rifampin to sterilize phagocytes containing bacteria was demonstrated by Mandell and colleagues[137] in the 1970s. Rifampin monotherapy was short lived, due to the rapid emergence of resistance, especially with high bacterial burdens seen in abscesses and endocarditis, resulting in combination regimens containing rifampin.

In vitro studies, including time kill and checkerboard studies, were inconsistent when rifampin was added to β-lactams, vancomycin, quinolones, linezolid, and daptomycin and did not correlate with in vivo results. When added to bactericidal antibiotics there was decreased or unchanged killing, whereas if added to a bacteriostatic antibiotic there was some increased bactericidal activity.[3] The rabbit model of *S. aureus* endocarditis[138] provided the first correlation to human infection. The combination of penicillin with rifampin was less effective than penicillin with gentamicin and led to emergence of rifampin-resistant strains.[138] In the mouse model of methicillin-sensitive *S. aureus* (MSSA) endocarditis, rifampin with nafcillin resulted in an improved survival rate of 77% without selection of resistance.[139] Animal studies of methicillin-resistant *S. aureus* (MRSA) bacteremia and endocarditis yielded variable results. Only daptomycin and linezolid were effective in animal models of MSSA and MRSA endocarditis in reducing colony-forming units in vegetations and septic pulmonary emboli, respectively.[140] In the 1960s there were reports of successful outcomes when rifampin was used in combination for patients with MSSA and MRSA bacteremia and native valve endocarditis (NVE).[3] Early retrospective data demonstrated emergence of resistance and treatment failure, leading to the conclusion that addition of rifampin to treat *S. aureus* bacteremia without surgery and/or drainage did not improve outcomes and selected for resistance.[3,141] A clinical study of complicated *S. aureus* infections, including NVE, comparing oxacillin or vancomycin with rifampin, showed no clinical difference and emergence of resistance.[142] Based on multiple studies, the IDSA Clinical Practice Guidelines for MRSA infections and the 2015 American Heart Association guidelines recommend against the addition of rifampin for the treatment of staphylococcal NVE.[143] In a study that addressed the role of rifampin therapy in patients with surgically treated staphylococcal endocarditis, patients given adjunctive rifampin for 3 or more days did not have a reoperation-free or survival benefit, suggesting that surgery significantly reduces or eliminates biofilm formation. Based on this study the authors do not recommend rifampin use in surgically treated staphylococcal endocarditis.[144]

A multicenter retrospective study of 357 patients with MSSA bacteremia associated with a deep focus of infection (including endocarditis, pneumonia, septic arthritis, osteomyelitis [OM], abscess, and foreign-body infection) demonstrated that rifampin therapy started within 7 days and continued for at least 14 days from the onset of bacteremia reduced the risk of a fatal outcome by one-third. The positive prognostic impact of adjunctive rifampin in this study merits additional investigation.[145] Rifampin in combination with other antimicrobials has been studied in *S. epidermidis* NVE. A rabbit model study of methicillin-resistant *S. epidermidis* endocarditis found increased sterilization rates with rifampin-gentamicin-vancomycin and ciprofloxacin plus rifampin.[146] Human data, however, do not support the routine use of rifampin in NVE caused by CoNS. One exception is *Staphylococcus lugdunensis,* a virulent biofilm-producing species that causes fulminant NVE, pacemaker lead endocarditis, and bone and joint infections, and is associated with a high mortality.[147] Combination therapy may be indicated for bactericidal effects, and rifampin has been used successfully in *S. lugdunensis* infections.[147]

Staphylococcal Biofilms: Foreign-Body Infections and the Role of Rifampin

The ability of staphylococci to produce biofilm significantly impacts chronicity of infections, particularly those with indwelling devices. Biofilm is a community of bacterial cells encased within a polymeric matrix produced by the organisms that adhere to a living or foreign body.[148] Within biofilms organisms exist in distinct populations, in different stages of growth, and exhibit heterogeneous gene expression. Antimicrobial resistance occurs by decreased penetration and tolerance induced by the anoxic environment and nutrient depletion.[149] Rifampin in vitro is effective against staphylococci in various stages of growth, including metabolically dormant bacteria, penetrates *S. epidermidis* biofilm, and can prevent biofilm formation within minutes. The lipid solubility of rifampin, activity within the acidic environment within some biofilms, and accumulation within neutrophils facilitate the activity of rifampin,[150] which is commonly used in combination regimens when biofilms are known or presumed to be present.

In vitro the addition of rifampin to *S. epidermidis* and MRSA biofilm infections improved the susceptibility to other antibiotics and decreased the adherence of bacteria to the foreign material.[151] Rifampin with linezolid and daptomycin in animal models of foreign-body infection showed higher activity against planktonic bacteria when rifampin was used.[152,153] When used with daptomycin, tigecycline, and linezolid against MRSA biofilms in catheter lock solutions, rifampin combinations were better at eradicating biofilm compared with vancomycin and linezolid alone.[154] New delivery systems of rifampin, including polymethylmethacrylate beads[155] and lipid-based nanoparticles,[156] show promise in vitro in reducing biomass-established biofilms and decreasing viability of intracellular bacteria.

In vivo studies and case reports have used combinations of rifampin with vancomycin, β-lactams, and aminoglycosides for the treatment of *S. epidermidis* prosthetic valve endocarditis (PVE). An early retrospective study of 23 patients with methicillin-resistant *S. epidermidis* PVE found a cure rate in 87% of patients treated with vancomycin with rifampin (900–1200 mg/day) or with rifampin and an aminoglycoside. Only 38%

of those receiving a β-lactam with rifampin, with or without an aminoglycoside, were cured. The lower response in the patients treated with β-lactams was attributed to heteroresistance within the *S. epidermidis* population.[157] This study and multiple case reports led to inclusion of rifampin as part of a triple therapeutic regimen for CoNS PVE with vancomycin, rifampin, and gentamicin for 2 weeks, followed by vancomycin and rifampin for at least 4 weeks. These recommendations were expanded to include *S. aureus* PVE, for which vancomycin plus rifampin (300 mg every 8 hours) for at least 6 weeks, with gentamicin for the first 2 weeks, is recommended.[158]

Vancomycin-Intermediate and Vancomycin-Resistant *Staphylococcus aureus* and Rifampin

Since the emergence of vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) strains, alternative antibiotics have been studied in vitro. Rifampin was active against 92% of VRSA isolates but only 51% of VISA isolates in one study.[159] A possible explanation may be found in another study that identified five *rpoB* mutations in 71% of VISA strains.[160] Among these strains, 55% were resistant to rifampin, supporting a possible link between resistance to vancomycin and rifampin exposure in *S. aureus.* In 29% of VISA strains there was no *rpoB* mutation, suggesting a different resistance mechanism. When rifampin-resistant mutants from nine clinical MRSA isolates were tested, more than 95% had decreased vancomycin susceptibilities. The *rpoB* mutations were observed in 31% of rifampin-susceptible VISA strains, raising the possibility that selection of resistance in these strains occurred by vancomycin and/or other antibiotics.[160]

Prosthetic Joint Infections

Most prosthetic joint infections (PJI) are caused by staphylococci and are a leading cause of morbidity. PJI usually require explantation of the device, prolonged antibiotic therapy, and reimplantation of a new device for cure. Rifampin has been shown to penetrate biofilm on the surface of the hardware. For patients who are not candidates for a two-stage procedure, débridement, antibiotics, and implant retention (DAIR) is used. Clinical outcomes vary with different species. In a study of 163 patients with staphylococcal orthopedic implant infections and different procedures, cure was achieved in 57% of MRSA, 72% of MSSA, and 82% of CoNS infections. Rifampin was used in combination with other antibiotics in 45% of MRSA, 55% of MSSA, and 64% of CoNS infections and did not influence cure. Infection with MRSA and an infected arthroplasty were factors inversely associated with cure.[161]

A 3- to 6-month regimen of rifampin with ciprofloxacin was evaluated in patients with PJI after débridement and a 2-week course of parenteral antibiotics. All patients in the rifampin-containing group who completed the study were cured.[162] The efficacy of a rifampin-based regimen with DAIR in staphylococcal PJI, according to practice guidelines with an oral regimen of rifampin (900 mg/day) and levofloxacin (750 mg/day), was compared with a historical cohort with and without rifampin. Patients treated according to guidelines in the prospective cohort had a lower failure rate (7%) compared with the historical rifampin and nonrifampin groups (32% and 37%, respectively).[163] In a retrospective series, 77% of patients with PJI due to MRSA treated with rifampin and fusidic acid were infection free at 2 years.[164] Treatment failure was associated with MRSA infection, a single or four or more débridements, and fewer than 90 days of antibiotics. The incidence of rifampin resistance was 7%. The IDSA recommendations for MRSA PJI with DAIR are parenteral therapy combined with rifampin for 2 weeks followed by a fluoroquinolone with rifampin for 3 months for hip prostheses and for 6 months for knee prostheses.[158] A small study of staphylococcal PJI managed with DAIR randomized patients to an 8-week course of levofloxacin plus rifampin versus the IDSA-recommended courses. The short course was noninferior to standard courses with hip prostheses, with inconclusive results for knee prostheses.[165] Additional studies are needed before shorter courses can be recommended. *Propionibacterium acnes* produces biofilm and causes PJI and other foreign-body infections, including ventriculoperitoneal shunts and PVE. In a guinea pig model of *P. acnes* biofilm, rifampin showed the highest activity in biofilm (MIC, 0.007 μg/mL). Rifampin with daptomycin had the highest in vivo success rate of 63% without detection of resistance.[166] In a review of 50 patients with *P. acnes* PJI treated with DAIR or one- or two-stage exchange arthroplasty or both, 35 patients received long-term parenteral and oral therapy with rifampin with either cefazolin or clindamycin. The overall cure rate was 92%; analysis by antibiotic regimen was not reported.[167]

Osteomyelitis

Chronic staphylococcal OM is associated with multiple relapses, repeated débridements, and long treatment courses. In vitro models demonstrate the ability of *S. aureus* to invade osteoblasts. The bacteria remain active for lengthy periods (up to decades) and recruit phagocytes, resulting in cytokine expression that contributes to chronic inflammation.[168] Therapeutic levels of rifampin are measurable 12 hours after administration in cancellous bone,[34] and rifampin eradicates slow-growing staphylococci at the chronic phase of OM. In animal models of chronic staphylococcal OM, rifampin is synergistic with other antibiotics.[169,170] In humans débridement followed by parenteral and oral antibiotics, including β-lactams, linezolid, clindamycin, and trimethoprim-sulfamethoxazole (TMP-SMX), is recommended for staphylococcal bone and joint infections.[158,171,172] In a retrospective study of 100 patients with staphylococcal deep sternal wound infection, a rifampin-containing regimen was the only factor associated with a decrease in failure rate.[173] For MRSA OM, many experts recommend the addition of an extended course of an oral rifampin-based combination with either TMP-SMX, a quinolone, clindamycin, and either doxycycline or minocycline, based on susceptibilities.[158] In a recent review of chronic OM, the authors recommend adding rifampin for all patients who can tolerate it.[174] In a murine model of *S. aureus* implant-associated OM, rifampin with vancomycin or linezolid resulted in a greater reduction in bacterial load. However, even rifampin-containing regimens were ineffective in eradicating infections when biofilms form on the implant surface.[175]

Central Nervous System Infections

Rifampin has good central nervous system (CNS) penetration and activity against many meningeal pathogens. Rifampin has been added to vancomycin for cephalosporin-resistant strains of *S. pneumoniae* and when dexamethasone is used with vancomycin.[176,177] A recent study showed that pretreatment with one dose of rifampin 30 minutes before ceftriaxone reduced CSF inflammatory markers in children with bacterial meningitis. The rates of neurologic sequelae were reduced at 3 months; the difference was not statistically significant, possibly due to the small sample size.[178] This observation may be clinically important, and thus confirmatory studies are needed. For MRSA meningitis, some experts recommend addition of rifampin. Rifampin with vancomycin is also recommended for the treatment of staphylococcal CNS shunt infections, especially when the shunt cannot be removed.[176,179]

Infections Caused by Other Bacteria

Streptococcus pneumoniae

Two studies of penicillin-resistant *S. pneumoniae* (PRSP) meningitis in the rabbit model found ceftriaxone with rifampin to be equivalent to ceftriaxone plus vancomycin.[180,181] Other animal studies showed poorer outcomes with rifampin. With the increasing incidence of PRSP, the IDSA recommends adding rifampin to a third-generation cephalosporin if resistance is documented and the isolate is rifampin sensitive or if there is an expected delay in clinical and/or bacteriologic response.[176] Emergence of rifampin-resistant isolates has been documented.[182]

Enterococci

Rifampin may be an adjunct therapy for enterococcal infections. When *Enterococcus faecalis* biofilm from hip and knee PJI was grown in microtiter wells or on beads of bone cement treated with multiple antibiotics alone and in combination with rifampin, ciprofloxacin or linezolid with rifampin were most effective in reducing the bacterial count.[181] Rifampin resistance developed when used alone and with ampicillin.[183] Rifampin and tigecycline were effective in a rat ureteral stent model of *Enterococcus faecium* in preventing infection.[184] Another effective combination in an *E. faecalis* mouse wound model is tigecycline with rifampin or daptomycin.[185] Rifampin with either vancomycin or

tigecycline was synergistic and improved survival in a *Galleria mellonella* (wax moth) infection model against strains of vancomycin-resistant *E. faecium*.[186] For serious urinary tract infections caused by MDR *Enterococcus,* aminoglycosides or rifampin are suggested as adjunct therapy.[187]

Legionella

Retrospective studies of rifampin, with a macrolide or quinolone for severe *Legionella pneumophila* pneumonia, showed the combination with erythromycin or pefloxacin to be superior to erythromycin alone. The quinolone alone and in combination with rifampin was the most active regimen.[188] The combination of clarithromycin with rifampin was evaluated in 32 patients with no additional benefit in the combination group and a longer length of stay, possibly due to adverse reactions and drug interactions from rifampin.[189] A literature review concluded that rifampin should be considered only for patients with severe *Legionella* infection or serious comorbid conditions. Caution is advised for drug interactions and other adverse events.[190]

Rhodococcus

Rhodococcus equi, typically a veterinary pathogen, can cause opportunistic infections in immunocompromised patients. Rifampin achieves high intracellular concentrations and is bactericidal against this organism. A combination of two to three antibiotics, including rifampin, vancomycin, a macrolide, quinolones, minocycline, and carbapenems for 6 to 9 months is recommended.[191,192]

Multidrug-Resistant Gram-Negative Bacilli

Rifampin is used in combination with other antibiotics to treat MDR strains of gram-negative bacteria, especially *A. baumannii*, *P. aeruginosa,* and *K. pneumoniae.* With the emergence of carbapenem-resistant (CR) strains, many in vitro studies use rifampin and polymyxin B (PMB) or colistin in combination. This is especially relevant with heteroresistant *A. baumannii,* where in vitro use of colistin with rifampin inhibited growth of colistin-resistant subpopulations and lowered the concentration required to block all single-step mutations.[193,194] In a time-kill study, rifampin and PMB demonstrated bactericidal killing in 42% of CR *A. baumannii* isolates and was the most effective combination tested.[195] An in vitro study of 20 CR isolates of *P. aeruginosa, A. baumannii, K. pneumoniae,* and *E. coli* found bactericidal activity in 90% of isolates using combinations of PMB, doripenem, and rifampin.[196] Rifampin in combination with sulbactam, colistin, and tigecycline, against 25 extensively drug-resistant *A. baumannii* strains, leads to good in vitro activity.[197] In an immunosuppressed mouse model of pneumonia using CR *A. baumannii* isolates with different resistance mechanisms, rifampin-based regimens (with imipenem, colistin, and tigecycline) were effective in clearing bacteremia and improved survival in all strains, but the antibacterial effects of rifampin differed according to the resistance mechanism.[198] Colistin with rifampin was active in vitro against eight strains of CR *K. pneumoniae* producing the New Delhi metallo-β-lactamase,[199] and imipenem with rifampin was effective in vitro against clinical isolates of MDR *P. aeruginosa* with a porin frameshift mutation.[200] A recent review and meta-analysis concluded that colistin and rifampin have significant in vitro synergy in MDR strains of *A. baumannii*.[201] The use of silver nanoparticles (AgNPs) with antibiotics has been studied for CR *A. baumannii* infections. An in vitro and in vivo study, using a mouse peritonitis model, found synergy with AgNPs with either rifampin or PMB against extremely drug-resistant *A. baumannii* patient isolates.[202] If safety in humans is established, this is a potential option for CR *A. baumannii* infections.

Human studies of MDR *A. baumannii* with rifampin and colistin show inconsistent results. This combination was used in 29 patients with pneumonia and bacteremia in isolates susceptible to colistin. Clinical and microbiologic responses were observed in 76% of patients, with an infection-related mortality rate of 21%.[203] A subsequent randomized study of colistin with rifampin versus colistin alone for serious infections caused by extensively drug-resistant *A. baumannii* from patients in intensive care units (ICUs) found that the 30-day mortality was not reduced by addition of rifampin (43% in both groups). Incidence of hepatotoxicity was higher in the rifampin group, but this group had more frequent eradication of the organism from the primary source.[204] A prospective study of colistin versus colistin with rifampin in patients with *A. baumannii* ventilator-associated pneumonia showed a shorter time to microbiologic clearance, more rapid radiologic improvement, and improved mortality in the combination group; however, the results were not statistically significant.[205] In summary, there is insufficient data to support the routine use of rifampin and a polymyxin in patients with serious infections caused by CR gram-negative bacilli, especially *A. baumannii.*

Brucella

The most widely used combination for treatment of brucellosis is doxycycline with either an aminoglycoside or rifampin. Other regimens include rifampin with a quinolone or triple combinations. In a meta-analysis doxycycline and streptomycin had lower relapse and higher response rates than rifampin and doxycycline.[206,207] However, parenteral therapy is problematic in areas of the world where brucellosis is endemic, and quinolones with rifampin were better tolerated than doxycycline-containing regimens in another review.[206] A recent study of patients with brucellosis in Egypt compared a 6-week regimen of doxycycline plus rifampin with a triple regimen of levofloxacin, doxycycline, and rifampin. The clinical response at 6 weeks was nearly equal, but the relapse rate at 6 months was significantly higher with dual therapy (22.6%) versus triple therapy (9.3%). Adverse events were higher with triple therapy but not statistically significant.[208] Larger studies are needed before recommending triple therapy. In addition, in vitro susceptibility testing of 355 *Brucella* spp. with rifampin in Egypt revealed a 19% rate of resistance in 2000 compared with 7% in 1999.[209] The significance of increasing resistance for treatment is unclear at this time. For laboratory and environmental exposures the recommended prophylaxis is a 3-week course of doxycycline and rifampin.[210]

Bartonella

Rifampin has potent in vitro activity against *Bartonella henselae* (MIC, 0.03–0.06 μg/mL), the agent of cat-scratch disease. Azithromycin is first-line therapy for extensive lymphadenopathy; doxycycline with rifampin is an alternative.[211] For complicated disease (retinitis, encephalitis, and hepatosplenic), doxycycline and rifampin is recommended in adults for 4 to 6 weeks and rifampin with azithromycin or TMP-SMZ for children.[211] *B. henselae* also causes endocarditis and bacillary angiomatosis in HIV-infected persons. Bacillary angiomatosis is usually treated with long courses of erythromycin or doxycycline. However, combination therapy with rifampin and either erythromycin or doxycycline is recommended for immunocompromised patients with life-threatening *Bartonella* infection, and doxycycline with rifampin is preferred for CNS disease.[211] *Bartonella quintana,* the etiologic agent of trench fever, is usually treated with doxycycline. However, in areas of the world such as Thailand, where doxycycline is less active, rifampin is more effective.[212]

Fungal Infections

Based on early evidence of synergistic activity of amphotericin B (AMB) with rifampin against fungi, Medoff[213] demonstrated synergy in vitro with this combination against *Histoplasma capsulatum, Aspergillus* spp., and *Saccharomyces cerevisiae.* In a mouse model, combination therapy with AMB and rifampin was more effective against *H. capsulatum, Blastomyces dermatitidis,* and *Aspergillus* spp. An in vitro study on killing of *Candida* biofilms using AMB alone or in combination with either rifampin or clarithromycin found a synergistic effect of rifampin and AMB in 66.6% of *C. parapsilosis,* 42.8% of *C. albicans,* and 33.3% of *C. glabrata* biofilms.[214] In vitro data show synergy with rifampin and AMB in 68.7% of *Fusarium* spp.[215] Rifampin with AMB significantly enhanced the activity of AMB alone in vitro against 95 clinical isolates of *Fusarium solani* and *Aspergillus flavus* spp. complex from patients with keratomycosis.[216] There are few clinical reports, with insufficient data to support the use of rifampin in combination with antifungal agents.

SECOND-LINE INDICATIONS FOR RIFAMYCINS

Rifabutin has been successful as "rescue therapy" for *H. pylori* infection. A combination of rifabutin with amoxicillin and a proton-pump inhibitor for 10 days used after failure of standard quadruple therapy was successful

and well tolerated in 50% to 66.6% of patients in two studies.[217,218] Q fever endocarditis is usually treated with doxycycline in combination with hydroxychloroquine. Doxycycline with rifampin (900 mg/day) was effective in some case reports, and erythromycin with rifampin was successful in chronic Q fever of pregnancy.[219] Doxycycline is first-line treatment for scrub typhus, but in areas where doxycycline resistance is present, rifampin is an alternative.[220] Doxycycline is also the treatment of choice for human granulocytic ehrlichiosis, but rifampin is successful in treating young children.[221] Rifampin at doses of 300 to 600 mg/day reduces pruritus associated with cholestasis, possibly by induction of microsomal enzymes that promote glucuronidation of toxic bile salts. A review of 12 trials documented a significant decrease in pruritus.[222]

Chemoprophylaxis

Antibiotics for chemoprophylaxis of *N. meningitidis* contacts include rifampin, ciprofloxacin, minocycline, and ceftriaxone. A 2-day course of rifampin (600 mg twice daily) is effective in eradicating the bacteria from 75% to 95% of carriers; however, adverse drug reactions, drug interactions, and selection of resistant isolates have limited use to young children. An extensive review found ceftriaxone to be more effective than rifampin after 1 to 4 weeks of follow-up. Rifampin was effective for up to 4 weeks after treatment, but resistant isolates were seen, raising concern that use of rifampin during an outbreak may lead to the circulation of resistant strains. Use of ciprofloxacin, ceftriaxone, or penicillin should be considered.[223]

The *H. influenzae* type b conjugate vaccines have significantly decreased the incidence of invasive disease in children. Chemoprophylaxis is recommended for close contacts of a child with invasive *H. influenzae* type b infection using rifampin at doses of 20 mg/kg in children and 600 mg in adults daily for 4 days, based on earlier studies showing elimination of oropharyngeal carriage of *H. influenzae* type b in 97% of household or daycare contacts.[224,225]

Another area of infection prophylaxis is the rifampin-minocycline–impregnated catheter, which has been demonstrated to be effective in decreasing catheter-related bacteremia.[226] Two studies in pediatric burn patients[227] and in immunocompromised patients with transplants, cancer, or on dialysis[228] concluded that these catheters are effective in reducing the incidence of catheter-associated bacteremia. The CATCH trial, comparing minocycline-rifampin–impregnated central venous catheters, heparin impregnated catheters, and standard catheters in children admitted to pediatric ICUs, found that the antibiotic-impregnated catheter reduced the risk of bloodstream infection by 57% compared with standard catheters and 58% compared with heparin-impregnated catheters.[229]

For decolonization of MRSA carriers, mupirocin ointment and chlorhexidine are effective in 60% of patients. Oral therapy is recommended if topical regimens fail, which is seen with mupirocin resistant isolates. Rifampin for 5 to 10 days in combination with another agent is recommended if the strain is susceptible and other regimens are ineffective.[158]

NOVEL AND FUTURE INDICATIONS FOR RIFAMPIN

Rifampin has been successful in the treatment of cholestasis of pregnancy, in combination with ursodeoxycholic acid, in women unresponsive to ursodeoxycholic acid alone.[230] The mechanism is thought to be due to enhancement of bile acid detoxification, bilirubin conjugation, and bilirubin excretion. A 6- to 9-month course of rifampin was effective treatment in 30 patients with idiopathic granulomatous lobular mastitis, a chronic inflammatory condition of unclear etiology, associated with masses, abscesses, and sinus tracts.[231] A recent study confirmed the effectiveness of an 8-week course of rifampin with streptomycin in curing Buruli ulcer, caused by *Mycobacterium ulcerans*, in Ghana.[232]

Two innovative studies of rifampin are for suppression of osteolysis after joint replacement and the prevention of neurodegenerative diseases. Using in vitro data and a mouse calvarial osteolysis model, rifampin inhibited titanium-induced osteolysis and osteoclastogenesis in vivo and reduced expression of osteoclast-specific markers and osteoclast formation through regulation of receptor activator of nuclear factor-κB ligand signaling.[233] Using a transgenic mouse model of Alzheimer disease, rifampin for 1 month reduced accumulation of amyloid-β oligomers, tau hyperphosphorylation, synapse loss, and microglial activation. The 1-mg/day dose improved memory similar to the nontransgenic littermates.[234] Future studies are needed to validate a role for rifampin in prevention of periimplant osteolysis, diseases with excessive osteoclast activity, and in neurodegenerative diseases.

RIFAXIMIN: A SELECTIVE GASTROINTESTINAL RIFAMYCIN

Rifaximin is a unique rifamycin with negligible systemic absorption, enhanced fecal concentrations, decreased systemic toxicity, and few drug interactions. Rifaximin is bactericidal against many enteric pathogens, including enterotoxigenic and enteroaggregative *E. coli, Salmonella, Shigella,* and *Campylobacter*,[56] and is active against *C. difficile,* although high-level resistance has been reported.[235] Rifaximin has antiprotozoal activity, including *Cryptosporidium parvum* and *Blastocystis hominis.*[56] In addition to traditional single-pathogen–based antibiotic activity, rifaximin affects the microbiome of the GI tract. Rifaximin can downregulate inflammation by inhibiting activation of nuclear factor-κB and reducing expression of the proinflammatory cytokines IL-1 and TNF-α.[236] Rifaximin may also modulate inflammatory and immune responses in gut epithelial cells.[237] Clinical trials of traveler's diarrhea demonstrate that rifaximin (400 mg twice daily) was similar to traditional antimicrobial agents in decreasing time to symptom resolution.[56] Rifaximin was 72% effective in chemoprophylaxis of traveler's diarrhea in Mexico, where most cases are caused by *E. coli.*[238] At subinhibitory concentrations, rifaximin reduced expression of bacterial enterotoxins and surface adhesion intestinal-binding factors of enterotoxigenic *E. coli.*[239] However, the fluoroquinolones are preferred for chemoprophylaxis due to an effectiveness of over 90% and activity against most invasive intestinal pathogens.[240] Rifaximin (550 mg twice daily) is approved for the treatment of hepatic encephalopathy. In one study rifaximin use led to fewer breakthrough episodes of hepatic encephalopathy and significantly reduced the risk for hospitalization compared with placebo.[241] The reduction of microbes that degrade nitrogenous compounds results in decreased ammonia levels and was more than or equally effective as lactulose and other agents and better tolerated.[242]

Small trials of rifaximin for *C. difficile* infection have been published, although rifaximin may best be used for recurrent *C. difficile* infection, with a response rate as high as 83% in one study.[243] A 2-week course of rifaximin is often used after a 6-week course of vancomycin for recurrent disease. There is concern about development of resistance, however. Using the rifampin Etest, one study found 14 of 80 clinical isolates had an MIC greater than 32 μg/mL. Of these 14 isolates, 9 (64%) belonged to the BI/NAP1/027 group.[244] In small bowel overgrowth, rifaximin may play a role in microbial decontamination.[227] Rifaximin is FDA approved for treatment of irritable bowel disease without constipation. Patients reported a modest improvement in bloating, abdominal pain, and stool consistency. Rifaximin may be beneficial in inflammatory bowel diseases, including ulcerative colitis, Crohn disease, and pouchitis as a steroid-sparing regimen,[235] possibly due to the effect on both the microbiome and the (subsequent) antiinflammatory effect. Studies of rifaximin alone or in combination with other therapies have demonstrated improved rates of remission and/or clinical improvement in Crohn disease, ulcerative colitis, and pouchitis.[245] There may be a role for rifaximin in the treatment of diverticular disease when used 7 days per month along with traditional therapies.[246] Caution is warranted for such empirical therapies because rifampin-resistant strains of *S. aureus* and CoNS were found in the perineum, hands, and upper extremities after rifaximin therapy that persisted up to 9 weeks after discontinuation, consistent with other studies demonstrating rifaximin-resistant *E. coli* in the intestinal tract.[247,248] In a recent study a delayed-release formulation of rifaximin had a protective effect in reducing the number and severity of small bowel mucosal lesions and large erosions and/or ulcers when used with a nonsteroidal anti-inflammatory drug. This effect is believed to be secondary to a shift in the microbiota away from proinflammatory gram-negative bacteria.[249]

RIFALAZIL

Rifalazil is a rifamycin that has an MIC 64-fold higher than rifampin against many *M. tuberculosis* isolates, has a half-life greater than 100

hours, achieves high intracellular concentrations, and has no CYP interactions.[250] Rifalazil has potent in vitro bactericidal activity against *Chlamydia* spp., with an MIC_{90} of 0.00025 μg/mL against *C. trachomatis,*[251] and is active against all stages of the life cycle. Initial development was limited by a flulike syndrome and leukopenia in phase I trials. A phase II trial in pulmonary tuberculosis with once-weekly dosing with isoniazid for 2 weeks, followed by 6 months of standard therapy, was better tolerated, but a higher incidence of adverse events was observed in the rifalazil arm.[252] A phase IIB study in men with nongonococcal urethritis showed superiority of 25 mg of rifalazil versus 1 g of azithromycin.[253] A phase II study of 25 mg of rifalazil versus 1 g of azithromycin in women with uncomplicated genital *C. trachomatis* infection demonstrated a cure rate of 85% in the rifalazil group versus 92% in the azithromycin group, and lower adverse reactions in the rifalazil group, but was unable to demonstrate noninferiority to azithromycin.[254] Rifalazil development in the United States was terminated in 2013 due to safety concerns.

RIFAMYCINS IN DEVELOPMENT

New rifamycins include aerosolized formulations, rifamycin-loaded scaffolds for prevention of orthopedic prosthetic infections, and compounds that circumvent development of resistance. Advantages of aerosol formulations are decreased dosing, improved compliance, decreased adverse events, and improved pharmacodynamics, because particles attain high intracellular concentrations in pulmonary macrophages. Two investigational compounds are a dry powder formulation with rifampin-derived microcrystals coated with polymers[255] and liposomes coated with chitosan-xanthan gum.[256] A new inhaled formulation of rifampin with colistin, aimed at delivering both drugs directly to the respiratory tract, was found to have synergistic activity, high aerosolization efficiency, and moisture protection, offering a less toxic formulation for resistant gram-negative respiratory infection.[257] Synthetic bone scaffolds constructed by electrospinning nanofiber poly(caprolactone) with concentrations of 10% and 20% rifampin when inoculated with *S. epidermidis* and *P. aeruginosa* completely inhibited bacterial growth and prevented biofilm formation within the scaffolds through the first 6 hours.[258]

Rifamycin SV MMX (RIF-MMX) is a semisynthetic derivative of rifamycin SV in a nonabsorbable modified-release multimatrix structure that delivers the active ingredient directly into the colon.[259] The bioavailability is less than 0.1%, and close to 90% of the dose is recovered in feces. RIF-MMX is under investigation for treatment of traveler's diarrhea, *C. difficile* infection, diverticulitis, inflammatory bowel diseases, and hepatic encephalopathy. A 3-day course of RIF-MMX versus placebo was well tolerated and effective in achieving clinical cure within 120 hours in patients with traveler's diarrhea (81.4% of RIF-MMX vs. 56.9% of placebo). There was decreased susceptibility in bacterial isolates remaining after therapy, but this was not associated with diminished efficacy, suggesting an additional nonbacterial mechanism of action.[260]

Studies of rifampin-loaded nanoparticles showed enhanced delivery of rifampin in vitro into the intracellular compartment of polymorphonuclear leukocytes[261] and targeted delivery to alveolar macrophages in vitro and in a rat model.[262] Nanoparticles carrying rifamycins are promising new delivery systems for the treatment of tuberculosis, *S. aureus,* and other intracellular bacterial infections.

Key References

The complete reference list is available online at Expert Consult.

1. Sensi P. History of the development of rifampin. *Rev Infect Dis*. 1983;5(suppl 3):S402–S406.
2. Forrest GN, Tamura K. Rifampin combination therapy for nonmycobacterial infections. *Clin Microbiol Rev*. 2010;23:14–34.
4. Artsimovitch I, Vassylyeva MN, Svetlov D, et al. Allosteric modulation of the RNA polymerase catalytic reaction is an essential component of transcription control by rifamycins. *Cell*. 2005;122:351–363.
5. Feklistov A, Mekler V, Jiang Q, et al. Rifamycins do not function by allosteric modulation of binding of mg^{3+} to the RNA polymerase active center. *Proc Natl Acad Sci USA*. 2008;105:14820–14825.
9. Ohno H, Koga H, Kohno S, et al. Relationship between rifampin MICs for and *rpoB* mutations of *Mycobacterium tuberculosis* strains isolated in Japan. *Antimicrob Agents Chemother*. 1996;40:1053–1056.
10. Floss HG, Yu TW. Rifamycin-mode of action, resistance, and biosynthesis. *Chem Rev*. 2005;105:621–632.
11. Blakemore R, Story E, Helb D, et al. Evaluation of the analytical performance of the Xpert MTB/RIF assay. *J Clin Microbiol*. 2010;48:2495–2501.
19. Van Rie A, Mellet K, John MA, et al. False-positive rifampicin resistance on xpert(R) MTB/RIF: case report and clinical implications. *Int J Tuberc Lung Dis*. 2012;16:206–208.
20. Availability of an assay for detecting *Mycobacterium tuberculosis*, including rifampin-resistant strains, and considerations for its use—United States, 2013. *MMWR Morb Mortal Wkly Rep*. 2013;62:821–827.
21. Jamieson FB, Guthrie JL, Neemuchwala A, et al. Profiling of *rpoB* mutations and MICs for rifampin and rifabutin in *Mycobacterium tuberculosis*. *J Clin Microbiol*. 2014;52:2157–2162.
23. Lin SY, Rodwell TC, Victor TC, et al. Pyrosequencing for rapid detection of extensively drug-resistant *Mycobacterium tuberculosis* in clinical isolates and clinical specimens. *J Clin Microbiol*. 2014;52:475–482.
24. Ocheretina O, Shen L, Escuyer VE, et al. Whole genome sequencing investigation of a tuberculosis outbreak in Port-au-Prince, Haiti caused by a strain with a "low-level" *rpoB* mutation L511P—insights into a mechanism of resistance escalation. *PLoS ONE*. 2015;10:e0129207.
25. Daum LT, Rodriguez JD, Worthy SA, et al. Next-generation ion torrent sequencing of drug resistance mutations in *Mycobacterium tuberculosis* strains. *J Clin Microbiol*. 2012;50:3831–3837.
26. Koser CU, Bryant JM, Becq J, et al. Whole-genome sequencing for rapid susceptibility testing of *M. tuberculosis*. *N Engl J Med*. 2013;369:290–292.
27. Burman WJ, Gallicano K, Peloquin C. Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. *Clin Pharmacokinet*. 2001;40:327–341.
28. Aristoff PA, Garcia GA, Kirchhoff PD, et al. Rifamycins—obstacles and opportunities. *Tuberculosis (Edinb)*. 2010;90:94–118.
30. Baciewicz AM, Chrisman CR, Finch CK, et al. Update on rifampin, rifabutin, and rifapentine drug interactions. *Curr Med Res Opin*. 2013;29:1–12.
35. Martinez E, Collazos J, Mayo J. Hypersensitivity reactions to rifampin: pathogenetic mechanisms, clinical manifestations, management strategies, and review of the anaphylactic-like reactions. *Medicine (Baltimore)*. 1999;78:361–369.
38. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. *Respirology*. 2006;11:699–707.
43. Thornsberry C, Hill BC, Swenson JM, et al. Rifampin: spectrum of antibacterial activity. *Rev Infect Dis*. 1983;5(suppl 3):S412–S417.
63. McIlleron H, Watkins ML, Folb PI, et al. Rifampin levels, interferon-gamma release and outcome in complicated pulmonary tuberculosis. *Tuberculosis (Edinb)*. 2007;87:557–564.
80. Ruslami R, Nijland HM, Alisjahbana B, et al. Pharmacokinetics and tolerability of a higher rifampin dose versus the standard dose in pulmonary tuberculosis patients. *Antimicrob Agents Chemother*. 2007;51:2546–2551.
85. van Ingen J, Aarnoutse R, de Vries G, et al. Low-level rifampicin-resistant *Mycobacterium tuberculosis* strains raise a new therapeutic challenge. *Int J Tuberc Lung Dis*. 2011;15:990–992.
92. Vernon A, Burman W, Benator D, et al. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Tuberculosis trials consortium. *Lancet*. 1999;353:1843–1847.
93. Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med*. 2014;371:1599–1608.
94. Rosenthal IM, Tasneen R, Peloquin CA, et al. Dose-ranging comparison of rifampin and rifapentine in two pathologically distinct murine models of tuberculosis. *Antimicrob Agents Chemother*. 2012;56:4331–4340.
95. Dorman SE, Goldberg S, Stout JE, et al. Substitution of rifapentine for rifampin during intensive phase treatment of pulmonary tuberculosis: study 29 of the tuberculosis trials consortium. *J Infect Dis*. 2012;206:1030–1040.
98. Dooley KE, Bliven-Sizemore EE, Weiner M, et al. Safety and pharmacokinetics of escalating daily doses of the antituberculosis drug rifapentine in healthy volunteers. *Clin Pharmacol Ther*. 2012;91:881–888.
105. Centers for Disease Control and Prevention. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *MMWR Morb Mortal Wkly Rep*. 2000;49:185–189.
116. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. *MMWR Recomm Rep*. 2000;49:1–51.
119. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365:2155–2166.
120. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent *Mycobacterium tuberculosis* infection. *MMWR Morb Mortal Wkly Rep*. 2011;60:1650–1653.
123. Rodrigues LC, Lockwood D. Leprosy now: epidemiology, progress, challenges, and research gaps. *Lancet Infect Dis*. 2011;11:464–470.
129. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*. 2007;175:367–416.
130. van Ingen J, Egelund EF, Levin A, et al. The pharmacokinetics and pharmacodynamics of pulmonary *Mycobacterium avium* complex disease treatment. *Am J Respir Crit Care Med*. 2012;186:559–565.
132. Benson CA, Williams PL, Currier JS, et al. A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated *Mycobacterium avium* complex disease in persons with acquired immunodeficiency syndrome. *Clin Infect Dis*. 2003;37:1234–1243.
138. Sande MA, Johnson ML. Antimicrobial therapy of experimental endocarditis caused by *Staphylococcus aureus*. *J Infect Dis*. 1975;131:367–375.
141. Riedel DJ, Weekes E, Forrest GN. Addition of rifampin to standard therapy for treatment of native valve infective endocarditis caused by *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2008;52:2463–2467.
143. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American heart association. *Circulation*. 2015;132:1435–1486.
144. Shrestha NK, Shah SY, Wang H, et al. Rifampin for surgically treated staphylococcal infective endocarditis: a propensity score-adjusted cohort study. *Ann Thorac Surg*. 2016;Feb 9 [Epub ahead of print].
145. Forsblom E, Ruotsalainen E, Jarvinen A. Improved outcome with early rifampicin combination treatment in methicillin-sensitive *Staphylococcus aureus* bacteraemia

with a deep infection focus—a retrospective cohort study. *PLoS ONE*. 2015;10:e0122824.

149. Archer NK, Mazaitis MJ, Costerton JW, et al. *Staphylococcus aureus* biofilms: properties, regulation, and roles in human disease. *Virulence*. 2011;2:445–459.
155. Sanchez CJ Jr, Shiels SM, Tennent DJ, et al. Rifamycin derivatives are effective against staphylococcal biofilms in vitro and elutable from PMMA. *Clin Orthop Relat Res*. 2015;473:2874–2884.
156. Fazly Bazzaz BS, Khameneh B, Zarei H, et al. Antibacterial efficacy of rifampin loaded solid lipid nanoparticles against *Staphylococcus epidermidis* biofilm. *Microb Pathog*. 2016;93:137–144.
157. Karchmer AW, Archer GL, Dismukes WE. *Staphylococcus epidermidis* causing prosthetic valve endocarditis: microbiologic and clinical observations as guides to therapy. *Ann Intern Med*. 1983;98:447–455.
158. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis*. 2011;52:285–292.
160. Watanabe Y, Cui L, Katayama Y, et al. Impact of *rpoB* mutations on reduced vancomycin susceptibility in *Staphylococcus aureus*. *J Clin Microbiol*. 2011;49:2680–2684.
163. El Helou OC, Berbari EF, Lahr BD, et al. Efficacy and safety of rifampin containing regimen for staphylococcal prosthetic joint infections treated with debridement and retention. *Eur J Clin Microbiol Infect Dis*. 2010;29:961–967.
164. Peel TN, Buising KL, Dowsey MM, et al. Outcome of debridement and retention in prosthetic joint infections by methicillin-resistant staphylococci, with special reference to rifampin and fusidic acid combination therapy. *Antimicrob Agents Chemother*. 2013;57:350–355.
171. Norden CW, Fierer J, Bryant RE. Chronic staphylococcal osteomyelitis: treatment with regimens containing rifampin. *Rev Infect Dis*. 1983;5(suppl 3):S495–S501.
173. Khanlari B, Elzi L, Estermann L, et al. A rifampicin-containing antibiotic treatment improves outcome of staphylococcal deep sternal wound infections. *J Antimicrob Chemother*. 2010;65:1799–1806.
174. Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. *Clin Infect Dis*. 2012;54:393–407.
190. Varner TR, Bookstaver PB, Rudisill CN, et al. Role of rifampin-based combination therapy for severe community-acquired *Legionella pneumophila* pneumonia. *Ann Pharmacother*. 2011;45:967–976.
195. Lim TP, Lee W, Tan TY, et al. Effective antibiotics in combination against extreme drug-resistant *Pseudomonas aeruginosa* with decreased susceptibility to polymyxin B. *PLoS ONE*. 2011;6:e28177.
197. Dong X, Chen F, Zhang Y, et al. In vitro activities of rifampin, colistin, sulbactam and tigecycline tested alone and in combination against extensively drug-resistant *Acinetobacter baumannii*. *J Antibiot (Tokyo)*. 2014;67:677–680.
203. Bassetti M, Repetto E, Righi E, et al. Colistin and rifampicin in the treatment of multidrug-resistant *Acinetobacter baumannii* infections. *J Antimicrob Chemother*. 2008;61:417–420.
207. Solis Garcia del Pozo J, Solera J. Systematic review and meta-analysis of randomized clinical trials in the treatment of human brucellosis. *PLoS ONE*. 2012;7:e32090.
217. Gisbert JP, Castro-Fernandez M, Perez-Aisa A, et al. Fourth-line rescue therapy with rifabutin in patients with three *Helicobacter pylori* eradication failures. *Aliment Pharmacol Ther*. 2012;35:941–947.
226. Lorente L, Lecuona M, Ramos MJ, et al. The use of rifampicin-miconazole–impregnated catheters reduces the incidence of femoral and jugular catheter–related bacteremia. *Clin Infect Dis*. 2008;47:1171–1175.
230. Geenes V, Chambers J, Khurana R, et al. Rifampicin in the treatment of severe intrahepatic cholestasis of pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2015;189:59–63.
235. DuPont HL. Biologic properties and clinical uses of rifaximin. *Exp Opin Pharmacother*. 2011;12:293–302.
237. Kane JS, Ford AC. Rifaximin for the treatment of diarrhea-predominant irritable bowel syndrome. *Expert Rev Gastroenterol Hepatol*. 2016;10:431–442.
241. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med*. 2010;362:1071–1081.
243. Garey KW, Jiang ZD, Bellard A, et al. Rifaximin in treatment of recurrent *Clostridium difficile*-associated diarrhea: an uncontrolled pilot study. *J Clin Gastroenterol*. 2009;43:91–93.
253. Stamm WE, Batteiger BE, McCormack WM, et al. A randomized, double-blind study comparing single-dose rifalazil with single-dose azithromycin for the empirical treatment of nongonococcal urethritis in men. *Sex Transm Dis*. 2007;34:545–552.
254. Geisler WM, Pascual ML, Mathew J, et al. Randomized, double-blind, multicenter safety and efficacy study of rifalazil compared with azithromycin for treatment of uncomplicated genital *Chlamydia trachomatis* infection in women. *Antimicrob Agents Chemother*. 2014;58:4014–4019.
257. Zhou QT, Gengenbach T, Denman JA, et al. Synergistic antibiotic combination powders of colistin and rifampicin provide high aerosolization efficiency and moisture protection. *AAPS J*. 2014;16:37–47.
260. DuPont HL, Petersen A, Zhao J, et al. Targeting of rifamycin SV to the colon for treatment of travelers' diarrhea: a randomized, double-blind, placebo-controlled phase 3 study. *J Travel Med*. 2014;21:369–376.
261. Smitha KT, Nisha N, Maya S, et al. Delivery of rifampicin-chitin nanoparticles into the intracellular compartment of polymorphonuclear leukocytes. *Int J Biol Macromol*. 2015;74:36–43.
262. Song X, Lin Q, Guo L, et al. Rifampicin loaded mannosylated cationic nanostructured lipid carriers for alveolar macrophage-specific delivery. *Pharm Res*. 2015;32:1741–1751.

References

1. Sensi P. History of the development of rifampin. *Rev Infect Dis*. 1983;5(suppl 3):S402–S406.
2. Forrest GN, Tamura K. Rifampin combination therapy for nonmycobacterial infections. *Clin Microbiol Rev*. 2010;23:14–34.
3. Campbell EA, Korzheva N, Mustaev A, et al. Structural mechanism for rifampicin inhibition of bacterial RNA polymerase. *Cell*. 2001;104:901–912.
4. Artsimovitch I, Vassylyeva MN, Svetlov D, et al. Allosteric modulation of the RNA polymerase catalytic reaction is an essential component of transcription control by rifamycins. *Cell*. 2005;122:351–363.
5. Feklistov A, Mekler V, Jiang Q, et al. Rifamycins do not function by allosteric modulation of binding of mg2+ to the RNA polymerase active center. *Proc Natl Acad Sci USA*. 2008;105:14820–14825.
6. Ramaswamy S, Musser JM. Molecular genetic basis of antimicrobial agent resistance in *Mycobacterium tuberculosis*: 1998 update. *Tuberc Lung Dis*. 1998; 79:3–29.
7. Hameed S, Moganeradj K, Mahmood N, et al. Sequence analysis of the rifampicin resistance determining region (RRDR) of *rpoB* gene in multidrug resistance confirmed and newly diagnosed tuberculosis patients of Punjab, Pakistan. *PLoS ONE*. 2017;12:e0183363.
8. Ullah I, Shah AA, Basit A, et al. Rifampicin resistance mutations in the 81 bp RRDR of *rpoB* gene in *Mycobacterium tuberculosis* clinical isolates using Xpert MTB/RIF in Khyber Pakhtunkhwa, Pakistan: a retrospective study. *BMC Infect Dis*. 2016;16:413.
9. Ohno H, Koga H, Kohno S, et al. Relationship between rifampin MICs for and *rpoB* mutations of *Mycobacterium tuberculosis* strains isolated in Japan. *Antimicrob Agents Chemother*. 1996;40:1053–1056.
10. Floss HG, Yu TW. Rifamycin-mode of action, resistance, and biosynthesis. *Chem Rev*. 2005;105:621–632.
11. Blakemore R, Story E, Helb D, et al. Evaluation of the analytical performance of the Xpert MTB/RIF assay. *J Clin Microbiol*. 2010;48:2495–2501.
12. Helb D, Jones M, Story E, et al. Rapid detection of *Mycobacterium tuberculosis* and rifampin resistance by use of on-demand, near-patient technology. *J Clin Microbiol*. 2010;48:229–237.
13. Steingart KR, Schiller I, Horne DJ, et al. Xpert(R) MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev*. 2014;(1):CD009593.
14. Vadwai V, Boehme C, Nabeta P, et al. Xpert MTB/RIF: a new pillar in diagnosis of extrapulmonary tuberculosis? *J Clin Microbiol*. 2011;49:2540–2545.
15. World Health Organization. *Xpert MTB/RIF System for the Diagnosis of Pulmonary and Extra-Pulmonary TB in Adults and Children. Policy Update*. Geneva, Switzerland: World Health Organization; 2013.
16. Singh BK, Sharma SK, Sharma R, et al. Diagnostic utility of a line probe assay for multidrug resistant-TB in smear-negative pulmonary tuberculosis. *PLoS ONE*. 2017;12:e0182988.
17. Ling DI, Zwerling AA, Pai M. Rapid diagnosis of drug-resistant TB using line probe assays: from evidence to policy. *Expert Rev Respir Med*. 2008;2:583–588.
18. Drobniewski F, Cooke M, Jordan J, et al. Systematic review, meta-analysis and economic modelling of molecular diagnostic tests for antibiotic resistance in tuberculosis. *Health Technol Assess*. 2015;19:1–188, vii–viii.
19. Van Rie A, Mellet K, John MA, et al. False-positive rifampicin resistance on xpert(R) MTB/RIF: case report and clinical implications. *Int J Tuberc Lung Dis*. 2012;16:206–208.
20. Availability of an assay for detecting *Mycobacterium tuberculosis*, including rifampin-resistant strains, and considerations for its use—United States, 2013. *MMWR Morb Mortal Wkly Rep*. 2013;62:821–827.
21. Jamieson FB, Guthrie JL, Neemuchwala A, et al. Profiling of *rpoB* mutations and MICs for rifampin and rifabutin in *Mycobacterium tuberculosis*. *J Clin Microbiol*. 2014;52:2157–2162.
22. Ao W, Aldous S, Woodruff E, et al. Rapid detection of *rpoB* gene mutations conferring rifampin resistance in *Mycobacterium tuberculosis*. *J Clin Microbiol*. 2012;50:2433–2440.
23. Lin SY, Rodwell TC, Victor TC, et al. Pyrosequencing for rapid detection of extensively drug-resistant *Mycobacterium tuberculosis* in clinical isolates and clinical specimens. *J Clin Microbiol*. 2014;52:475–482.
24. Ocheretina O, Shen L, Escuyer VE, et al. Whole genome sequencing investigation of a tuberculosis outbreak in Port-au-Prince, Haiti caused by a strain with a "low-level" *rpoB* mutation L511P—insights into a mechanism of resistance escalation. *PLoS ONE*. 2015;10:e0129207.
25. Daum LT, Rodriguez JD, Worthy SA, et al. Next-generation ion torrent sequencing of drug resistance mutations in *Mycobacterium tuberculosis* strains. *J Clin Microbiol*. 2012;50:3831–3837.
26. Koser CU, Bryant JM, Becq J, et al. Whole-genome sequencing for rapid susceptibility testing of *M. tuberculosis*. *N Engl J Med*. 2013;369:290–292.
27. Burman WJ, Gallicano K, Peloquin C. Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. *Clin Pharmacokinet*. 2001;40:327–341.
28. Aristoff PA, Garcia GA, Kirchhoff PD, et al. Rifamycins—obstacles and opportunities. *Tuberculosis (Edinb)*. 2010;90:94–118.
29. Cook SV, Fujiwara PI, Frieden TR. Rates and risk factors for discontinuation of rifampicin. *Int J Tuberc Lung Dis*. 2000;4:118–122.
30. Baciewicz AM, Chrisman CR, Finch CK, et al. Update on rifampin, rifabutin, and rifapentine drug interactions. *Curr Med Res Opin*. 2013;29:1–12.
31. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services; 2016. http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.
32. Patel GK, Anstey AV. Rifampicin-induced lupus erythematosus. *Clin Exp Dermatol*. 2001;26:260–262.
33. Donald PR. Cerebrospinal fluid concentrations of antituberculosis agents in adults and children. *Tuberculosis (Edinb)*. 2010;90:279–292.
34. Roth B. Penetration of parenterally administered rifampicin into bone tissue. *Chemotherapy*. 1984;30:358–365.
35. Martinez E, Collazos J, Mayo J. Hypersensitivity reactions to rifampin: pathogenetic mechanisms, clinical manifestations, management strategies, and review of the anaphylactic-like reactions. *Medicine (Baltimore)*. 1999;78:361–369.
36. Chen G, He JQ. Rifampin-induced disseminated intravascular coagulation in pulmonary tuberculosis treatment. A case report and literature review. *Medicine (Baltimore)*. 2017;96:e6135.
37. De Vriese AS, Robbrecht DL, Vanholder RC, et al. Rifampicin-associated acute renal failure: pathophysiologic, immunologic, and clinical features. *Am J Kidney Dis*. 1998;31:108–115.
38. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. *Respirology*. 2006;11:699–707.
39. Ohno M, Yamaguchi I, Yamamoto I, et al. Slow *N*-acetyltransferase 2 genotype affects the incidence of isoniazid and rifampicin-induced hepatotoxicity. *Int J Tuberc Lung Dis*. 2000;4:256–261.
40. World Health Organization. *Treatment of Tuberculosis: Guidelines*. Geneva: World Health Organization; 2010.
41. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations—United States, 2001. *MMWR Morb Mortal Wkly Rep*. 2001;50:733–735.
42. Li LM, Chen L, Deng GH, et al. SLCO1b1 *15 haplotype is associated with rifampin-induced liver injury. *Mol Med Rep*. 2012;6:75–82.
43. Thornsberry C, Hill BC, Swenson JM, et al. Rifampin: spectrum of antibacterial activity. *Rev Infect Dis*. 1983;5(suppl 3):S412–S417.
44. Saito H, Sato K, Tomioka H. Comparative in vitro and in vivo activity of rifabutin and rifampicin against *Mycobacterium avium* complex. *Tubercle*. 1988;69:187–192.
45. Nielsen K, Bangsborg JM, Hoiby N. Susceptibility of *Legionella* species to five antibiotics and development of resistance by exposure to erythromycin, ciprofloxacin, and rifampicin. *Diagn Microbiol Infect Dis*. 2000;36:43–48.
46. Dorbecker C, Sander A, Oberle K, et al. In vitro susceptibility of *Bartonella* species to 17 antimicrobial compounds: comparison of etest and agar dilution. *J Antimicrob Chemother*. 2006;58:784–788.
47. Blaschke TF, Skinner MH. The clinical pharmacokinetics of rifabutin. *Clin Infect Dis*. 1996;22(suppl 1):S15–S21, discussion S2.
48. Product Information: Pharmacia & Upjohn, Kalamzoo, MI. Mycobutin, rifabutin. 2002.
49. Griffith DE, Brown BA, Girard WM, et al. Adverse events associated with high-dose rifabutin in macrolide-containing regimens for the treatment of *Mycobacterium avium* complex lung disease. *Clin Infect Dis*. 1995;21:594–598.
50. Nichols CW. *Mycobacterium avium* complex infection, rifabutin, and uveitis—is there a connection? *Clin Infect Dis*. 1996;22(suppl 1):S43–S47, discussion S7–S9.
51. Havlir D, Torriani F, Dube M. Uveitis associated with rifabutin prophylaxis. *Ann Intern Med*. 1994;121: 510–512.
52. Jarvis B, Lamb HM. Rifapentine. *Drugs*. 1998;56:607–616, discussion 617.
53. Jiang ZD, Ke S, Palazzini E, et al. In vitro activity and fecal concentration of rifaximin after oral administration. *Antimicrob Agents Chemother*. 2000;44:2205–2206.
54. Rivkin A, Gim S. Rifaximin: new therapeutic indication and future directions. *Clin Ther*. 2011;33:812–827.
55. Hynicka LM, Silva KN. Probable rifaximin-induced neutropenia. *Am J Health Sys Pharm*. 2012;69:583–586.
56. Koo HL, DuPont HL. Rifaximin: a unique gastrointestinal-selective antibiotic for enteric diseases. *Curr Opin Gastroenterol*. 2010;26:17–25.
57. Ziglam HM, Daniels I, Finch RG. Immunomodulating activity of rifampicin. *J Chemother*. 2004;16:357–361.
58. Yuhas Y, Berent E, Ashkenazi S. Effect of rifampin on production of inflammatory mediators in HepG2 liver epithelial cells. *Antimicrob Agents Chemother*. 2011;55:5541–5546.
59. Smani Y, Dominguez-Herrera J, Pachon J. Rifampin protects human lung epithelial cells against cytotoxicity induced by clinical multi and pandrug-resistant *Acinetobacter baumannii*. *J Infect Dis*. 2011;203:1110–1119.
60. Spreer A, Lugert R, Stoltefaut V, et al. Short-term rifampicin pretreatment reduces inflammation and neuronal cell death in a rabbit model of bacterial meningitis. *Crit Care Med*. 2009;37:2253–2258.
61. Bottcher T, Gerber J, Wellmer A, et al. Rifampin reduces production of reactive oxygen species of cerebrospinal fluid phagocytes and hippocampal neuronal apoptosis in experimental *Streptococcus pneumoniae* meningitis. *J Infect Dis*. 2000;181:2095–2098.
62. Gil D, Garcia LF, Rojas M. Modulation of macrophage apoptosis by antimycobacterial therapy: physiological role of apoptosis in the control of *Mycobacterium tuberculosis*. *Toxicol Appl Pharmacol*. 2003;190:111–119.
63. McIlleron H, Watkins ML, Folb PI, et al. Rifampin levels, interferon-gamma release and outcome in complicated pulmonary tuberculosis. *Tuberculosis (Edinb)*. 2007;87:557–564.
64. Goble M, Iseman MD, Madsen LA, et al. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med*. 1993;328:527–532.
65. Alfarisi O, Alghamdi WA, Al-Shaer MH, et al. Rifampin vs. rifapentine: what is the preferred rifamycin for tuberculosis? *Expert Rev Clin Pharmacol*. 2017;10:1027–1036.
66. Dickinson JM, Mitchison DA. Experimental models to explain the high sterilizing activity of rifampin in the chemotherapy of tuberculosis. *Am Rev Respir Dis*. 1981;123:367–371.
67. Furesz S, Scotti R, Pallanza R, et al. Rifampicin: a new rifamycin. 3. Absorption, distribution, and elimination in man. *Arzneimittelforschung*. 1967;17:534–537.
68. Nitti V, Delli Veneri F, Ninni A, et al. Rifampicin blood serum levels and half-life during prolonged administration in tuberculous patients. *Chemotherapy*. 1972;17:121–129.
69. Long MW, Snider DE Jr, Farer LS. U.S. Public health service cooperative trial of three rifampin-isoniazid regimens in treatment of pulmonary tuberculosis. *Am Rev Respir Dis*. 1979;119:879–894.
70. Poole G, Stradling P, Worlledge S. Potentially serious side effects of high-dose twice-weekly rifampicin. *BMJ*. 1971;3:343–347.
71. Fox W, Nunn AJ. The cost of antituberculous drug regimens. *Am Rev Respir Dis*. 1979;120:503–509.
72. Gumbo T, Louie A, Deziel MR, et al. Concentration-dependent *Mycobacterium tuberculosis* killing and prevention of resistance by rifampin. *Antimicrob Agents Chemother*. 2007;51:3781–3788.
73. Jayaram R, Gaonkar S, Kaur P, et al. Pharmacokinetics-pharmacodynamics of rifampin in an aerosol infection model of tuberculosis. *Antimicrob Agents Chemother*. 2003;47:2118–2124.
74. Diacon AH, Patientia RF, Venter A, et al. Early bactericidal activity of high-dose rifampin in patients with pulmonary tuberculosis evidenced by positive sputum smears. *Antimicrob Agents Chemother*. 2007;51:2994–2996.
75. Jindani A, Aber VR, Edwards EA, et al. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. *Am Rev Respir Dis*. 1980;121:939–949.
76. Kreis B, Pretet S, Birenbaum J, et al. Two three-month treatment regimens for pulmonary tuberculosis. *Bull Int Union Tuberc Lung Dis*. 1976;51:71–75.
77. Boeree MJ, Diacon AH, Dawson R, et al. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. *Am J Respir Crit Care Med*. 2015;191:1058–1065.

78. Boeree MJ, Heinrich N, Aarnoutse R, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *Lancet Infect Dis*. 2017;17:39–49.
79. Verbist L, Rollier F. Pharmacological study of rifampicin after repeated high dosage during intermittent combined therapy, II. Bilirubin levels and other biochemical determinations. *Respiration*. 1971;28(suppl):S17–S28.
80. Ruslami R, Nijland HM, Alisjahbana B, et al. Pharmacokinetics and tolerability of a higher rifampin dose versus the standard dose in pulmonary tuberculosis patients. *Antimicrob Agents Chemother*. 2007;51:2546–2551.
81. Girling DJ. Adverse reactions to rifampicin in antituberculosis regimens. *J Antimicrob Chemother*. 1977;3:115–132.
82. Bertrand A. Antibiotic treatment of brucellosis. *Presse Med*. 1994;23:1128–1131, [in French].
83. Drancourt M, Stein A, Argenson JN, et al. Oral treatment of *Staphylococcus* spp. infected orthopaedic implants with fusidic acid or ofloxacin in combination with rifampicin. *J Antimicrob Chemother*. 1997;39:235–240.
84. Kochar DK, Aseri S, Sharma BV, et al. The role of rifampicin in the management of cutaneous leishmaniasis. *Q J Med*. 2000;93:733–737.
85. van Ingen J, Aarnoutse R, de Vries G, et al. Low-level rifampicin-resistant *Mycobacterium tuberculosis* strains raise a new therapeutic challenge. *Int J Tuberc Lung Dis*. 2011;15:990–992.
86. Drlica K, Zhao X. Mutant selection window hypothesis updated. *Clin Infect Dis*. 2007;44:681–688.
87. Ruslami R, Ganiem AR, Dian S, et al. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. *Lancet Infect Dis*. 2013;13:27–35.
88. Heifets LB, Lindholm-Levy PJ, Flory MA. Bactericidal activity in vitro of various rifamycins against *Mycobacterium avium* and *Mycobacterium tuberculosis*. *Am Rev Respir Dis*. 1990;141:626–630.
89. Langdon G, Wilkins JJ, Smith PJ, et al. Consecutive-dose pharmacokinetics of rifapentine in patients diagnosed with pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2004;8:862–867.
90. Weiner M, Bock N, Peloquin CA, et al. Pharmacokinetics of rifapentine at 600, 900, and 1,200 mg during once-weekly tuberculosis therapy. *Am J Respir Crit Care Med*. 2004;169:1191–1197.
91. Benator D, Bhattacharya M, Bozeman L, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet*. 2002;360:528–534.
92. Vernon A, Burman W, Benator D, et al. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Tuberculosis trials consortium. *Lancet*. 1999;353:1843–1847.
93. Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med*. 2014;371:1599–1608.
94. Rosenthal IM, Tasneen R, Peloquin CA, et al. Dose-ranging comparison of rifampin and rifapentine in two pathologically distinct murine models of tuberculosis. *Antimicrob Agents Chemother*. 2012;56:4331–4340.
95. Dorman SE, Goldberg S, Stout JE, et al. Substitution of rifapentine for rifampin during intensive phase treatment of pulmonary tuberculosis: study 29 of the tuberculosis trials consortium. *J Infect Dis*. 2012;206:1030–1040.
96. Siegler DI, Bryant M, Burley DM, et al. Effect of meals on rifampicin absorption. *Lancet*. 1974;2:197–198.
97. Zvada SP, Van Der Walt JS, Smith PJ, et al. Effects of four different meal types on the population pharmacokinetics of single-dose rifapentine in healthy male volunteers. *Antimicrob Agents Chemother*. 2010;54:3390–3394.
98. Dooley KE, Bliven-Sizemore EE, Weiner M, et al. Safety and pharmacokinetics of escalating daily doses of the antituberculosis drug rifapentine in healthy volunteers. *Clin Pharmacol Ther*. 2012;91:881–888.
99. Dorman SE, Savic RM, Goldberg S, et al. Daily rifapentine for treatment of pulmonary tuberculosis. A randomized, dose-ranging trial. *Am J Respir Crit Care Med*. 2015;191:333–343.
100. Gonzalez-Montaner LJ, Natal S, Yongchaiyud P, et al. Rifabutin for the treatment of newly-diagnosed pulmonary tuberculosis: a multinational, randomized, comparative study versus rifampicin. Rifabutin study group. *Tuberc Lung Dis*. 1994;75:341–347.
101. Schwander S, Rusch-Gerdes S, Mateega A, et al. A pilot study of antituberculosis combinations comparing rifabutin with rifampicin in the treatment of HIV-1 associated tuberculosis: a single-blind randomized evaluation in ugandan patients with HIV-1 infection and pulmonary tuberculosis. *Tuberc Lung Dis*. 1995;76:210–218.
102. Williamson B, Dooley KE, Zhang Y, et al. Induction of influx and efflux transporters and cytochrome P450 3a4 in primary human hepatocytes by rifampin, rifabutin, and rifapentine. *Antimicrob Agents Chemother*. 2013;57:6366–6369.
103. Moreno S, Podzamczer D, Blazquez R, et al. Treatment of tuberculosis in HIV-infected patients: safety and antiretroviral efficacy of the concomitant use of ritonavir and rifampin. *AIDS*. 2001;15:1185–1187.
104. Burman WJ, Gallicano K, Peloquin C. Therapeutic implications of drug interactions in the treatment of human immunodeficiency virus-related tuberculosis. *Clin Infect Dis*. 1999;28:419–429, quiz 30.
105. Centers for Disease Control and Prevention. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *MMWR Morb Mortal Wkly Rep*. 2000;49:185–189.
106. Li J, Munsiff SS, Driver CR, et al. Relapse and acquired rifampin resistance in HIV-infected patients with tuberculosis treated with rifampin- or rifabutin-based regimens in new york city, 1997-2000. *Clin Infect Dis*. 2005;41:83–91.
107. Naiker S, Connolly C, Wiesner L, et al. Randomized pharmacokinetic evaluation of different rifabutin doses in African HIV-infected tuberculosis patients on lopinavir/ritonavir-based antiretroviral therapy. *BMC Pharmacol Toxicol*. 2014;15:61.
108. Horne DJ, Spitters C, Narita M. Experience with rifabutin replacing rifampin in the treatment of tuberculosis. *Int J Tuberc Lung Dis*. 2011;15:1485–1489, i.
109. Lopez-Montes A, Gallego E, Lopez E, et al. Treatment of tuberculosis with rifabutin in a renal transplant recipient. *Am J Kidney Dis*. 2004;44:e59–e63.
110. Lecoeur HF, Truffot-Pernot C, Grosset JH. Experimental short-course preventive therapy of tuberculosis with rifampin and pyrazinamide. *Am Rev Respir Dis*. 1989;140:1189–1193.
111. Gordin F, Chaisson RE, Matts JP, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health Organization, and the Centers for Disease Control and Prevention Study Group. *JAMA*. 2000;283:1445–1450.
112. Halsey NA, Coberly JS, Desormeaux J, et al. Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. *Lancet*. 1998;351:786–792.
113. Jasmer RM, Saukkonen JJ, Blumberg HM, et al. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. *Ann Intern Med*. 2002;137:640–647.
114. Jasmer RM, Snyder DC, Chin DP, et al. Twelve months of isoniazid compared with four months of isoniazid and rifampin for persons with radiographic evidence of previous tuberculosis: an outcome and cost-effectiveness analysis. *Am J Respir Crit Care Med*. 2000;162:1648–1652.
115. Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. *N Engl J Med*. 1997;337:801–808.
116. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. *MMWR Recomm Rep*. 2000;49:1–51.
117. Chapuis L, Ji B, Truffot-Pernot C, et al. Preventive therapy of tuberculosis with rifapentine in immunocompetent and nude mice. *Am J Respir Crit Care Med*. 1994;150:1355–1362.
118. Miyazaki E, Chaisson RE, Bishai WR. Analysis of rifapentine for preventive therapy in the cornell mouse model of latent tuberculosis. *Antimicrob Agents Chemother*. 1999;43:2126–2130.
119. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365:2155–2166.
120. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent *Mycobacterium tuberculosis* infection. *MMWR Morb Mortal Wkly Rep*. 2011;60:1650–1653.
121. Pease C, Hutton B, Yazdi F, et al. Efficacy and completion rates of rifapentine and isoniazid (3HP) compared to other treatment regimens for latent tuberculosis infection: a systematic review with network meta-analyses. *BMC Infect Dis*. 2017;17:265.
122. Bullock WE. Rifampin in the treatment of leprosy. *Rev Infect Dis*. 1983;5(suppl 3):S606–S613.
123. Rodrigues LC, Lockwood D. Leprosy now: epidemiology, progress, challenges, and research gaps. *Lancet Infect Dis*. 2011;11:464–470.
124. Vedithi S, Lavania M, Kumar M, et al. A report of rifampin-resistant leprosy from northern and eastern India: identification and in silico analysis of molecular interactions. *Med Microbiol Immunolo*. 2015;204:193–203.
125. Lavania M, Nigam A, Turankar R, et al. Emergence of primary drug resistance to rifampicin in *Mycobacterium leprae* strains from leprosy patients in India. *Clin Microbiol Infect*. 2015;21:e85–e86.
126. Moet FJ, Pahan D, Oskam L, et al. Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. *BMJ*. 2008;336:761–764.
127. Piersimoni C, Tortoli E, Mascellino MT, et al. Activity of seven antimicrobial agents, alone and in combination, against AIDS-associated isolates of *Mycobacterium avium* complex. *J Antimicrob Chemother*. 1995;36:497–502.
128. Kobashi Y, Yoshida K, Miyashita N, et al. Relationship between clinical efficacy of treatment of pulmonary *Mycobacterium avium* complex disease and drug-sensitivity testing of *Mycobacterium avium* complex isolates. *J Infect Chemother*. 2006;12:195–202.
129. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*. 2007;175:367–416.
130. van Ingen J, Egelund EF, Levin A, et al. The pharmacokinetics and pharmacodynamics of pulmonary *Mycobacterium avium* complex disease treatment. *Am J Respir Crit Care Med*. 2012;186:559–565.
131. Kunin CM. Antimicrobial activity of rifabutin. *Clin Infect Dis*. 1996;22(suppl 1):S3–S13, discussion S4.
132. Benson CA, Williams PL, Currier JS, et al. A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated *Mycobacterium avium* complex disease in persons with acquired immunodeficiency syndrome. *Clin Infect Dis*. 2003;37:1234–1243.
133. Kaplan JE, Benson C, Holmes KH, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2009;58:1–207, quiz CE1–CE4.
134. Ahn CH, Lowell JR, Ahn SS, et al. Short-course chemotherapy for pulmonary disease caused by *Mycobacterium kansasii*. *Am Rev Respir Dis*. 1983;128:1048–1050.
135. Pezzia W, Raleigh JW, Bailey MC, et al. Treatment of pulmonary disease due to *Mycobacterium kansasii*: recent experience with rifampin. *Rev Infect Dis*. 1981;3:1035–1039.
136. Santin M, Dorca J, Alcaide F, et al. Long-term relapses after 12-month treatment for *Mycobacterium kansasii* lung disease. *Eur Respir J*. 2009;33:148–152.
137. Mandell GL. The antimicrobial activity of rifampin: emphasis on the relation to phagocytes. *Rev Infect Dis*. 1983;5(suppl 3):S463–S467.
138. Sande MA, Johnson ML. Antimicrobial therapy of experimental endocarditis caused by *Staphylococcus aureus*. *J Infect Dis*. 1975;131:367–375.
139. Mandell GL, Moorman DR. Treatment of experimental staphylococcal infections: effect of rifampin alone and in combination on development of rifampin resistance. *Antimicrob Agents Chemother*. 1980;17:658–662.
140. Gomez EO, Jafary A, Dever LL. Daptomycin and rifampin for the treatment of methicillin-resistant *Staphylococcus aureus* septic pulmonary emboli in the absence of endocarditis. *Microbial Drug Resist*. 2010;16:241–244.
141. Riedel DJ, Weekes E, Forrest GN. Addition of rifampin to standard therapy for treatment of native valve infective endocarditis caused by *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2008;52:2463–2467.
142. Van der Auwera P, Klastersky J, Thys JP, et al. Double-blind, placebo-controlled study of oxacillin combined with rifampin in the treatment of staphylococcal infections. *Antimicrob Agents Chemother*. 1985;28:467–472.
143. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132:1435–1486.
144. Shrestha NK, Shah SY, Wang H, et al. Rifampin for surgically treated staphylococcal infective endocarditis: a

propensity score-adjusted cohort study. *Ann Thorac Surg*. 2016 [Epub ahead of print].

145. Forsblom E, Ruotsalainen E, Jarvinen A. Improved outcome with early rifampicin combination treatment in methicillin-sensitive *Staphylococcus aureus* bacteraemia with a deep infection focus—a retrospective cohort study. *PLoS ONE*. 2015;10:e0122824.
146. Kobasa WD, Kaye KL, Shapiro T, et al. Therapy for experimental endocarditis due to *Staphylococcus epidermidis*. *Rev Infect Dis*. 1983;5(suppl 3):S533–S537.
147. Frank KL, Del Pozo JL, Patel R. From clinical microbiology to infection pathogenesis: how daring to be different works for *Staphylococcus lugdunensis*. *Clin Microbiol Rev*. 2008;21:111–133.
148. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. *Science*. 1999;284:1318–1322.
149. Archer NK, Mazaitis MJ, Costerton JW, et al. *Staphylococcus aureus* biofilms: properties, regulation, and roles in human disease. *Virulence*. 2011;2:445–459.
150. Kiedrowski MR, Horswill AR. New approaches for treating staphylococcal biofilm infections. *Ann NY Acad Sci*. 2011;1241:104–121.
151. Saginur R, Stdenis M, Ferris W, et al. Multiple combination bactericidal testing of staphylococcal biofilms from implant-associated infections. *Antimicrob Agents Chemother*. 2006;50:55–61.
152. Baldoni D, Haschke M, Rajacic Z, et al. Linezolid alone or combined with rifampin against methicillin-resistant *Staphylococcus aureus* in experimental foreign-body infection. *Antimicrob Agents Chemother*. 2009;53:1142–1148.
153. John AK, Baldoni D, Haschke M, et al. Efficacy of daptomycin in implant-associated infection due to methicillin-resistant *Staphylococcus aureus*: importance of combination with rifampin. *Antimicrob Agents Chemother*. 2009;53:2719–2724.
154. Raad I, Hanna H, Jiang Y, et al. Comparative activities of daptomycin, linezolid, and tigecycline against catheter-related methicillin-resistant *Staphylococcus* bacteremic isolates embedded in biofilm. *Antimicrob Agents Chemother*. 2007;51:1656–1660.
155. Sanchez CJ Jr, Shiels SM, Tennent DJ, et al. Rifamycin derivatives are effective against staphylococcal biofilms in vitro and elutable from PMMA. *Clin Orthop Relat Res*. 2015;473:2874–2884.
156. Fazly Bazzaz BS, Khameneh B, Zarei H, et al. Antibacterial efficacy of rifampin loaded solid lipid nanoparticles against *Staphylococcus epidermidis* biofilm. *Microb Pathog*. 2016;93:137–144.
157. Karchmer AW, Archer GL, Dismukes WE. *Staphylococcus epidermidis* causing prosthetic valve endocarditis: microbiologic and clinical observations as guides to therapy. *Ann Intern Med*. 1983;98:447–455.
158. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis*. 2011;52:285–292.
159. Saravolatz LD, Pawlak J, Johnson LB. In vitro susceptibilities and molecular analysis of vancomycin-intermediate and vancomycin-resistant staphylococcus aureus isolates. *Clin Infect Dis*. 2012;55:582–586.
160. Watanabe Y, Cui L, Katayama Y, et al. Impact of *rpoB* mutations on reduced vancomycin susceptibility in *Staphylococcus aureus*. *J Clin Microbiol*. 2011;49:2680–2684.
161. Teterycz D, Ferry T, Lew D, et al. Outcome of orthopedic implant infections due to different staphylococci. *Int J Infect Dis*. 2010;14:e913–e918.
162. Zimmerli W, Widmer AF, Blatter M, et al. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. Foreign-body infection (FBI) study group. *JAMA*. 1998;279:1537–1541.
163. El Helou OC, Berbari EF, Lahr BD, et al. Efficacy and safety of rifampin containing regimen for staphylococcal prosthetic joint infections treated with debridement and retention. *Eur J Clin Microbiol Infect Dis*. 2010;29:961–967.
164. Peel TN, Buising KL, Dowsey MM, et al. Outcome of debridement and retention in prosthetic joint infections by methicillin-resistant staphylococci, with special reference to rifampin and fusidic acid combination therapy. *Antimicrob Agents Chemother*. 2013;57:350–355.
165. Lora-Tamayo J, Euba G, Cobo J, et al. Short- versus long-duration levofloxacin plus rifampicin for acute staphylococcal prosthetic joint infection managed with implant retention: a randomized clinical trial. *Int J Antimicrob Agents*. 2016;48:310–316.
166. Furustrand Tafin U, Corvec S, Betrisey B, et al. Role of rifampin against *Propionibacterium acnes* biofilm in vitro and in an experimental foreign-body infection model. *Antimicrob Agents Chemother*. 2012;56:1885–1891.
167. Zeller V, Ghorbani A, Strady C, et al. *Propionibacterium acnes*: an agent of prosthetic joint infection and colonization. *J Infect*. 2007;55:119–124.
168. Shi S, Zhang X. Interaction of *Staphylococcus aureus* with osteoblasts [review]. *Exp Ther Med*. 2012;3:367–370.
169. Dworkin R, Modin G, Kunz S, et al. Comparative efficacies of ciprofloxacin, pefloxacin, and vancomycin in combination with rifampin in a rat model of methicillin-resistant *Staphylococcus aureus* chronic osteomyelitis. *Antimicrob Agents Chemother*. 1990;34:1014–1016.
170. Norden CW, Shinners E, Niederriter K. Clindamycin treatment of experimental chronic osteomyelitis due to *Staphylococcus aureus*. *J Infect Dis*. 1986;153:956–959.
171. Norden CW, Fierer J, Bryant RE. Chronic staphylococcal osteomyelitis: treatment with regimens containing rifampin. *Rev Infect Dis*. 1983;5(suppl 3):S495–S501.
172. Fraimow HS. Systemic antimicrobial therapy in osteomyelitis. *Semin Plastic Surg*. 2009;23:90–99.
173. Khanlari B, Elzi L, Estermann L, et al. A rifampicin-containing antibiotic treatment improves outcome of staphylococcal deep sternal wound infections. *J Antimicrob Chemother*. 2010;65:1799–1806.
174. Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. *Clin Infect Dis*. 2012;54:393–407.
175. Jørgensen N, Skovdal S, Meyer R, et al. Rifampicin-containing combinations are superior to combinations of vancomycin, linezolid and daptomycin against *Staphylococcus aureus* biofilm infection in vivo and in vitro. *Pathog Dis*. 2016;74:[Epub April 1].
176. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39:1267–1284.
177. Klugman KP, Friedland IR, Bradley JS. Bactericidal activity against cephalosporin-resistant *Streptococcus pneumoniae* in cerebrospinal fluid of children with acute bacterial meningitis. *Antimicrob Agents Chemother*. 1995;39:1988–1992.
178. Uppal L, Singhi S, Singhi P, et al. Role of rifampin in reducing inflammation and neuronal damage in childhood bacterial meningitis. *Pediatr Infect Dis J*. 2017;36:556–559.
179. Orvin K, Bilavsky E, Weiner E, et al. Successful antibiotic eradication of *Streptococcus pneumoniae* infection of a ventriculoatrial shunt. *Int J Infect Dis*. 2009;13:e101–e103.
180. Ribes S, Taberner F, Domenech A, et al. Evaluation of ceftriaxone, vancomycin and rifampicin alone and combined in an experimental model of meningitis caused by highly cephalosporin-resistant *Streptococcus pneumoniae* ATCC 51916. *J Antimicrob Chemother*. 2005;56:979–982.
181. Suntur BM, Yurtseven T, Sipahi OR, et al. Rifampicin+ceftriaxone versus vancomycin+ceftriaxone in the treatment of penicillin- and cephalosporin-resistant pneumococcal meningitis in an experimental rabbit model. *Int J Antimicrob Agents*. 2005;26:258–260.
182. van Tilburg PM, Bogaert D, Sluijter M, et al. Emergence of rifampin-resistant *Streptococcus pneumoniae* as a result of antimicrobial therapy for penicillin-resistant strains. *Clin Infect Dis*. 2001;33:e93–e96.
183. Holmberg A, Morgelin M, Rasmussen M. Effectiveness of ciprofloxacin or linezolid in combination with rifampicin against *Enterococcus faecalis* in biofilms. *J Antimicrob Chemother*. 2012;67:433–439.
184. Minardi D, Cirioni O, Ghiselli R, et al. Efficacy of tigecycline and rifampin alone and in combination against *Enterococcus faecalis* biofilm infection in a rat model of ureteral stent. *J Surg Res*. 2012;176:1–6.
185. Silvestri C, Cirioni O, Arzeni D, et al. In vitro activity and in vivo efficacy of tigecycline alone and in combination with daptomycin and rifampin against gram-positive cocci isolated from surgical wound infection. *Eur J Clin Microbiol Infect Dis*. 2012;31:1759–1764.
186. Skinner K, Sandoe J, Rajendran R, et al. Efficacy of rifampicin combination therapy for the treatment of enterococcal infections assessed in vivo using a *Galleria mellonella* infection model. *Int J Antimicrob Agents*. 2017;49:507–511.
187. Swaminathan S, Alangaden GJ. Treatment of resistant enterococcal urinary tract infections. *Curr Infect Dis Rep*. 2010;12:455–464.
188. Dournon E, Mayaud C, Wolff M, et al. Comparison of the activity of three antibiotic regimens in severe legionnaires' disease. *J Antimicrob Chemother*. 1990;26(supplB):129–139.
189. Grau S, Antonio JM, Ribes E, et al. Impact of rifampicin addition to clarithromycin in *Legionella pneumophila* pneumonia. *Int J Antimicrob Agents*. 2006;28:249–252.
190. Varner TR, Bookstaver PB, Rudisill CN, et al. Role of rifampin-based combination therapy for severe community-acquired *Legionella pneumophila* pneumonia. *Ann Pharmacother*. 2011;45:967–976.
191. Tse KC, Tang SC, Chan TM, et al. *Rhodococcus* lung abscess complicating kidney transplantation: successful management by combination antibiotic therapy. *Transpl Infect Dis*. 2008;10:44–47.
192. Cronin SM, Abidi MH, Shearer CJ, et al. *Rhodococcus* equi lung infection in an allogeneic hematopoietic stem cell transplant recipient. *Transpl Infect Dis*. 2008;10:48–51.
193. Li J, Rayner CR, Nation RL, et al. Heteroresistance to colistin in multidrug-resistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother*. 2006;50:2946–2950.
194. Nordqvist H, Nilsson L, Claesson C. Mutant prevention concentration of colistin alone and in combination with rifampicin for multidrug-resistant *Acinetobacter baumannii*. *Eur J Clin Microbiol Infect Dis*. 2016;35:1845–1850.
195. Lim TP, Lee W, Tan TY, et al. Effective antibiotics in combination against extreme drug-resistant *Pseudomonas aeruginosa* with decreased susceptibility to polymyxin B. *PLoS ONE*. 2011;6:e28177.
196. Urban C, Mariano N, Rahal JJ. In vitro double and triple bactericidal activities of doripenem, polymyxin B, and rifampin against multidrug-resistant *Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Escherichia coli*. *Antimicrob Agents Chemother*. 2010;54:2732–2734.
197. Dong X, Chen F, Zhang Y, et al. In vitro activities of rifampin, colistin, sulbactam and tigecycline tested alone and in combination against extensively drug-resistant *Acinetobacter baumannii*. *J Antibiot (Tokyo)*. 2014;67:677–680.
198. Song JY, Cheong HJ, Lee J, et al. Efficacy of monotherapy and combined antibiotic therapy for carbapenem-resistant *Acinetobacter baumannii* pneumonia in an immunosuppressed mouse model. *Int J Antimicrob Agents*. 2009;33:33–39.
199. Lagerbäck P, Khine W, Giske C, et al. Evaluation of antibacterial activities of colistin, rifampicin and meropenem combinations against NDM-1-producing *Klebsiella pneumoniae* in 24 h in vitro time-kill experiments. *J Antimicrob Chemother*. 2016;71:2321–2325.
200. Hu Y, Liu C, Wang N, et al. In vitro antibacterial activity of rifampicin in combination with imipenem, meropenem and doripenem against multidrug-resistant clinical isolates of *Pseudomonas aeruginosa*. *BMC Infect Dis*. 2016;16:444–453.
201. Mohammadi M, Khayat H, Sayehmiri K, et al. Synergistic effect of colistin and rifampin against multidrug resistant *Acinetobacter baumannii:* a systematic review and meta-analysis. *Open Microbiol J*. 2017;11:63–71.
202. Wan G, Ruan L, Yin Y, et al. Effects of silver nanoparticles in combination with antibiotics on the resistant bacteria *Acinetobacter baumannii*. *Int J Nanomedicine*. 2016;11:3789–3800.
203. Bassetti M, Repetto E, Righi E, et al. Colistin and rifampicin in the treatment of multidrug-resistant *Acinetobacter baumannii* infections. *J Antimicrob Chemother*. 2008;61:417–420.
204. Durante-Mangoni E, Signoriello G, Andini R, et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant *Acinetobacter baumannii*: a multicenter, randomized clinical trial. *Clin Infect Dis*. 2013;57:349–358.
205. Aydemir H, Akduman D, Piskin N, et al. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *Epidemiol Infect*. 2013;141:1214–1222.
206. Yousefi-Nooraie R, Mortaz-Hejri S, Mehrani M, et al. Antibiotics for treating human brucellosis. *Cochrane Database Syst Rev*. 2012;(10):CD007179.
207. Solis Garcia del Pozo J, Solera J. Systematic review and meta-analysis of randomized clinical trials in the treatment of human brucellosis. *PLoS ONE*. 2012;7:e32090.
208. Hasanain A, Mahdy R, Mohamed A, et al. A randomized, comparative study of dual therapy (doxycycline-rifampin) versus triple therapy (doxycycline-rifampin-levofloxacin) for treating acute/subacute brucellosis. *Braz J Infect Dis*. 2016;20:250–254.
209. Abdel-Maksoud M, House B, Wasfy M, et al. In vitro antibiotic susceptibility testing of *Brucella* isolates from Egypt between 1999 and 2007 and evidence of probable rifampin resistance. *Ann Clin Microbiol Antimicrob*. 2012;11:24.
210. Centers for Disease Control and Prevention. Laboratory-acquired brucellosis—Indiana and Minnesota, 2006. *Morb Mortal Wkly Rep*. 2008;57:39–42.

211. Rolain JM, Brouqui P, Koehler JE, et al. Recommendations for treatment of human infections caused by *Bartonella* species. *Antimicrob Agents Chemother*. 2004;48:1921–1933.
212. Watt G, Kantipong P, Jongsakul K, et al. Doxycycline and rifampicin for mild scrub-typhus infections in northern Thailand: a randomised trial. *Lancet*. 2000;356:1057–1061.
213. Medoff G. Antifungal action of rifampin. *Rev Infect Dis*. 1983;5(suppl 3):S614–S619.
214. Del Pozo JL, Frances ML, Hernaez S, et al. Effect of amphotericin B alone or in combination with rifampicin or clarithromycin against *Candida* species biofilms. *Int J Artif Organs*. 2011;34:766–770.
215. Spader TB, Venturini TP, Cavalheiro AS, et al. In vitro interactions between amphotericin B and other antifungal agents and rifampin against *Fusarium* spp. *Mycoses*. 2011;54:131–136.
216. He Y, Zhou L, Gao C, et al. Rifampin enhances the activity of amphotericin B against *Fusarium solani* species complex and *Aspergillus flavus* species complex isolates from keratitis patients. *Antimicrob Agents Chemother*. 2017;61:e02069-16.
217. Gisbert JP, Castro-Fernandez M, Perez-Aisa A, et al. Fourth-line rescue therapy with rifabutin in patients with three *Helicobacter pylori* eradication failures. *Aliment Pharmacol Ther*. 2012;35:941–947.
218. Perri F, Festa V, Clemente R, et al. Randomized study of two "rescue" therapies for *Helicobacter pylori*-infected patients after failure of standard triple therapies. *Am J Gastroenterol*. 2001;96:58–62.
219. Bental T, Fejgin M, Keysary A, et al. Chronic Q fever of pregnancy presenting as *Coxiella burnetii* placentitis: successful outcome following therapy with erythromycin and rifampin. *Clin Infect Dis*. 1995;21:1318–1321.
220. Rajapakse S, Rodrigo C, Fernando SD. Drug treatment of scrub typhus. *Trop Doct*. 2011;41:1–4.
221. Krause PJ, Corrow CL, Bakken JS. Successful treatment of human granulocytic ehrlichiosis in children using rifampin. *Pediatrics*. 2003;112:e252–e253.
222. Tandon P, Rowe BH, Vandermeer B, et al. The efficacy and safety of bile acid binding agents, opioid antagonists, or rifampin in the treatment of cholestasis-associated pruritus. *Am J Gastroenterol*. 2007;102:1528–1536.
223. Zalmanovici Trestioreanu A, Fraser A, Gafter-Gvili A, et al. Antibiotics for preventing meningococcal infections. *Cochrane Database Syst Rev*. 2011;(8):CD004785.
224. *Haemophilus influenzae* infections. In: Pickering LK, Baker CJ, Kimberlin DW, et al, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases*. Elk Ridge, IL: American Academy of Pediatrics; 2012:345–352.
225. Band JD, Fraser DW, Ajello G. Prevention of *Haemophilus influenzae* type b disease. *JAMA*. 1984;251:2381–2386.
226. Lorente L, Lecuona M, Ramos MJ, et al. The use of rifampicin-miconazole–impregnated catheters reduces the incidence of femoral and jugular catheter–related bacteremia. *Clin Infect Dis*. 2008;47:1171–1175.
227. Weber JM, Sheridan RL, Fagan S, et al. Incidence of catheter-associated bloodstream infection after introduction of minocycline and rifampin antimicrobial-coated catheters in a pediatric burn population. *J Burn Care Res*. 2012;33:539–543.
228. Schierholz JM, Nagelschmidt K, Nagelschmidt M, et al. Antimicrobial central venous catheters in oncology: efficacy of a rifampicin-miconazole-releasing catheter. *Anticancer Res*. 2010;30:1353–1358.
229. Gilbert R, Mok Q, Dwan K, et al. Impregnated central venous catheters for prevention of bloodstream infection in children (the CATCH trial): a randomized controlled trial. *Lancet*. 2016;387:1932–1942.
230. Geenes V, Chambers J, Khurana R, et al. Rifampicin in the treatment of severe intrahepatic cholestasis of pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2015;189:59–63.
231. Farouk O, Abdelkhalek M, Abdallah A, et al. Rifampicin for idiopathic granulomatous lobular mastitis: a promising alternative for treatment. *World J Surg*. 2017;41:1313–1321.
232. Iddrisah F, Yeboah-Manu D, Nortey P, et al. Outcome of streptomycin-rifampicin treatment of buruli ulcer in two Ghanaian distracts. *Pan Afr Med J*. 2016;25(suppl 1):13.
233. Zhu L, Kang H, Guo C, et al. Rifampin suppresses osteoclastogenesis and titanium-particle induced osteolysis via modulating RANKL signaling pathways. *Biochem Biophys Res Commun*. 2017;484:64–70.
234. Umeda T, Ono K, Sakai A, et al. Rifampicin is a candidate preventive medicine against amyloid-β and tau oligomers. *Brain*. 2016;139(Pt 5):1568–1586.
235. DuPont HL. Biologic properties and clinical uses of rifaximin. *Exp Opin Pharmacother*. 2011;12:293–302.
236. Hirota SA. Understanding the molecular mechanisms of rifaximin in the treatment of gastrointestinal disorders–a focus on the modulation of host tissue function. *Mini Rev Med Chem*. 2015;16:206–217.
237. Kane JS, Ford AC. Rifaximin for the treatment of diarrhea-predominant irritable bowel syndrome. *Expert Rev Gastroenterol Hepatol*. 2016;10:431–442.
238. DuPont HL, Jiang ZD, Okhuysen PC, et al. A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travelers' diarrhea. *Ann Intern Med*. 2005;142:805–812.
239. Jiang ZD, Ke S, Dupont HL. Rifaximin-induced alteration of virulence of diarrhoea-producing *Escherichia coli* and *Shigella sonnei*. *Int J Antimicrob Agents*. 2010;35:278–281.
240. Hill DR, Ericsson CD, Pearson RD, et al. The practice of travel medicine: guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2006;43:1499–1539.
241. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med*. 2010;362:1071–1081.
242. Paik YH, Lee KS, Han KH, et al. Comparison of rifaximin and lactulose for the treatment of hepatic encephalopathy: a prospective randomized study. *Yonsei Med J*. 2005;46:399–407.
243. Garey KW, Jiang ZD, Bellard A, et al. Rifaximin in treatment of recurrent *Clostridium difficile*-associated diarrhea: an uncontrolled pilot study. *J Clin Gastroenterol*. 2009;43:91–93.
244. O'Connor JR, Galang MA, Sambol SP, et al. Rifampin and rifaximin resistance in clinical isolates of *Clostridium difficile*. *Antimicrob Agents Chemother*. 2008;52:2813–2817.
245. Guslandi M. Rifaximin in the treatment of inflammatory bowel disease. *World J Gastroenterol*. 2011;17:4643–4646.
246. Colecchia A, Vestito A, Pasqui F, et al. Efficacy of long term cyclic administration of the poorly absorbed antibiotic rifaximin in symptomatic, uncomplicated colonic diverticular disease. *World J Gastroenterol*. 2007;13:264–269.
247. Valentin T, Leitner E, Rohn A, et al. Rifaximin intake leads to emergence of rifampin-resistant staphylococci. *J Infect*. 2011;62:34–38.
248. Ruiz J, Mensa L, Pons MJ, et al. Development of *Escherichia coli* rifaximin-resistant mutants: frequency of selection and stability. *J Antimicrob Chemother*. 2008;61:1016–1019.
249. Scarpignato C, Dolak W, Lanas A, et al. Rifaximin reduces the number and severity of intestinal lesions associated with use of nonsteroidal anti-inflammatory drugs in humans. *Gastroenterology*. 2017;152:980–982.
250. Hirata T, Saito H, Tomioka H, et al. In vitro and in vivo activities of the benzoxazinorifamycin KRM-1648 against *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother*. 1995;39:2295–2303.
251. Xia M, Suchland RJ, Carswell JA, et al. Activities of rifamycin derivatives against wild-type and *rpoB* mutants of *Chlamydia trachomatis*. *Antimicrob Agents Chemother*. 2005;49:3974–3976.
252. Dietze R, Teixeira L, Rocha LM, et al. Safety and bactericidal activity of rifalazil in patients with pulmonary tuberculosis. *Antimicrob Agents Chemother*. 2001;45:1972–1976.
253. Stamm WE, Batteiger BE, McCormack WM, et al. A randomized, double-blind study comparing single-dose rifalazil with single-dose azithromycin for the empirical treatment of nongonococcal urethritis in men. *Sex Transm Dis*. 2007;34:545–552.
254. Geisler WM, Pascual ML, Mathew J, et al. Randomized, double-blind, multicenter safety and efficacy study of rifalazil compared with azithromycin for treatment of uncomplicated genital *Chlamydia trachomatis* infection in women. *Antimicrob Agents Chemother*. 2014;58:4014–4019.
255. Son YJ, McConville JT. A new respirable form of rifampicin. *Eur J Pharm Biopharm*. 2011;78:366–376.
256. Manca ML, Manconi M, Valenti D, et al. Liposomes coated with chitosan-xanthan gum (chitosomes) as potential carriers for pulmonary delivery of rifampicin. *J Pharm Sci*. 2012;101:566–575.
257. Zhou QT, Gengenbach T, Denman JA, et al. Synergistic antibiotic combination powders of colistin and rifampicin provide high aerosolization efficiency and moisture protection. *AAPS J*. 2014;16:37–47.
258. Ruckh TT, Oldinski RA, Carroll DA, et al. Antimicrobial effects of nanofiber poly(caprolactone) tissue scaffolds releasing rifampicin. *J Mater Sci Mater Med*. 2012;23:1411–1420.
259. Di Stefano AF, Rusca A, Loprete L, et al. Systemic absorption of rifamycin SV MMX administered as modified-release tablets in healthy volunteers. *Antimicrob Agents Chemother*. 2011;55:2122–2128.
260. DuPont HL, Petersen A, Zhao J, et al. Targeting of rifamycin SV to the colon for treatment of travelers' diarrhea: a randomized, double-blind, placebo-controlled phase 3 study. *J Travel Med*. 2014;21:369–376.
261. Smitha KT, Nisha N, Maya S, et al. Delivery of rifampicin-chitin nanoparticles into the intracellular compartment of polymorphonuclear leukocytes. *Int J Biol Macromol*. 2015;74:36–43.
262. Song X, Lin Q, Guo L, et al. Rifampicin loaded mannosylated cationic nanostructured lipid carriers for alveolar macrophage-specific delivery. *Pharm Res*. 2015;32:1741–1751.

28 Metronidazole

Jerod L. Nagel and David M. Aronoff

SHORT VIEW SUMMARY

Description

- Metronidazole is a nitroimidazole drug that is widely prescribed as a first-line agent for various anaerobic and parasitic infections and is recommended as an alternative agent (in patients unable to take oral vancomycin or fidaxomicin) for treatment of *Clostridioides difficile* (formerly *Clostridium difficile*) colitis.

Spectrum

- There is minimal resistance to *Bacteroides* and other gastrointestinal anaerobes. However, emerging resistance is noted with *Gardnerella vaginalis*, *Helicobacter pylori*, and *C. difficile*, and metronidazole lacks activity against a number of non–spore-forming, gram-positive anaerobic bacteria including *Actinomyces, Bifidobacterium, Lactobacillus, Propionibacterium*,[1,2,3] and *Cutibacterium acnes* (formerly *Propionibacterium acnes*).

Clinical Pharmacology

- Metronidazole is available in many formulations; it has excellent bioavailability and excellent tissue penetration, including penetration into the central nervous system (CNS).

Toxicity

- Most patients tolerate metronidazole, but common adverse effects include nausea, diarrhea, dry mouth, metallic taste, candidal vaginitis, and stomatitis. Serious adverse effects include dizziness, headache, confusion, vertigo, insomnia, Stevens-Johnson syndrome, pancreatitis, ophthalmologic toxicity (myopia and blurred vision), ototoxicity, bullous pemphigoid, and hemolytic-uremic syndrome.

HISTORY

Metronidazole was first synthesized in the 1950s when the pharmaceutical company Rhône-Poulenc was searching for an effective antitrichomonal drug for the treatment of vaginal trichomoniasis.[4] Initially, a crude extract of a *Streptomyces* bacterium was found to kill *Trichomonas vaginalis,* and the active component was determined to be azomycin, a previously characterized nitroimidazole antibiotic.[5] Metronidazole was a synthetic analogue of azomycin that was both more active against *T. vaginalis* and less toxic.[4,6] It was initially called 8823 R.P.[4] This discovery soon led to its successful use in human clinical studies of trichomoniasis.[7,8] The presumed antibacterial activity of metronidazole was discovered incidentally in 1962 by Shinn, who reported improvement in ulcerative gingivitis in a patient treated for a concomitant *T. vaginalis* infection, a result he confirmed in a series of patients with ulcerative stomatitis.[9]

MECHANISM OF ACTION

Metronidazole and other nitroimidazoles (e.g., nimorazole, ornidazole, ronidazole, secnidazole, tinidazole) are inert, and their spectrum of antimicrobial activity is determined by the capacity of susceptible organisms to activate the drugs once they enter the cell via passive diffusion. The structures of metronidazole and related compounds are illustrated in Fig. 28.1. Their bactericidal and parasiticidal activities are rapid and proportional to the concentration of the activated drugs within the target cell.[10] The members of this class of antibiotics are therefore best considered as prodrugs, which are activated through a reduction step to form highly reactive products that interact with intracellular targets (see later).[11] Metronidazole's mechanism of action describes that of the other nitroimidazoles.

The nitroimidazoles share a heterocyclic structure consisting of an imidazole-based nucleus with a nitro group, NO_2, in position 5. There are four major steps involved in the mechanism of action of metronidazole that result in the intracellular formation of critical redox intermediate metabolites.[12] In the first two steps, the drug enters cells by passive diffusion and an electron is transferred to the nitro group of metronidazole, resulting in the production of a short-lived nitroso free radical, which is cytotoxic and can interact with cellular DNA.[1] This process of activating the prodrug creates a concentration gradient that augments the increased uptake of the drug by the organism, further increasing its antimicrobial effect. The third step in metronidazole's action relates to the cytotoxic effect of the reduced product because the activated metronidazole compound can inhibit DNA synthesis and induce DNA damage via oxidation, resulting in single-strand and double-strand breaks.[1] Thus, metronidazole induces DNA degradation and cell death.[1] Finally, there is the release of inactive end products of the drug.[13]

The microbial selectivity of metronidazole reflects the inability of aerobic bacteria to activate the prodrug because they lack the necessary electron transport proteins with sufficient negative redox potential.[1] However, in susceptible anaerobic bacteria, the redox potential of components of the electron transport chain is sufficiently negative to reduce the nitro group of metronidazole. The drug is activated in anaerobic bacteria when it receives an electron from ferredoxin or flavodoxin, which are themselves reduced by iron-sulfur proteins called pyruvate:ferredoxin oxidoreductases (PFORs).[14] The exact electron donors involved in nitroimidazole reduction vary depending on the organism.[1] In the microaerophile *Helicobacter pylori,* for example, a separate mechanism appears to be involved in metronidazole susceptibility, involving a two-electron transfer step mediated by an oxygen-insensitive nitroreductase (RdxA).[1] Several microaerophilic protists (*Giardia lamblia, Entamoeba histolytica,* and *T. vaginalis*) have bacteria-like enzymes (nitroreductases) capable of activating metronidazole.[15]

SPECTRUM OF ACTIVITY

Metronidazole and related nitroimidazoles are active against a variety of anaerobic bacteria, in addition to microaerophilic bacteria and protozoa. Resistance, as detailed later, has been increasingly detected in certain organisms, although this may not be identified easily because sensitivity testing for anaerobes is not performed routinely. However, the emergence of resistance suggests that ongoing surveillance is important.[1]

Many gram-negative anaerobes are susceptible to metronidazole.[16,17] As a rule, members of the genera *Bacteroides* and *Parabacteroides* are susceptible to metronidazole, with resistance generally detected in fewer than 5% of isolates.[18,19,20,21,22,23] Higher rates of resistance have been reported among *Bacteroides* isolates in South Africa.[24] *Desulfovibrio* species are also highly susceptible,[25] and clinically relevant members of the *Fusobacterium, Porphyromonas, Prevotella,* and *Bilophila* genera are usually sensitive.[16,26] However, nonsusceptible *Prevotella* strains have been described.[16] Metronidazole resistance has been reported in oral

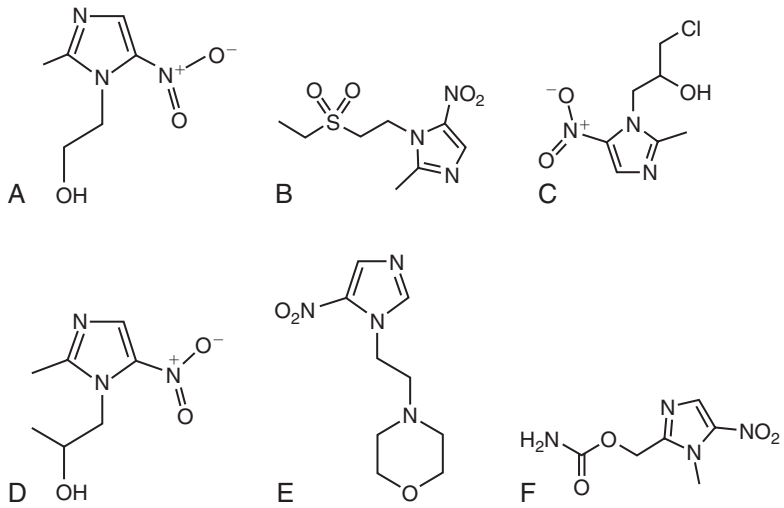

FIG. 28.1 Structures of nitroimidazoles. (A) Metronidazole. (B) Tinidazole. (C) Ornidazole. (D) Secnidazole. (E) Nimorazole. (F) Ronidazole.

isolates of *Porphyromonas gingivalis.*[27] Reduced susceptibility has also been noted in isolates of *Sutterella*[16] and in the gram-negative coccus *Veillonella.*[17,28] The bacterial vaginitis–associated bacteria of the genus *Mobiluncus* are usually not susceptible to metronidazole.[29,30]

Facultative anaerobes have variable susceptibility to metronidazole and in general are not empirically treated with this agent. *Aggregatibacter actinomycetemcomitans* is occasionally susceptible, but resistance is sufficiently common that empirical metronidazole should not be used for these infections.[27,31] Another oral, facultative anaerobe, *Eikenella corrodens,* is generally resistant to the nitroimidazoles.[32] The CO_2-requiring members of the genus *Capnocytophaga* are generally resistant to metronidazole.[33] Although *Campylobacter jejuni* and *Campylobacter coli* isolates may be susceptible in vitro to metronidazole, the drug is not recommended for therapy against these pathogens.[34] *Gardnerella vaginalis,* which is associated with bacterial vaginosis, is variable in its sensitivity, with nearly 30% of isolates in one series demonstrating resistance, suggesting that resistance should be considered in cases of treatment failure.[35] A survey from India documented that nearly 70% of *G. vaginalis* strains were metronidazole resistant, but the cases included metronidazole-exposed women exhibiting recurrent infection.[36] The clinical relevance of in vitro resistance of *Gardnerella* to metronidazole is difficult to interpret because a hydroxy metabolite of metronidazole is actually more active against *G. vaginalis* than the parent compound.[37,38]

H. pylori is a facultative anaerobe that was initially sensitive to metronidazole but has increasingly developed clinically important resistance. Globally, the prevalence of resistance to metronidazole in *H. pylori* is as high as 41.6% to 99.5% depending on the setting (including the United States) and the method of testing.[39,40] Treatment failure for *H. pylori* was a significant risk factor for harboring a metronidazole-resistant isolate.[41]

Among the gram-positive anaerobes, the clostridia remain quite susceptible to metronidazole.[2] However, reduced susceptibility to metronidazole has been increasingly noted among strains of *Clostridioides difficile* (formerly *Clostridium difficile*).[42,43,44,45] In Europe and Israel, resistance to metronidazole has been noted in 13.3% and 18% of *C. difficile* isolates, respectively.[45] Notably, the Etest overestimates metronidazole susceptibility in *C. difficile* isolates, compared with the more involved agar incorporation–based methods for determining minimal inhibitory concentrations (MICs).[42,44] Whether the clinical response to metronidazole is affected by reduced in vitro susceptibility remains to be determined. However, this deserves closer attention in light of the highly variable concentrations of metronidazole in the stools of treated patients[46,47] and increasing reports of treatment failure and recurrence of *C. difficile* infection (CDI) in metronidazole-treated patients.[48]

An important hole in the anaerobic spectrum of metronidazole is found in its lack of activity against a number of non–spore-forming, gram-positive anaerobic bacteria that possess intrinsic resistance to the drug. These include isolates of *Actinomyces, Bifidobacterium, Lactobacillus,* and *Propionibacterium.*[1,2,3] *Cutibacterium acnes* (formerly *Propionibacterium acnes*) is highly resistant.[2,17,49] Metronidazole should not be routinely used to treat infections with these organisms unless susceptibility is confirmed. In contrast, the genus *Eubacterium* is generally sensitive to metronidazole in vitro.[2]

The nitroimidazoles possess good activity against several protozoa. Apart from *T. vaginalis,* metronidazole has activity against *Giardia* (syn. *G. duodenalis, G. lamblia, G. intestinalis*) and *E. histolytica.* Resistance is uncommon in *Giardia,* and clinical efficacy is generally greater than 90%, but in vitro testing has revealed reduced susceptibility to metronidazole in clinical isolates, causing concern.[50,51] Nitroimidazoles exhibit in vitro activity against *Dientamoeba fragilis,* which is a trichomonad known to cause gastroenteritis.[52]

Apart from its antimicrobial actions, metronidazole exhibits immunosuppressive and antiinflammatory actions[53] and has been used effectively in the treatment of rosacea,[54] although the extent to which this relates to metronidazole's antibacterial properties is unclear.

EFFECTS ON THE HUMAN MICROBIOME

Metronidazole, like many antimicrobials, affects the human microbiome. However, because this has mostly been examined in subjects exposed to metronidazole in combination with other antimicrobials, it is difficult to fully understand the impact of metronidazole itself.[1,55] Although traditionally thought of as a narrow-spectrum agent, metronidazole has a broadly antianaerobic activity, which could significantly shift microbial populations rich in anaerobes, such as the gastrointestinal tract. Although early culture-based studies of the impact of metronidazole monotherapy on bacterial communities in the human gastrointestinal tract described little impact of the drug on microbial populations,[47,56] some investigators reported a suppression of anaerobes and a relative increase in the abundance of certain aerobic bacteria (*Escherichia coli* and fecal streptococci).[57] The reasons for the relatively low impact on normal gut microbes are not well understood but may relate to the pharmacology of metronidazole, which achieves low concentrations in the feces of healthy adults.[46,58] Substitution of similar (but metronidazole-resistant) bacteria could also occur in the setting of metronidazole therapy, which could be missed with use of standard culture-based techniques. At present there are few studies of metronidazole's impact on the gastrointestinal microbiome that have used culture-independent techniques such as DNA pyrosequencing, apart from studies involving antibiotic combinations.[55] This is an area in need of new research.

Nucleic acid sequencing methods have been applied to understand the impact of metronidazole on the microbiome of the female

reproductive tract, particularly in the context of bacterial vaginosis. Topical metronidazole has been evaluated for its impact on the vaginal microbiome in women with bacterial vaginosis.[59–61] Use of metronidazole for 5 to 7 days consistently reduced the diversity of bacterial communities in these studies of bacterial vaginosis, compared with no treatment, and for many women it restored a more normal, *Lactobacillus*-dominated mucosal microbiome.[59–61]

PHARMACOLOGY

Metronidazole is commercially available in a variety of formulations: oral capsules and tablets (immediate and extended release); intravenous solution; topical gels, creams, and lotions; and vaginal gels.[10,62] Although oral metronidazole suspension is not commercially available, it is commonly compounded in pharmacies by crushing immediate-release tablets and mixing in a 1:1 ratio with an aqueous suspending solution and buffered oral syrup.[63] The dose and duration of treatment are dependent on the specific product and indication (Table 28.1). An intravenous loading dose of 15 mg/kg, followed by 7.5 mg/kg every 6 to 8 hours, is recommended in the package insert, with a maximum daily dose limit of 4 g.[10] A fixed dose of 500 mg given intravenously every 8 hours maintains concentrations above typical MICs for *Bacteroides* species and is effective for treatment of intraabdominal infections.[64,65,66] An infusion time of 1 hour is traditionally recommended, but 20- to 30-minute infusions have been used.[67] Given the long half-life and concentration-dependent activity, high-dose metronidazole, administered as 1 to 1.5 g every 24 hours, may be a safe and effective alternative to 500 mg every 6 to 8 hours.[68,69] The typical duration of oral or intravenous metronidazole courses ranges from 1 to 10 days depending on the indication and patient condition. Longer durations may be prescribed, but caution should be exercised with durations greater than 1 month owing to increased risk of peripheral neuropathy and central nervous system (CNS) adverse effects, which is likely due to the effects of metronidazole on mitochondrial function.[70,71,72]

Oral metronidazole is rapidly and almost completely absorbed, with bioavailability approaching 100%.[10,62] When rectally administered, metronidazole is also well absorbed, with reported bioavailability of 59% to 94%; topical and vaginal metronidazole achieve detectable systemic concentrations with bioavailability ranging from 2% to 25%.[10,62,73] Administration of oral metronidazole with food is encouraged to minimize gastrointestinal adverse effects and does not affect bioavailability but may delay the time to peak serum concentrations. Peak serum concentrations range from 12 to 40 μg/mL and occur 1 to 2 hours after oral administration and approximately 3 hours after rectal administration.[10,62]

Metronidazole is a lipophilic molecule with low protein binding and a moderate-to-large volume of distribution, allowing extensive distribution into various tissues (Table 28.2).[10,62] Penetration into inflamed cerebrospinal fluid, epithelial lining fluid, saliva, and bile is excellent and concentrations are similar to those in serum.[10,62,74] Patients with noninflamed meninges still achieve therapeutic concentrations of approximately 43% in serum.[75] In addition, penetration into abscesses, appendix tissue, peritoneal fluid, and pancreatic tissue is very good, ranging from 2.3 to 7.2 μg/mL.[10,62,76] However, patients with obstructive cholecystitis have negligible amounts of drug detected in the bile.[10,62] Metronidazole crosses the placental barrier and penetrates into breast milk and may be teratogenic during the first trimester (see "Precautions").[77] Stool concentrations during *C. difficile* colitis are highest at the beginning of infection and taper as inflammation subsides and stool becomes formed, but concentrations generally remain well above reported MICs.[46] This effect of higher stool concentrations when diarrhea is present is also noted during flares of Crohn disease.[47]

Metronidazole undergoes oxidation as the primary step in eliminating the drug from the body, and 6% to 18% of active unchanged drug is found in the urine.[10,62,78] Oxidation, glucuronidation, and metabolism by cytochrome P-450 system yield five major metabolites, including 1-2 hydroxyethyl-2-hydroxy-methyl-5-nitroimidazole (hydroxy metabolite), which maintains antimicrobial activity; 2-methyl-5-nitroimidazole-1-acetic acid (acetic acid metabolite) is another major metabolite but has no antimicrobial activity.[10,62,78] All metabolites are extensively excreted in the feces or urine and undergo enterohepatic circulation. The enterohepatic circulation and metronidazole pharmacokinetic properties are altered with renal dysfunction, hepatic dysfunction, and severity of diarrhea.[10] The half-life of metronidazole is approximately 8 hours in healthy patients and 18 to 20 hours with end-stage hepatic failure.[79] Patients with moderate-to-severe hepatic diseases should receive a 50% dose reduction.[10] In addition, patients with end-stage renal disease (creatinine clearance <10 mL/min) will have slightly longer half-life of metronidazole and significantly impaired clearance and accumulation of the hydroxy and acetic metabolites.[10,80–86] Metronidazole and metabolites are removed through conventional, continuous, and peritoneal hemodialysis. During a 4-hour conventional hemodialysis session, 45% of drug is removed, and patients should receive a supplemental dose after dialysis. Patients receiving continuous renal replacement therapy also experience significant removal of metronidazole and its metabolites and do not require dose adjustment.[79] Peritoneal dialysis removes approximately 10% of drug.[87] Patients on peritoneal dialysis and those with creatinine clearance less than 10 mL/min not receiving conventional or continuous hemodialysis will have accumulation of active metabolites.[79,80,81,83,84,86] Renal dose adjustment is currently not recommended because the ramifications of metabolite accumulation are not well understood, but caution should be used in long-term therapy.[62] Finally, preterm infants 32 weeks' gestational age or younger will have impaired clearance and may require dose adjustment depending on chronologic age.[88,89]

ADVERSE EFFECTS, CONTRAINDICATIONS, AND PRECAUTIONS

Contraindications

Metronidazole is associated with carcinogenic activity in rats and mice. It should be avoided during the first trimester of pregnancy and used during the second and third trimesters only if clearly necessary.[10,62] There are case reports of fetal malformation occurring with metronidazole exposure during pregnancy, but three large studies failed to demonstrate a link of fetal malformations compared with the general population.[77,90,91] Metronidazole is also excreted in breast milk[92] and has been shown to achieve infant plasma concentrations approximately one-fifth of those observed in the mother's plasma.[93] It has been recommended that nursing be withheld during metronidazole therapy for 12 to 24 hours after oral single doses.[93]

Whenever possible, metronidazole should be avoided during lactation because of its effects on the developing microbiota. Infants may have increased risk of diarrhea, but there is a lack of evidence linking breast milk with carcinogenic effectors or developmental disorders.[93]

Precautions

Patients should avoid metronidazole if there is a history of hypersensitivity with metronidazole, parabens, or nitroimidazole agents or intake of alcohol within 3 days of therapy and/or concomitant use of disulfiram within 2 weeks of metronidazole therapy. Disulfiram-like reactions with alcohol can occur with all routes of administration, including topical and vaginal administration.[10,62] Caution should be exercised when prescribing metronidazole in patients with peripheral neuropathy, hepatic disease, history of seizures, or a history of antibiotic-associated vaginal candidiasis.[10,62] In addition, patients currently taking metronidazole who develop aseptic meningitis, conjunctivitis, edema, seizure, local skin lesions, and peripheral neuropathy should discontinue therapy until drug-related adverse effects can be excluded.[10,62]

Adverse Effects

Metronidazole is generally well tolerated. The most common adverse effects are dose dependent, mild, and reversible. Nausea, diarrhea, dry mouth, metallic taste, candidal vaginitis, and stomatitis occur in 2% to 10% of patients.[10,62] Serious CNS adverse effects (ataxia, encephalopathy, dysarthria, seizure, aseptic meningitis, and peripheral neuropathy) have been reported most commonly with prolonged therapy but are reversible.[77,94] Caution should be used when prescribing metronidazole in patients with seizure history. Other mild CNS effects have been reported, including dizziness, headache, confusion, vertigo, and insomnia. In addition, rare and serious adverse effects associated with metronidazole

TABLE 28.1 Major Preparations and Indications for Metronidazole: Administration and Dosage

PRODUCT	DOSAGE FORM	STRENGTHS	INDICATIONS	DOSE AND ADMINISTRATION
Metronidazole tablet (Flagyl) Metronidazole capsule (Flagyl)	Tablet Capsule	250 mg 500 mg 375 mg	Symptomatic trichomoniasis, asymptomatic trichomoniasis, treatment of asymptomatic consorts, amebiasis, anaerobic bacterial infections, intraabdominal infections, skin and skin suture infections, gynecologic infections, bacterial septicemia, bone and joint infections, CNS infections, lower respiratory tract infections, endocarditis	**Adults** *Acute intestinal amebiasis:* 750 mg tid for 5–10 days *Amebic liver abscess:* 500 or 750 mg tid for 5–10 days *Anaerobic bacteria:* 7.5 mg/kg every 6 h for 7–10 days (may be longer) *Trichomoniasis:* 250 mg tid daily for 7 days 375 mg (capsule) bid for 7 days 2 g single dose or 1 g bid for 1 day **Children** 35–50 mg/kg daily divided into 3 doses for 10 days
Metronidazole extended-release tablet (Flagyl ER)	Extended-release tablet	750 mg[a]	Bacterial vaginosis	**Adults** 750 mg once daily for 7 days
Metronidazole intravenous solution (Metro)	Intravenous solution	500 mg/100 mL (0.74% NaCl) 5 mg/mL (0.74% NaCl)	Anaerobic infections, intraabdominal infections, skin and skin structure infections, gynecologic infections, bacterial septicemia, bone and joint infections, CNS infections, lower respiratory tract infections, endocarditis, prophylaxis	**Adults** *Anaerobic infections:* Loading dose of 15 mg/kg IV over 1 h Maintenance dose: 7.5 mg/kg IV over 1 h every 6 h; usual duration 7–10 days *Colorectal surgery prophylaxis:* Initial: 15 mg/kg IV over 30–60 min about 1 h before surgery Maintenance: 7.5 mg/kg IV over 20–60 min at 6 and 12 h after initial dose
Metronidazole gel (MetroGel-Vaginal, Vandazole)	Vaginal gel	0.75%	Bacterial vaginosis	**Adults** *Bacterial vaginosis:* 1 applicatorful (approximately 5 g containing metronidazole 37.5 mg) intravaginally once or twice daily for 5 days. For once-a-day dosing, administer at bedtime
Metronidazole cream (MetroCream, Rosadan—0.75%) (Noritate—1.0%) Metronidazole gel (Metrogel—1.0%) (Rosadan—0.75%) Metronidazole lotion (MetroLotion) Metronidazole Kit (Rosadan)	Cream Gel Lotion Kit	0.75% 1.0%[a] 0.75% 1.0%[a] 0.75% Metronidazole 0.75% cream + wash[a]	Rosacea	**Adults** *1% strength:* apply a thin film once daily *0.75% strength:* apply a thin film twice daily
Tinidazole (Tindamax)	Tablet	250 mg 500 mg	Trichomoniasis, amebiasis, anaerobic bacterial vaginosis, intraabdominal surgical prophylaxis, giardiasis, and *Helicobacter pylori* infection, nongonococcal urethritis	**Adults** *Acute intestinal amebiasis:* 2 g qd for 3 days *Amebic liver abscess:* 2 g qd for 3–5 days *Trichomoniasis:* 2 g one-time dose *Giardiasis:* 2 g one-time dose *Bacterial vaginosis:* 2 g qd for 2 days **Children** *Acute intestinal amebiasis:* 50 mg/kg qd for 3 days *Amebic liver abscess:* 50 mg/kg qd for 3–5 days *Giardiasis:* 50 mg/kg one-time dose
Secnidazole	Tablet	1000 mg		**Adults** *Acute intestinal amebiasis:* 2 g one-time dose *Trichomoniasis:* 2 g one-time dose *Giardiasis:* 2 g one-time dose *Bacterial vaginosis:* 2 g one-time dose **Children** *Acute intestinal amebiasis:* 30 mg/kg one-time dose *Giardiasis:* 30 mg/kg one-time dose
Ornidazole	Tablet	500 mg		**Adults** *Acute intestinal amebiasis:* 1.5 g qd for 3 days *Bacterial vaginosis:* 1.5 g qd for 3 days **Children** *Acute intestinal amebiasis:* 25 mg/kg qd for 5–10 days *Giardiasis:* 40–50 mg/kg one-time dose

[a]No generic available.
CNS, Central nervous system.

therapy include Stevens-Johnson syndrome, pancreatitis, ophthalmologic toxicity (myopia and blurred vision), ototoxicity, bullous pemphigoid, and hemolytic-uremic syndrome.[10,62,95]

MECHANISMS OF RESISTANCE

Resistance to metronidazole (and other nitroimidazoles) in strict anaerobes remains unusual, and not all mechanisms that reduce susceptibility to the nitroimidazoles have been characterized.[1] On the basis of critical steps in its mechanism of action, several models of drug resistance have been proposed, including reduced antibiotic uptake, active drug efflux, reduced drug activation (e.g., by decreased expression of activating nitroreductase enzymes), drug inactivation (e.g., *nim*-encoded nitroimidazole reductase), and altered DNA repair.[1]

Metronidazole resistance (MIC ≥32 μg/mL) among *Bacteroides* strains is uncommon, generally occurring in less than 5% of isolates.[17,18,23] Although many mechanisms of resistance have been induced in vitro,[96] the best-characterized mechanism in clinical isolates is encoded by the

TABLE 28.2 Pharmacokinetic and Pharmacologic Properties of Metronidazole

PHARMACOLOGIC OR PHARMACOKINETIC FACTOR	RESULT	COMMENTS
Absorption		
Oral	98%–100%	
Rectal	59%–94%	
Vaginal cream	20%	
Vaginal gel	56%	
Topical	2%	
Time to peak		
Oral	1–2 h	
Rectal	3 h	
Topical	8–12 h	
Peak serum concentrations		
Intravenous	25 and 18 μg/mL	After 15 mg/kg load and 7.5 mg/kg every 6 h
Oral	6, 12, 21.4, and 40 μg/mL	After single dose of 250 mg, 500 mg, 750 mg, and 2000 mg
Rectal	18.5 μg/mL	After 500-mg dose
Topical	27.5 μg/mL	After application of 1% cream
Volume of distribution		
Adults	0.55 L/kg	
Neonates	0.54–0.81 L/kg	
Tissue and fluid penetration		
CSF (inflamed meninges)	Approximates serum concentration	
CSF (noninflamed meninges)	45% of serum concentration	
Bile	Approximates serum concentration	
Epithelial lining fluid	Approximates serum concentration	
Saliva	Approximates serum concentration	
Abscess	Variable, but high concentration	
Peritoneal fluid	High concentrations: 7.2–14.2 μg/mL	
Pancreatic tissue	High concentration: 5.1–8.5 μg/mL	
Metabolism		
Oxidation	Primary mechanism of elimination	
Glucuronidation	Secondary mechanism of elimination	
Cytochrome P450	Secondary mechanism of elimination	
Excretion		
Unchanged drug	6%–18%	
Metabolites	60%–80%	
Hemodialysis	Removes 25%–45% over 4 h	
Peritoneal dialysis	Removes 10% over 7.5 h	
Protein binding	<20%	
Pregnancy	Avoid in first trimester Category B	
Lactation	Avoid	Significant penetration into breast milk

CSF, Cerebrospinal fluid.

nim (5-nitroimidazole reductase) genes *(nimA–H* and *nimJ).*[97,98] The *nim* genes induce the reduction of the nitrate residue of metronidazole (and related compounds) into an inert amino derivate without any toxicity for the bacterial chromosome.[18] These genes may occur in all *Bacteroides* species and are located either on plasmids or on the chromosome.[21] In a recent survey of 640 *Bacteroides* isolates obtained from across Europe, 21 strains (3.3%) had MIC values greater than or equal to 4 μg/mL. Notably, of only three isolates (two *Bacteroides fragilis* strains and one *Bacteroides thetaiotaomicron* isolate) harboring *nim* genes, one was resistant to metronidazole.[21] The two metronidazole-susceptible *B. fragilis* isolates had chromosomal *nimA* and *nimC* genes, whereas a *nimE* gene was identified on a plasmid in the resistant *B. thetaiotaomicron* strain.[21] It was speculated that a small number of *nim*-negative, but metronidazole-resistant, *Bacteroides* strains identified in this study might have used diverse resistance strategies, including reduced uptake, nitroreductase and/or PFOR activities, increased lactate dehydrogenase activity, or mutations that alter the carbohydrate utilization affecting the redox state.[21] Studies have suggested that alterations in the *recA* gene encoding the RecA protein involved in DNA damage repair might be a resistance strategy in *Bacteroides.*[99]

Resistance and heteroresistance of *C. difficile* have been reported for metronidazole, and the mechanisms are unclear but appear to be multifactorial, including the assay and testing condition.[100] A recent review noted that metronidazole resistance in *C. difficile* likely reflects several mechanisms, including exclusion by biofilms and alterations in yet to be defined metabolic pathways, such as those involving the activity of nitroreductases, iron uptake, and DNA repair.[45] The high prevalence of metronidazole resistance among *H. pylori* strains is concerning and appears to be due primarily to decreased activation of the drug, which would also be expected to affect its accumulation within the bacterium. Mutations in the oxygen-insensitive reduced nicotinamide adenine dinucleotide phosphate (NADPH) nitroreductase RdxA or the NADPH-flavin-oxidoreductase FrxA confer resistance to metronidazole in *H. pylori.*[101] Mutations in *rdxA* and *frxA* are frequently associated with metronidazole resistance, but next-generation sequencing studies have revealed that a gene, *rpsU,* might also play a role in *H. pylori* resistance.[102] *H. pylori* might use other strategies to protect itself against nitroimidazole-induced damage, but the relative importance of such mechanisms in vivo remains speculative.[103,104]

Resistance to metronidazole has emerged in protozoal pathogens. Trichomonal resistance was suspected on the basis of clinical treatment failure as early as 1960[105] and was documented in vitro in 1962 in treatment-refractory clinical isolates,[106] but prevalence has generally remained below 10%.[107] A survey from six US cities tested 538 *T. vaginalis* isolates for nitroimidazole resistance (aerobic minimal lethal concentration [MLC] >50 μg/mL) and found that 23 (4.3%) exhibited low-level in vitro metronidazole resistance (MLC, 50–100 μg/mL).[107] However, there were no isolates identified with moderate- to high-level nitroimidazole resistance.[107] An unsettling report from New Guinea revealed that 17.4% of *T. vaginalis* strains (4 out of 23 isolates) exhibited metronidazole resistance under aerobic conditions (MIC >200 μM), but the number of isolates tested was relatively small and the organisms were sensitive under anaerobic conditions.[108]

The mechanisms of resistance in *T. vaginalis* appear to differ between laboratory-generated nitroimidazole resistance and those found in clinical isolates.[109] Laboratory-induced resistance manifests in anaerobic conditions and results from a loss of the aforementioned drug-activating pathways that reduce the inert prodrug metronidazole to active metabolites.[109] Clinical resistance, on the other hand, typically occurs under aerobic conditions owing to actions of oxygen itself.[109] For example, a study of resistance in clinical strains of *T. vaginalis* found that flavin reductase activity was downregulated, or even absent, in metronidazole-resistant strains.[109] It was postulated that because flavin reductase can reduce oxygen to hydrogen peroxide, its downregulation might impair oxygen scavenging.[109] This would result in resistance because oxygen interferes with the activation of nitroimidazoles by either inhibiting drug-activating pathways or by reoxidizing a critical, toxic, nitroradical anion intermediate, also resulting in reduced metronidazole uptake.[109] A genome sequencing–based approach of *T. vaginalis* identified 72 single nucleotide polymorphisms (SNPs) associated with metronidazole resistance, and a comparison of SNPs within several laboratory-derived resistant lines revealed an overlap with the clinically resistant isolates.[110] Although several SNPs occurred in genes for which no function has yet been assigned, many involved functionally characterized genes implicated in metronidazole resistance (e.g., *PFOR*). Common changes in the expression of genes involved in drug activation (e.g., flavin reductase), accumulation (e.g., multidrug resistance pump), and detoxification (e.g., nitroreductase) were observed.[110] Metronidazole should still be considered first-line therapy for *T. vaginalis,* but resistance should be suspected in patients who do not respond to therapy.

As noted, in *Giardia,* clinical resistance occurs in approximately 20% of cases.[51] Microbiologic resistance to metronidazole is complex but appears to be due to a lack of activation of the prodrug to the active nitroso free radical.[111] Resistance to metronidazole has traditionally been explained by a loss of ferredoxin and PFOR activities.[112] However, recent studies have suggested that some metronidazole-resistant *G. lamblia* strains have normal activity levels of these redox proteins, and metronidazole can be activated by a flavin adenine dinucleotide (FAD)–dependent *G. lamblia* thioredoxin reductase.[111] Although not entirely clear, drug resistance in those isolates appeared to be related to lower availability of reduced FAD.[111] Resistance to metronidazole in amebas has been associated with an increase in iron-containing superoxide dismutase, without a significant decrease of the PFOR activity.[112]

CLINICAL USES

Parasitic Infections

Trichomonas

Metronidazole was developed for its use as an antitrichomonal agent.[6] The nitroimidazoles remain the most important pharmaceutical class for these infections, and tinidazole appears to be equivalent or superior to metronidazole in this regard.[113] The emergence of nitroimidazole resistance (see earlier) and treatment failures is problematic because alternative therapies are not reliably curative.[113] Metronidazole appears to be safe for use in pregnant women with *T. vaginalis* infections.[114] Although trichomoniasis is associated with adverse pregnancy outcomes, including low birth weight, premature membrane rupture, and preterm birth, it is not clear that treatment alters the incidence of such complications.[115] Symptomatic pregnant women, regardless of pregnancy stage, should be tested and considered for treatment with single-dose (2 g) oral metronidazole.[115]

Dientamoeba

Symptomatic gastrointestinal *D. fragilis* infections of adults and children have been treated successfully with metronidazole.[116,117] A parallel, placebo-controlled, double-blind trial of metronidazole in children with chronic symptoms attributed to *D. fragilis* failed to find a benefit of this antimicrobial.[118] The nitroimidazoles are among the most potent agents against this parasite in vitro.[52]

Entamoeba

Amebic infections caused by *E. histolytica* are treated with metronidazole, depending on whether the infection is luminal within the intestinal tract or invasive, such as occurs with hepatic abscess.[119] Metronidazole is the most commonly used medication for amebic colitis, although tinidazole was reported to be better tolerated and more efficacious.[119,120] The treatment of amebic liver abscess includes metronidazole (or tinidazole) with or without aspiration.[119] Treatment for colitis or hepatic abscess with a tissue amebicide such as metronidazole should be followed by an agent active against luminal amebas, such as paromomycin.[119]

Giardia

Giardiasis is primarily treated with nitroimidazole drugs such as metronidazole, tinidazole, and nitazoxanide[119] Tinidazole and nitazoxanide are recommend first-line options, are indicated for patients older than 3, and can be given as a single-dose regimen and a 3-day regimen, respectively.[121] Metronidazole is also an option for treatment of *Giardia* but should be prescribed for 5 to 7 days. There are limited data evaluating tinidazole in patients younger than 3 years, and nitazoxanide in patients younger than 1 year. It might be prudent to use metronidazole, because there are established safety and efficacy data in patients younger than 1 year. Refractory or relapsed *Giardia* infection could be the result of resistance, secondary downregulation of nitroreductase 1 (NTR1), and upregulation of (NTR2); use of alternative classes of antiparasitic agents, such as albendazole, mebendazole, or paromomycin (possibly in combination with a nitroimidazole agent), should be considered.[122]

Anaerobic Infections

In light of metronidazole's potent bactericidal activity against anaerobes and its favorable pharmacodynamics profile (distributing throughout the body, including the CNS and into abscess cavities), it is effective for the management of myriad anaerobic infections.[1,10] Metronidazole is commonly used to treat anaerobic infections of the abdomen, CNS infections (including meningitis and brain abscess), gynecologic infections, bacteremia, endocarditis, bone and joint infections, respiratory tract infections, skin and skin structure infections, oral and dental infections, and tetanus.[1,10,123]

The role of metronidazole in the management of lung abscesses is unclear.[124] Small clinical studies have demonstrated striking clinical

failures of metronidazole monotherapy in the management of anaerobic lung abscess,[125,126] including a comparative trial with clindamycin that was halted prematurely because of poor response in the metronidazole arm. Metronidazole failed in patients with lung abscess or necrotizing pneumonia.[126] It has been postulated that the lack of response in lung abscess therapy reflects metronidazole's lack of activity against aerobic and microaerophilic streptococci, and the inclusion of a β-lactam could surmount this challenge.[124]

The emergence of antimicrobial resistance has created new difficulties in treating previously susceptible infections, as described earlier. However, metronidazole is not effective in the treatment of actinomycosis and infections with *C. acnes* owing to intrinsic resistance.[127,128] These exceptions to metronidazole use should be kept in mind.

Metronidazole, tinidazole, and clindamycin are each approved for use to treat bacterial vaginosis.[129] Both metronidazole and clindamycin are approved for either oral or topical application.[129] Head-to-head trials have demonstrated equal efficacy of oral and vaginal clindamycin and metronidazole, although in the majority of studies clindamycin tended to have fewer adverse effects, with oral metronidazole primarily causing a disturbing metallic taste and gastrointestinal upset.[129] Metronidazole appears to be safe for use to treat bacterial vaginosis in pregnancy, although this has not reduced preterm births, a complication associated with bacterial vaginosis.[129,130]

Clostridioides difficile Infection

Metronidazole was once the first-line drug of choice for the treatment of CDI, but increasing reports of treatment failures, recurrent disease after treatment, and inferior performance compared with oral vancomycin in some clinical trials have led to changes to metronidazole's place in CDI therapy.[131,132] A meta-analysis found that vancomycin was superior to metronidazole for the initial treatment of acute, severe CDI but not different for mild-to-moderate disease, and recurrence rates did not differ between the regimens.[133] A large retrospective study of more than 10,000 initial CDI cases conducted through the US Veterans Affairs Healthcare System compared metronidazole and vancomycin and found no difference in initial response to therapy or recurrent infection, but patients with more severe CDI had lower 30-day mortality if treated with vancomycin.[134] In addition, a Cochrane review of clinical trial data concluded that oral vancomycin or fidaxomicin is superior to metronidazole for the treatment of CDI.[135] The emergence of metronidazole resistance in *C. difficile* might also play a role in its diminishing usefulness as a first-line agent.[45,136] In 2017 guidelines for CDI in adults from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America, oral metronidazole is recommended as a first-line agent for mild-to-moderate CDI.[131] Vancomycin is recommended as first-line therapy for severe infection.[131] More recent guidelines are similar with regard to metronidazole's role in CDI management.[137] Metronidazole resistance in *C. difficile* isolates remains uncommon but a concern for the future (see earlier).

Helicobacter pylori Infection

Despite increasing antimicrobial resistance in *H. pylori*, metronidazole remains an important agent for use against infection with this organism.[138] It is recommended as part of a combination three- or four-drug approach to treatment, and metronidazole should be used as part of the regimen whenever possible, even in the presence of resistance.[138]

Other Therapeutic Uses

Metronidazole has been used to treat a number of (apparently) noninfectious diseases. For example, metronidazole has been applied in the treatment of inflammatory bowel disease, with the best evidence for benefit in the settings of perianal Crohn's disease and ulcerative colitis–associated pouchitis.[139] A number of dermatologic disorders have been treated successfully with topical metronidazole, including rosacea and acne vulgaris.[10] In neoplastic diseases, metronidazole has been used in high doses as a radiosensitizing agent.[140]

Prophylactic Use

Metronidazole has held an important place in surgical prophylaxis, particularly for procedures involving mucosal organs colonized by anaerobes, such as the gastrointestinal tract and female reproductive tract. According to surgical prophylaxis guidelines,[141] metronidazole (usually in combination with other antimicrobials) is a first-line recommended agent for the prevention of infection in appendectomy for uncomplicated appendicitis, obstructed small intestinal surgery, colorectal surgery, clean contaminated head and neck cancer surgery, and clean contaminated urologic surgery (extensively reviewed by Bratzler and colleagues[141]). However, the indications for surgical prophylaxis with metronidazole given in Chapter 313 are much more limited. Metronidazole is also recommended as an alternative agent for β-lactam–allergic or intolerant patients for many surgical indications that carry risk for anaerobic infection, in combination with other antimicrobials.[141]

In obstetric and gynecologic procedures, metronidazole has been recommended for preoperative prophylaxis. For example, data suggest that metronidazole reduces infectious complications of surgical abortion.[142] It has been recommended for manual removal of the placenta after parturition and for repair of third- and fourth-degree vaginal tears.[143] It has also been recommended in patients undergoing hysterectomy, hysterosalpingography, or hysteroscopy and for chromotubation in patients with dilated tubes or a history of pelvic inflammatory disease or tubal damage.[143]

DRUG INTERACTIONS AND INTERFERENCE WITH LABORATORY TESTS

The major interactions between metronidazole and other pharmaceuticals or food are listed in Table 28.3. An important and serious interaction exists between warfarin and metronidazole; metronidazole increases the blood levels and hypothrombotic effects of warfarin through inhibition of enzymes responsible for oxygenation of *S*-warfarin.[144] Preemptive

TABLE 28.3 Drug-Drug and Drug-Food Interactions

INTERACTING AGENT	RESULT	COMMENTS
Alcohol	Disulfiram reaction	Symptoms include vomiting, tachycardia, palpitations, or nausea Possible acute psychosis or confusion in severe cases
Amiodarone	May increase amiodarone levels	May increase risk for torsades de pointes and ventricular tachycardia
Amprenavir oral solution	Disulfiram reaction	Propylene glycol in oral solution may cause disulfiram reaction
Busulfan	May increase busulfan levels	Avoid metronidazole administration if possible
Carbamazepine	May increase carbamazepine levels	May increase risk for dizziness, diplopia, nausea
Cimetidine	May increase metronidazole levels	
Cyclosporine	May increase cyclosporine levels	Monitor levels and adjust accordingly
Lithium	May increase lithium levels	Monitor levels and adjust accordingly
Phenytoin	May increase phenytoin levels	Monitor levels and adjust accordingly
Rifampin	May decrease metronidazole levels	
Tacrolimus	May increase tacrolimus levels	Monitor levels and adjust accordingly
Warfarin	May increase warfarin levels	Monitor levels and adjust accordingly Empirical dose adjustment may be considered depending on anticoagulation indication and international normalized ratio

dose reduction of warfarin and close monitoring of prothrombin activity have been recommended if the two drugs require concomitant administration.[145] An uncommonly reported interaction suggests that metronidazole reduces the clearance of the alkylating chemotherapy agent busulfan, increasing the levels of the latter drug.[146] Metronidazole therapy should be avoided with concomitant busulfan whenever possible.

Several case reports have proposed that metronidazole use can increase the systemic concentration of concomitant CYP3A substrates, including amiodarone, carbamazepine, quinidine, tacrolimus, and cyclosporine.[147] However, in vitro studies have not consistently supported CYP3A inhibition as a mechanism of metronidazole drug interaction.[147] Empirical dose adjustments are not required for potential CYP3A interactions, but increased monitoring and patient education are prudent.

Although it is not commonly thought of as a drug that poses a risk for inducing QT interval prolongation or arrhythmias, reports have linked metronidazole to long QT and torsades de pointes.[148,149] In most cases, this appeared to be due to impairment by metronidazole of the cytochrome P-450 metabolism of other agents that were responsible for lengthening the QT interval.[148] Anecdotal reports suggest that metronidazole itself can prolong the QT interval, but this is likely rare.[149]

Metronidazole is largely believed to cause a disulfiram-like effect on ethanol metabolism, leading to symptoms such as severe nausea and vomiting.[150] Adverse effects similar to disulfiram-like reactions have been reported with topical metronidazole administration, including vaginal administration, so ethanol should be avoided during therapy.[150] However, there is controversy about the actual risk for and nature of ethanol-metronidazole interactions.[150,151] Although disulfiram inhibits hepatic aldehyde dehydrogenase, resulting in the accumulation of blood acetaldehyde concentrations after ethanol consumption, metronidazole has not been demonstrated to share this ability.[150] Thus, although metronidazole is associated with disulfiram-like symptoms when administered with ethanol, the mechanism is poorly defined and the incidence is not well understood.[150]

OTHER NITROIMIDAZOLE ANTIMICROBIALS

Tinidazole, secnidazole, and ornidazole are other members of the 5-nitroimidazole class. Trindiazole, which has been widely prescribed in Europe and developing countries, was approved for used in the United States in 2004. All agents in the class exhibit similar mechanism of action, spectrum of activity, toxicity, and adverse effects.[152] However, the distinguishing feature among agents is the half-life and need for less-frequent administration compared with metronidazole.[152] The half-lives for tinidazole, secnidazole, and ornidazole are 10 to 15 hours, 17 to 28.8 hours, and 11 to 14 hours, respectively, which allows for a once-daily dose (see Table 28.1).[152] These agents offer a potential advantage over metronidazole, as a single-dose option for the treatment of intestinal amebiasis, giardiasis, and bacterial vaginosis. However, metronidazole should be considered the drug of choice for life-threatening anaerobic infections because there are limited data evaluating the efficacy and safety of other nitroimidazole agents.[153,154]

Key References

The complete reference list is available online at Expert Consult.

1. Lofmark S, Edlund C, Nord CE. Metronidazole is still the drug of choice for treatment of anaerobic infections. *Clin Infect Dis*. 2010;50(suppl 1):S16–S23.
3. Goldstein EJ, Citron DM, Vreni Merriam C, et al. Comparative *in vitro* activities of ertapenem (MK-0826) against 1,001 anaerobes isolated from human intra-abdominal infections. *Antimicrob Agents Chemother*. 2000;44:2389–2394.
4. Jolles GE. Origins and anti-infective activities of metronidazole. In: Finegold SM, Conference IM, eds. *Metronidazole: Proceedings of the International Metronidazole Conference, Montreal, Quebec, Canada, May 26-28, 1976*. Excerpta Med.; 1977.
10. Freeman CD, Klutman NE, Lamp KC. Metronidazole. A therapeutic review and update. *Drugs*. 1997;54:679–708.
11. Edwards DI. Nitroimidazole drugs—action and resistance mechanisms. I. mechanisms of action. *J Antimicrob Chemother*. 1993;31:9–20.
17. Hecht DW. *Clinical and Laboratory Standards Institute. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria: Approved Standard-Eighth Edition (M11-A8)*. 8th ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2012.
18. Dubreuil L, Odou MF. Anaerobic bacteria and antibiotics: what kind of unexpected resistance could I find in my laboratory tomorrow? *Anaerobe*. 2010;16:555–559.
20. Karlowsky JA, Walkty AJ, Adam HJ, et al. Prevalence of antimicrobial resistance among clinical isolates of *Bacteroides fragilis* group in Canada in 2010-2011: CANWARD surveillance study. *Antimicrob Agents Chemother*. 2012;56:1247–1252.
26. Erwin ME, Fix AM, Jones RN. Three independent yearly analyses of the spectrum and potency of metronidazole: a multicenter study of 1,108 contemporary anaerobic clinical isolates. *Diagn Microbiol Infect Dis*. 2001;39:129–132.
32. Merriam CV, Citron DM, Tyrrell KL, et al. In vitro activity of azithromycin and nine comparator agents against 296 strains of oral anaerobes and 31 strains of *Eikenella corrodens*. *Int J Antimicrob Agents*. 2006;28:244–248.
41. Miendje Deyi VY, Bontems P, Vanderpas J, et al. Multicenter survey of routine determinations of resistance of *Helicobacter pylori* to antimicrobials over the last 20 years (1990 to 2009) in Belgium. *J Clin Microbiol*. 2011;49:2200–2209.
42. Baines SD, O'Connor R, Freeman J, et al. Emergence of reduced susceptibility to metronidazole in *Clostridium difficile*. *J Antimicrob Chemother*. 2008;62:1046–1052.
44. Moura I, Spigaglia P, Barbanti F, et al. Analysis of metronidazole susceptibility in different *Clostridium difficile* PCR ribotypes. *J Antimicrob Chemother*. 2013;68:362–365.
46. Bolton RP, Culshaw MA. Faecal metronidazole concentrations during oral and intravenous therapy for antibiotic associated colitis due to *Clostridium difficile*. *Gut*. 1986;27:1169–1172.
48. Al-Nassir WN, Sethi AK, Nerandzic MM, et al. Comparison of clinical and microbiological response to treatment of *Clostridium difficile*-associated disease with metronidazole and vancomycin. *Clin Infect Dis*. 2008;47:56–62.
50. Farthing MJ. Giardiasis. *Gastroenterol Clin North Am*. 1996;25:493–515.
53. Shakir L, Javeed A, Ashraf M, et al. Metronidazole and the immune system. *Pharmazie*. 2011;66:393–398.
54. van Zuuren EJ, Kramer SF, Carter BR, et al. Effective and evidence-based management strategies for rosacea: summary of a Cochrane systematic review. *Br J Dermatol*. 2011;165:760–781.
62. Lau AH, Lam NP, Piscitelli SC, et al. Clinical pharmacokinetics of metronidazole and other nitroimidazole anti-infectives. *Clin Pharmacokinet*. 1992;23:328–364.
63. Allen LV Jr, Erickson MA 3rd. Stability of ketoconazole, metolazone, metronidazole, procainamide hydrochloride, and spironolactone in extemporaneously compounded oral liquids. *Am J Health Syst Pharm*. 1996;53:2073–2078.
64. Prospective, randomized comparison of metronidazole and clindamycin, each with gentamicin, for the treatment of serious intra-abdominal infection. *Surgery*. 1983;93(1 Pt 2):221–229.
68. Sprandel KA, Schriever CA, Pendland SL, et al. Pharmacokinetics and pharmacodynamics of intravenous levofloxacin at 750 milligrams and various doses of metronidazole in healthy adult subjects. *Antimicrob Agents Chemother*. 2004;48:4597–4605.
69. Wang S, Cunha BA, Hamid NS, et al. Metronidazole single versus multiple daily dosing in serious intraabdominal/pelvic and diabetic foot infections. *J Chemother*. 2007;19:410–416.
70. Boyce EG, Cookson ET, Bond WS. Persistent metronidazole-induced peripheral neuropathy. *Ann Pharmacother*. 1990;24:19–21.
71. Dreger LM, Gleason PP, Chowdhry TK. Gazzuolo DJ. Intermittent-dose metronidazole-induced peripheral neuropathy. *Ann Pharmacother*. 1998;32:267–268.
72. Kusumi RK, Plouffe JF, Wyatt RH, et al. Central nervous system toxicity associated with metronidazole therapy. *Ann Intern Med*. 1980;93:59–60.
77. Diav-Citrin O, Shechtman S, Gotteiner T, et al. Pregnancy outcome after gestational exposure to metronidazole: a prospective controlled cohort study. *Teratology*. 2001;63:186–192.
78. Plaisance KI, Quintiliani R, Nightingale CH. The pharmacokinetics of metronidazole and its metabolites in critically ill patients. *J Antimicrob Chemother*. 1988;21:195–200.
79. Somogyi A, Kong C, Sabto J, et al. Disposition and removal of metronidazole in patients undergoing haemodialysis. *Eur J Clin Pharmacol*. 1983;25:683–687.
80. Gabriel R, Page CM, Collier J, et al. Removal of metronidazole by haemodialysis. *Br J Surg*. 1980;67:553.
81. Holten E, Smith-Erichsen N. Concentration of metronidazole in serum during peritoneal dialysis. *Chemotherapy*. 1981;27:414–415.
82. Houghton GW, Dennis MJ, Gabriel R. Pharmacokinetics of metronidazole in patients with varying degrees of renal failure. *Br J Clin Pharmacol*. 1985;19:203–209.
85. Somogyi AA, Kong CB, Gurr FW, et al. Metronidazole pharmacokinetics in patients with acute renal failure. *J Antimicrob Chemother*. 1984;13:183–189.
88. Paap CM, Nahata MC. Clinical pharmacokinetics of antibacterial drugs in neonates. *Clin Pharmacokinet*. 1990;19:280–318.
90. Czeizel AE, Rockenbauer M. A population based case-control teratologic study of oral metronidazole treatment during pregnancy. *Br J Obstet Gynaecol*. 1998;105:322–327.
91. Sorensen HT, Larsen H, Jensen ES, et al. Safety of metronidazole during pregnancy: a cohort study of risk of congenital abnormalities, preterm delivery and low birth weight in 124 women. *J Antimicrob Chemother*. 1999;44:854–856.
93. Chung AM, Reed MD, Blumer JL. Antibiotics and breast-feeding: a critical review of the literature. *Paediatr Drugs*. 2002;4:817–837.
94. Kuriyama A, Jackson JL, Doi A, et al. Metronidazole-induced central nervous system toxicity: a systematic review. *Clin Neuropharmacol*. 2011;34:241–247.
95. Moitra S, Sen S, Banerjee I, et al. Metronidazole-induced bullous pemphigoid: a case report. *J Clin Diagn Res*. 2015;9:FD1–FD3.
100. Chong PM, Lynch T, McCorrister S, et al. Canadian nosocomial infection surveillance program (CNISP). Proteomic analysis of a NAP1 *Clostridium difficile* clinical isolate resistant to metronidazole. *PLoS ONE*. 2014;9:e82622.
102. Binh TT, Suzuki R, Trang TT, et al. Search for novel candidate mutations for metronidazole resistance in *Helicobacter pylori* using next-generation sequencing. *Antimicrob Agents Chemother*. 2015;59:2343–2348.
107. Kirkcaldy RD, Augostini P, Asbel LE, et al. *Trichomonas vaginalis* antimicrobial drug resistance in 6 US cities, STD surveillance network, 2009-2010. *Emerg Infect Dis*. 2012;18:939–943.
112. Upcroft P, Upcroft JA. Drug targets and mechanisms of resistance in the anaerobic protozoa. *Clin Microbiol Rev*. 2001;14:150–164.

114. Coleman JS, Gaydos CA, Witter F. *Trichomonas vaginalis* vaginitis in obstetrics and gynecology practice: new concepts and controversies. *Obstet Gynecol Surv*. 2013;68:43–50.
119. Wright SG. Protozoan infections of the gastrointestinal tract. *Infect Dis Clin North Am*. 2012;26:323–339.
118. Röser D, Simonsen J, Stensvold CR, et al. Metronidazole therapy for treating dientamoebiasis in children is not associated with better clinical outcomes: a randomized, double-blinded and placebo-controlled clinical trial. *Clin Infect Dis*. 2014;58:1692–1699.
130. Koss CA, Baras DC, Lane SD, et al. Investigation of metronidazole use during pregnancy and adverse birth outcomes. *Antimicrob Agents Chemother*. 2012;56:4800–4805.
131. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31:431–455.
137. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol*. 2013;108:478–498.
141. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 2013;70:195–283.
145. Holt RK, Anderson EA, Cantrell MA, et al. Preemptive dose reduction of warfarin in patients initiating metronidazole. *Drug Metabol Drug Interact*. 2010;25:35–39.
150. Williams CS, Woodcock KR. Do ethanol and metronidazole interact to produce a disulfiram-like reaction? *Ann Pharmacother*. 2000;34:255–257.

References

1. Lofmark S, Edlund C, Nord CE. Metronidazole is still the drug of choice for treatment of anaerobic infections. *Clin Infect Dis*. 2010;50(suppl 1):S16–S23.
2. Roberts SA, Shore KP, Paviour SD, et al. Antimicrobial susceptibility of anaerobic bacteria in New Zealand: 1999-2003. *J Antimicrob Chemother*. 2006;57:992–998.
3. Goldstein EJ, Citron DM, Vreni Merriam C, et al. Comparative in vitro activities of ertapenem (MK-0826) against 1,001 anaerobes isolated from human intra-abdominal infections. *Antimicrob Agents Chemother*. 2000;44:2389–2394.
4. Jolles GE. Origins and anti-infective activities of metronidazole. In: Finegold SM, Conference IM, eds. *Metronidazole: Proceedings of the International Metronidazole Conference, Montreal, Quebec, Canada, May 26-28, 1976*. Excerpta Med.; 1977.
5. Maeda K, Osato T, Umezawa H. A new antibiotic, azomycin. *J Antibiot (Tokyo)*. 1953;6:182.
6. Cosar C, Julou L. [The activity of 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (R. P. 8823) against experimental *Trichomonas vaginalis* infections]. *Ann Inst Pasteur (Paris)*. 1959;96:238–241.
7. Durel P, Roiron V, Siboulet A, et al. [Trial of an antitrichomonal drug derived from imidazole: RP-8823]. *C R Soc Fr Gyncol*. 1959;29:36–45.
8. Durel P, Roiron V, Siboulet A, et al. Systemic treatment of human trichomoniasis with a derivative of nitro-imidazole, 8823 RP. *Br J Vener Dis*. 1960;36:21–26.
9. Shinn DLS. Metronidazole in acute ulcerative gingivitis. *Lancet*. 1962;279:1191.
10. Freeman CD, Klutman NE, Lamp KC. Metronidazole. A therapeutic review and update. *Drugs*. 1997;54:679–708.
11. Edwards DI. Nitroimidazole drugs—action and resistance mechanisms. I. Mechanisms of action. *J Antimicrob Chemother*. 1993;31:9–20.
12. Soares GM, Figueiredo LC, Faveri M, et al. Mechanisms of action of systemic antibiotics used in periodontal treatment and mechanisms of bacterial resistance to these drugs. *J Appl Oral Sci*. 2012;20:295–309.
13. Muller M. Mode of action of metronidazole on anaerobic bacteria and protozoa. *Surgery*. 1983;93(1 Pt 2):165–171.
14. Samuelson J. Why metronidazole is active against both bacteria and parasites. *Antimicrob Agents Chemother*. 1999;43:1533–1541.
15. Pal D, Banerjee S, Cui J, et al. *Giardia, Entamoeba,* and *Trichomonas* enzymes activate metronidazole (nitroreductases) and inactivate metronidazole (nitroimidazole reductases). *Antimicrob Agents Chemother*. 2009;53:458–464.
16. Wexler HM, Molitoris D, St John S, et al. In vitro activities of faropenem against 579 strains of anaerobic bacteria. *Antimicrob Agents Chemother*. 2002;46:3669–3675.
17. Hecht DW. *Clinical and Laboratory Standards Institute. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria: Approved Standard-Eighth Edition (M11-A8)*. 8th ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2012.
18. Dubreuil L, Odou MF. Anaerobic bacteria and antibiotics: what kind of unexpected resistance could I find in my laboratory tomorrow? *Anaerobe*. 2010;16:555–559.
19. Cordero-Laurent E, Rodriguez C, Rodriguez-Cavallini E, et al. Resistance of *Bacteroides isolates* recovered among clinical samples from a major Costa Rican hospital between 2000 and 2008 to ss-lactams, clindamycin, metronidazole, and chloramphenicol. *Rev Esp Quimioter*. 2012;25:261–265.
20. Karlowsky JA, Walkty AJ, Adam HJ, et al. Prevalence of antimicrobial resistance among clinical isolates of *Bacteroides fragilis* group in Canada in 2010-2011: CANWARD surveillance study. *Antimicrob Agents Chemother*. 2012;56:1247–1252.
21. Soki J, Eitel Z, Urban E, et al. On behalf of the ESGoAI. Molecular analysis of the carbapenem and metronidazole resistance mechanisms of *Bacteroides* strains reported in a Europe-wide antibiotic resistance survey. *Int J Antimicrob Agents*. 2013;41:122–125.
22. Hansen KCM, Schwensen SAF, Henriksen DP, et al. Antimicrobial resistance in the *Bacteroides fragilis* group in faecal samples from patients receiving broad-spectrum antibiotics. *Anaerobe*. 2017;47:79–85.
23. Snydman DR, Jacobus NV, McDermott LA, et al. Trends in antimicrobial resistance among *Bacteroides* species and *Parabacteroides* species in the United States from 2010-2012 with comparison to 2008-2009. *Anaerobe*. 2017;43:21–26.
24. Naidoo S, Perovic O, Richards GA, et al. Clinically significant anaerobic bacteria isolated from patients in a South African academic hospital: antimicrobial susceptibility testing. *S Afr Med J*. 2011;101:732–734.
25. Goldstein EJC, Citron DM, Peraino VA, et al. *Desulfovibrio desulfuricans* bacteremia and review of human *Desulfovibrio* infections. *J Clin Microbiol*. 2003;41:2752–2754.
26. Erwin ME, Fix AM, Jones RN. Three independent yearly analyses of the spectrum and potency of metronidazole: a multicenter study of 1,108 contemporary anaerobic clinical isolates. *Diagn Microbiol Infect Dis*. 2001;39:129–132.
27. Ardila CM, Lopez MA, Guzman IC. High resistance against clindamycin, metronidazole and amoxicillin in *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* isolates of periodontal disease. *Med Oral Patol Oral Cir Bucal*. 2010;15:e947–e951.
28. Chow AW, Patten V, Guze LB. Susceptibility of anaerobic bacteria to metronidazole: relative resistance of non-spore-forming gram-positive bacilli. *J Infect Dis*. 1975;131:182–185.
29. Bahar H, Torun MM, Ocer F, et al. Mobiluncus species in gynaecological and obstetric infections: antimicrobial resistance and prevalence in a Turkish population. *Int J Antimicrob Agents*. 2005;25:268–271.
30. Puapermpoonsiri S, Watanabe K, Kato N, et al. In vitro activities of 10 antimicrobial agents against bacterial vaginosis-associated anaerobic isolates from pregnant Japanese and Thai women. *Antimicrob Agents Chemother*. 1997;41:2297–2299.
31. Pavičić MJ, van Winkelhoff AJ, Pavičić-Temming YA, et al. Metronidazole susceptibility factors in *Actinobacillus actinomycetemcomitans*. *J Antimicrob Chemother*. 1995;35:263–269.
32. Merriam CV, Citron DM, Tyrrell KL, et al. In vitro activity of azithromycin and nine comparator agents against 296 strains of oral anaerobes and 31 strains of *Eikenella corrodens*. *Int J Antimicrob Agents*. 2006;28:244–248.
33. Kolokotronis A. Susceptibility of *Capnocytophaga* to antimicrobial agents. *J Chemother*. 1995;7:414–416.
34. Feodoroff B, Lauhio A, Ellstrom P, et al. A nationwide study of *Campylobacter jejuni* and *Campylobacter coli* bacteremia in Finland over a 10-year period, 1998-2007, with special reference to clinical characteristics and antimicrobial susceptibility. *Clin Infect Dis*. 2011;53:e99–e106.
35. Goldstein EJ, Citron DM, Merriam CV, et al. In vitro activities of garenoxacin (BMS 284756) against 108 clinical isolates of *Gardnerella vaginalis*. *Antimicrob Agents Chemother*. 2002;46:3995–3996.
36. Nagaraja P. Antibiotic resistance of *Gardnerella vaginalis* in recurrent bacterial vaginosis. *Indian J Med Microbiol*. 2008;26:155–157.
37. Bannatyne RM, Jackowski J, Cheung R, et al. Susceptibility of *Gardnerella vaginalis* to metronidazole, its bioactive metabolites, and tinidazole. *Am J Clin Pathol*. 1987;87:640–641.
38. Shanker S, Munro R. Sensitivity of *Gardnerella vaginalis* to metabolites of metronidazole and tinidazole. *Lancet*. 1982;1:167.
39. Chen D, Cunningham SA, Cole NC, et al. Phenotypic and molecular antimicrobial susceptibility of *Helicobacter pylori*. *Antimicrob Agents Chemother*. 2017;61.
40. Hu Y, Zhu Y, Lu NH. Novel and effective therapeutic regimens for *Helicobacter pylori* in an era of increasing antibiotic resistance. *Front Cell Infect Microbiol*. 2017;7:168.
41. Miendje Deyi VY, Bontems P, Vanderpas J, et al. Multicenter survey of routine determinations of resistance of *Helicobacter pylori* to antimicrobials over the last 20 years (1990 to 2009) in Belgium. *J Clin Microbiol*. 2011;49:2200–2209.
42. Baines SD, O'Connor R, Freeman J, et al. Emergence of reduced susceptibility to metronidazole in *Clostridium difficile*. *J Antimicrob Chemother*. 2008;62:1046–1052.
43. Lynch T, Chong P, Zhang J, et al. Characterization of a stable, metronidazole-resistant *Clostridium difficile* clinical isolate. *PLoS ONE*. 2013;8:e53757.
44. Moura I, Spigaglia P, Barbanti F, et al. Analysis of metronidazole susceptibility in different *Clostridium difficile* PCR ribotypes. *J Antimicrob Chemother*. 2013;68:362–365.
45. Peng Z, Jin D, Kim HB, et al. An update on antimicrobial resistance in *Clostridium difficile*: resistance mechanisms and antimicrobial susceptibility testing. *J Clin Microbiol*. 2017.
46. Bolton RP, Culshaw MA. Faecal metronidazole concentrations during oral and intravenous therapy for antibiotic associated colitis due to *Clostridium difficile*. *Gut*. 1986;27:1169–1172.
47. Krook A, Lindstrom B, Kjellander J, et al. Relation between concentrations of metronidazole and *Bacteroides* spp in faeces of patients with Crohn's disease and healthy individuals. *J Clin Pathol*. 1981;34:645–650.
48. Al-Nassir WN, Sethi AK, Nerandzic MM, et al. Comparison of clinical and microbiological response to treatment of *Clostridium difficile*-associated disease with metronidazole and vancomycin. *Clin Infect Dis*. 2008;47:56–62.
49. Citron DM, Kwok YY, Appleman MD. In vitro activity of oritavancin (LY333328), vancomycin, clindamycin, and metronidazole against *Clostridium perfringens, Propionibacterium acnes,* and anaerobic Gram-positive cocci. *Anaerobe*. 2005;11:93–95.
50. Farthing MJ. Giardiasis. *Gastroenterol Clin North Am*. 1996;25:493–515.
51. Lalle M. Giardiasis in the post genomic era: treatment, drug resistance and novel therapeutic perspectives. *Infect Disord Drug Targets*. 2010;10:283–294.
52. Nagata N. In vitro susceptibility testing of *Dientamoeba fragilis*. *Antimicrob Agents Chemother*. 2012;56:487–494.
53. Shakir L, Javeed A, Ashraf M, et al. Metronidazole and the immune system. *Pharmazie*. 2011;66:393–398.
54. van Zuuren EJ, Kramer SF, Carter BR, et al. Effective and evidence-based management strategies for rosacea: summary of a Cochrane systematic review. *Br J Dermatol*. 2011;165:760–781.
55. Jakobsson HE, Jernberg C, Andersson AF, et al. Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. *PLoS ONE*. 2010;5:e9836.
56. Arabi Y, Dimock F, Burdon DW, et al. Influence of neomycin and metronidazole on colonic microflora of volunteers. *J Antimicrob Chemother*. 1979;5:531–537.
57. Krook A. Effect of metronidazole and sulfasalazine on the normal human faecal flora. *Scand J Gastroenterol*. 1981;16:587–592.
58. Schwartz DE, Jeunet F. Comparative pharmacokinetic studies of ornidazole and metronidazole in man. *Chemotherapy*. 1976;22:19–29.
59. Ferris MJ, Norori J, Zozaya-Hinchliffe M, et al. Cultivation-independent analysis of changes in bacterial vaginosis flora following metronidazole treatment. *J Clin Microbiol*. 2007;45:1016–1018.
60. Srinivasan S, Liu C, Mitchell CM, et al. Temporal variability of human vaginal bacteria and relationship with bacterial vaginosis. *PLoS ONE*. 2010;5:e10197.
61. Ling Z, Liu X, Chen W, et al. The restoration of the vaginal microbiota after treatment for bacterial vaginosis with metronidazole or probiotics. *Microb Ecol*. 2013;65:773–780.
62. Lau AH, Lam NP, Piscitelli SC, et al. Clinical pharmacokinetics of metronidazole and other nitroimidazole anti-infectives. *Clin Pharmacokinet*. 1992;23:328–364.
63. Allen LV Jr, Erickson MA 3rd. Stability of ketoconazole, metolazone, metronidazole, procainamide hydrochloride, and spironolactone in extemporaneously compounded oral liquids. *Am J Health Syst Pharm*. 1996;53:2073–2078.
64. Prospective, randomized comparison of metronidazole and clindamycin, each with gentamicin, for the treatment of serious intra-abdominal infection. *Surgery*. 1983;93(1 Pt 2):221–229.
65. Paakkonen M, Alhava EM, Huttunen R, et al. Piperacillin compared with cefuroxime plus metronidazole in diffuse peritonitis. *Eur J Surg*. 1991;157:535–537.
66. Huizinga WK, Warren BL, Baker LW, et al. Antibiotic monotherapy with meropenem in the surgical management of intra-abdominal infections. *J Antimicrob Chemother*. 1995;36(supplA):179–189.
67. Mattila J, Nerdrum K, Rouhiainen H, et al. Penetration of metronidazole and tinidazole into the aqueous humor in man. *Chemotherapy*. 1983;29:188–191.
68. Sprandel KA, Schriever CA, Pendland SL, et al. Pharmacokinetics and pharmacodynamics of intravenous levofloxacin at 750 milligrams and various doses of metronidazole in healthy adult subjects. *Antimicrob Agents Chemother*. 2004;48:4597–4605.
69. Wang S, Cunha BA, Hamid NS, et al. Metronidazole single versus multiple daily dosing in serious intraabdominal/pelvic and diabetic foot infections. *J Chemother*. 2007;19:410–416.
70. Boyce EG, Cookson ET, Bond WS. Persistent metronidazole-induced peripheral neuropathy. *Ann Pharmacother*. 1990;24:19–21.
71. Dreger LM, Gleason PP, Chowdhry TK. Gazzuolo DJ. Intermittent-dose metronidazole-induced peripheral neuropathy. *Ann Pharmacother*. 1998;32:267–268.
72. Kusumi RK, Plouffe JF, Wyatt RH, et al. Central nervous system toxicity associated with metronidazole therapy. *Ann Intern Med*. 1980;93:59–60.
73. Ioannides L, Somogyi A, Spicer J, et al. Rectal administration of metronidazole provides therapeutic plasma levels in postoperative patients. *N Engl J Med*. 1981;305:1569–1570.

74. Sattar MA, Sankey MG, Cawley MI, et al. The penetration of metronidazole into synovial fluid. *Postgrad Med J*. 1982;58:20–24.
75. Jokipii AM, Myllyla VV, Hokkanen E, et al. Penetration of the blood brain barrier by metronidazole and tinidazole. *J Antimicrob Chemother*. 1977;3:239–245.
76. Nagar H, Berger SA, Hammar B, et al. Penetration of clindamycin and metronidazole into the appendix and peritoneal fluid in children. *Eur J Clin Pharmacol*. 1989;37:209–210.
77. Diav-Citrin O, Shechtman S, Gotteiner T, et al. Pregnancy outcome after gestational exposure to metronidazole: a prospective controlled cohort study. *Teratology*. 2001;63:186–192.
78. Plaisance KI, Quintiliani R, Nightingale CH. The pharmacokinetics of metronidazole and its metabolites in critically ill patients. *J Antimicrob Chemother*. 1988;21:195–200.
79. Somogyi A, Kong C, Sabto J, et al. Disposition and removal of metronidazole in patients undergoing haemodialysis. *Eur J Clin Pharmacol*. 1983;25:683–687.
80. Gabriel R, Page CM, Collier J, et al. Removal of metronidazole by haemodialysis. *Br J Surg*. 1980;67: 553.
81. Holten E, Smith-Erichsen N. Concentration of metronidazole in serum during peritoneal dialysis. *Chemotherapy*. 1981;27:414–415.
82. Houghton GW, Dennis MJ, Gabriel R. Pharmacokinetics of metronidazole in patients with varying degrees of renal failure. *Br J Clin Pharmacol*. 1985;19:203–209.
83. Kreeft JH, Ogilvie RI, Dufresne LR. Metronidazole kinetics in dialysis patients. *Surgery*. 1983;93(1 Pt 2):149–153.
84. Roux AF, Moirot E, Delhotal B, et al. Metronidazole kinetics in patients with acute renal failure on dialysis: a cumulative study. *Clin Pharmacol Ther*. 1984;36: 363–368.
85. Somogyi AA, Kong CB, Gurr FW, et al. Metronidazole pharmacokinetics in patients with acute renal failure. *J Antimicrob Chemother*. 1984;13:183–189.
86. Stambaugh JE, Feo LG, Manthei RW. The isolation and identification of the urinary oxidative metabolites of metronidazole in man. *J Pharmacol Exp Ther*. 1968;161:373–381.
87. Cassey JG, Clark DA, Merrick P, et al. Pharmacokinetics of metronidazole in patients undergoing peritoneal dialysis. *Antimicrob Agents Chemother*. 1983;24: 950–951.
88. Paap CM, Nahata MC. Clinical pharmacokinetics of antibacterial drugs in neonates. *Clin Pharmacokinet*. 1990;19:280–318.
89. Upadhyaya P, Bhatnagar V, Basu N. Pharmacokinetics of intravenous metronidazole in neonates. *J Pediatr Surg*. 1988;23:263–265.
90. Czeizel AE, Rockenbauer M. A population based case-control teratologic study of oral metronidazole treatment during pregnancy. *Br J Obstet Gynaecol*. 1998;105:322–327.
91. Sorensen HT, Larsen H, Jensen ES, et al. Safety of metronidazole during pregnancy: a cohort study of risk of congenital abnormalities, preterm delivery and low birth weight in 124 women. *J Antimicrob Chemother*. 1999;44:854–856.
92. Passmore CM, McElnay JC, Rainey EA, et al. Metronidazole excretion in human milk and its effect on the suckling neonate. *Br J Clin Pharmacol*. 1988;26: 45–51.
93. Chung AM, Reed MD, Blumer JL. Antibiotics and breast-feeding: a critical review of the literature. *Paediatr Drugs*. 2002;4:817–837.
94. Kuriyama A, Jackson JL, Doi A, et al. Metronidazole-induced central nervous system toxicity: a systematic review. *Clin Neuropharmacol*. 2011;34:241–247.
95. Moitra S, Sen S, Banerjee I, et al. Metronidazole-induced bullous pemphigoid: a case report. *J Clin Diagn Res*. 2015;9:FD1–FD3.
96. Diniz CG, Farias LM, Carvalho MA, et al. Differential gene expression in a *Bacteroides fragilis* metronidazole-resistant mutant. *J Antimicrob Chemother*. 2004;54:100–108.
97. Otte E, Nielsen HL, Hasman H, et al. First report of metronidazole resistant, nimd-positive, *Bacteroides stercoris* isolated from an abdominal abscess in a 70-year-old woman. *Anaerobe*. 2017;43:91–93.
98. Alauzet C, Berger S, Jean-Pierre H, et al. Nimh, a novel nitroimidazole resistance gene contributing to metronidazole resistance in *Bacteroides fragilis*. *J Antimicrob Chemother*. 2017;72:2673–2675.
99. Steffens LS, Nicholson S, Paul LV, et al. *Bacteroides fragilis* RecA protein overexpression causes resistance to metronidazole. *Res Microbiol*. 2010;161:346–354.
100. Chong PM, Lynch T, McCorrister S, et al. Canadian nosocomial infection surveillance program (CNISP). Proteomic analysis of a NAP1 *Clostridium difficile* clinical isolate resistant to metronidazole. *PLoS ONE*. 2014;9:e82622.
101. Gerrits MM, van der Wouden EJ, Bax DA, et al. Role of the rdxA and frxA genes in oxygen-dependent metronidazole resistance of *Helicobacter pylori*. *J Med Microbiol*. 2004;53(Pt 11):1123–1128.
102. Binh TT, Suzuki R, Trang TT, et al. Search for novel candidate mutations for metronidazole resistance in *Helicobacter pylori* using next-generation sequencing. *Antimicrob Agents Chemother*. 2015;59:2343–2348.
103. Bereswill S, Krainick C, Stahler F, et al. Analysis of the rdxA gene in high-level metronidazole-resistant clinical isolates confirms a limited use of rdxA mutations as a marker for prediction of metronidazole resistance in *Helicobacter pylori*. *FEMS Immunol Med Microbiol*. 2003;36:193–198.
104. Choi SS, Chivers PT, Berg DE. Point mutations in *Helicobacter pylori*'s fur regulatory gene that alter resistance to metronidazole, a prodrug activated by chemical reduction. *PLoS ONE*. 2011;6:e18236.
105. Watt L, Jennison RF. Clinical evaluation of metronidazole. A new systemic trichomonacide. *Br Med J*. 1960;2:902–905.
106. Robinson SC. Trichomonal vaginitis resistant to metranidazole. *Can Med Assoc J*. 1962;86:665.
107. Kirkcaldy RD, Augustini P, Asbel LE, et al. *Trichomonas vaginalis* antimicrobial drug resistance in 6 US cities, STD surveillance network, 2009-2010. *Emerg Infect Dis*. 2012;18:939–943.
108. Upcroft JA, Dunn LA, Wal T, et al. Metronidazole resistance in *Trichomonas vaginalis* from highland women in Papua New Guinea. *Sex Health*. 2009;6:334–338.
109. Leitsch D, Drinic M, Kolarich D, et al. Down-regulation of flavin reductase and alcohol dehydrogenase-1 (ADH1) in metronidazole-resistant isolates of *Trichomonas vaginalis*. *Mol Biochem Parasitol*. 2012;183: 177–183.
110. Bradic M, Warring SD, Tooley GE, et al. Genetic indicators of drug resistance in the highly repetitive genome of *Trichomonas vaginalis*. *Genome Biol Evol*. 2017;9:1658–1672.
111. Leitsch D, Burgess AG, Dunn LA, et al. Pyruvate:ferredoxin oxidoreductase and thioredoxin reductase are involved in 5-nitroimidazole activation while flavin metabolism is linked to 5-nitroimidazole resistance in *Giardia lamblia*. *J Antimicrob Chemother*. 2011;66:1756–1765.
112. Upcroft P, Upcroft JA. Drug targets and mechanisms of resistance in the anaerobic protozoa. *Clin Microbiol Rev*. 2001;14:150–164.
113. Bachmann LH, Hobbs MM, Sena AC, et al. *Trichomonas vaginalis* genital infections: progress and challenges. *Clin Infect Dis*. 2011;53(suppl 3):S160–S172.
114. Coleman JS, Gaydos CA, Witter F. *Trichomonas vaginalis* vaginitis in obstetrics and gynecology practice: new concepts and controversies. *Obstet Gynecol Surv*. 2013;68:43–50.
115. Centers for Disease Control and Prevention. Trichomoniasis—2015 STD Treatment Guidelines; 2015.
116. Banik GR, Barratt JL, Marriott D, et al. A case-controlled study of *Dientamoeba fragilis* infections in children. *Parasitology*. 2011;1–5.
117. Barratt JL, Harkness J, Marriott D, et al. A review of *Dientamoeba fragilis* carriage in humans: several reasons why this organism should be considered in the diagnosis of gastrointestinal illness. *Gut Microbes*. 2011;2:3–12.
118. Röser D, Simonsen J, Stensvold CR, et al. Metronidazole therapy for treating dientamoebiasis in children is not associated with better clinical outcomes: a randomized, double-blinded and placebo-controlled clinical trial. *Clin Infect Dis*. 2014;58:1692–1699.
119. Wright SG. Protozoan infections of the gastrointestinal tract. *Infect Dis Clin North Am*. 2012;26:323–339.
120. Gonzales ML, Dans LF, Martinez EG. Antiamoebic drugs for treating amoebic colitis. *Cochrane Database Syst Rev*. 2009;(2):CD006085.
121. Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis*. 2017;65:1963–1973.
122. Escobedo AA, Lalle M, Hrastnik NI, et al. Combination therapy in the management of giardiasis: what laboratory and clinical studies tell us, so far. *Acta Trop*. 2016;162:196–205.
123. Ganesh Kumar AV, Kothari VM, Krishnan A, et al. Benzathine penicillin, metronidazole and benzyl penicillin in the treatment of tetanus: a randomized, controlled trial. *Ann Trop Med Parasitol*. 2004;98: 59–63.
124. Bartlett JG. Anaerobic bacterial infection of the lung. *Anaerobe*. 2012;18:235–239.
125. Sanders CV, Hanna BJ, Lewis AC. Metronidazole in the treatment of anaerobic infections. *Am Rev Respir Dis*. 1979;120:337–343.
126. Perlino CA. Metronidazole vs clindamycin treatment of anaerobic pulmonary infection. Failure of metronidazole therapy. *Arch Intern Med*. 1981;141:1424–1427.
127. Collignon PJ, Munro R, Morris G. Susceptibility of anaerobic bacteria to antimicrobial agents. *Pathology*. 1988;20:48–52.
128. LeCorn DW, Vertucci FJ, Rojas MF, et al. *In vitro* activity of amoxicillin, clindamycin, doxycycline, metronidazole, and moxifloxacin against oral *Actinomyces*. *J Endod*. 2007;33:557–560.
129. Donders G. Diagnosis and management of bacterial vaginosis and other types of abnormal vaginal bacterial flora: a review. *Obstet Gynecol Surv*. 2010;65: 462–473.
130. Koss CA, Baras DC, Lane SD, et al. Investigation of metronidazole use during pregnancy and adverse birth outcomes. *Antimicrob Agents Chemother*. 2012;56:4800–4805.
131. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31:431–455.
132. Johnson S, Louie TJ, Gerding DN, et al. Polymer alternative for CDI treatment (PACT) investigators. Vancomycin, metronidazole, or tolevamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis*. 2014;59:345–354.
133. Li R, Lu L, Lin Y, et al. Efficacy and safety of metronidazole monotherapy versus vancomycin monotherapy or combination therapy in patients with *Clostridium difficile* infection: A systematic review and Meta-analysis. *PLoS ONE*. 2015;10:e0137252.
134. Stevens VW, Nelson RE, Schwab-Daugherty EM, et al. Comparative effectiveness of vancomycin and metronidazole for the prevention of recurrence and death in patients with *Clostridium difficile* infection. *JAMA Intern Med*. 2017;177:546–553.
135. Nelson RL, Suda KJ, Evans CT. Antibiotic treatment for *Clostridium difficile*-associated diarrhoea in adults. *Cochrane Database Syst Rev*. 2017;(3):CD004610.
136. Barkin JA, Sussman DA, Fifadara N, et al. *Clostridium difficile* infection and patient-specific antimicrobial resistance testing reveals a high metronidazole resistance rate. *Dig Dis Sci*. 2017;62:1035–1042.
137. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol*. 2013;108: 478–498.
138. McColl KE. Clinical practice. *Helicobacter pylori* infection. *N Engl J Med*. 2010;362:1597–1604.
139. Pineton de Chambrun GP, Torres J, Darfeuille-Michaud A, et al. The role of anti(myco)bacterial interventions in the management of IBD: is there evidence at all? *Dig Dis*. 2012;30:358–367.
140. Skoropad VY, Berdov BA, Zagrebin VM. Preoperative radiotherapy in combination with metronidazole for resectable gastric cancer: long-term results of a phase 2 study. *Eur J Surg Oncol*. 2003;29:166–170.
141. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 2013;70: 195–283.
142. Norman WV. Metronidazole prophylaxis before surgical abortion: retrospective review of 51 330 cases. *J Obstet Gynaecol Can*. 2012;34:648–652.
143. Clifford V, Daley A. Antibiotic prophylaxis in obstetric and gynaecological procedures: a review. *Aust N Z J Obstet Gynaecol*. 2012;52:412–419.
144. O'Reilly RA. The stereoselective interaction of warfarin and metronidazole in man. *N Engl J Med*. 1976;295:354–357.
145. Holt RK, Anderson EA, Cantrell MA, et al. Preemptive dose reduction of warfarin in patients initiating metronidazole. *Drug Metabol Drug Interact*. 2010;25:35–39.
146. Gulbis AM, Culotta KS, Jones RB, et al. Busulfan and metronidazole: an often forgotten but significant drug interaction. *Ann Pharmacother*. 2011;45:e39.
147. Roedler R, Neuhauser MM, Penzak SR. Does metronidazole interact with CYP3A substrates by inhibiting their metabolism through this metabolic pathway? Or should other mechanisms be considered? *Ann Pharmacother*. 2007;41:653–658.
148. Armahizer MJ, Seybert AL, Smithburger PL, et al. Drug-drug interactions contributing to QT prolongation in cardiac intensive care units. *J Crit Care*. 2013;28:243–249.

149. Cohen O, Saar N, Swartzon M, et al. First report of metronidazole-induced QT interval prolongation. *Int J Antimicrob Agents*. 2008;31:180–181.
150. Williams CS, Woodcock KR. Do ethanol and metronidazole interact to produce a disulfiram-like reaction? *Ann Pharmacother*. 2000;34:255–257.
151. Visapaa JP, Tillonen JS, Kaihovaara PS, et al. Lack of disulfiram-like reaction with metronidazole and ethanol. *Ann Pharmacother*. 2002;36:971–974.
152. Lamp KC, Freeman CD, Klutman NE, et al. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. *Clin Pharmacokinet*. 1999;36:353–373.
153. Malhotra M, Sharma JB, Batra S, et al. Ciprofloxacin-tinidazole combination, fluconazole- azithromicin-secnidazole-kit and doxycycline-metronidazole combination therapy in syndromic management of pelvic inflammatory disease: a prospective randomized controlled trial. *Indian J Med Sci*. 2003;57:549–555.
154. Joshi S, Maroli S, Moulick ND, et al. Efficacy and tolerability of a combination of ofloxacin and tinidazole in the management of infectious diabetic foot ulcer. *J Indian Med Assoc*. 2003;101:329–332.

29 Macrolides and Clindamycin

Whitney J. Nesbitt and David M. Aronoff

SHORT VIEW SUMMARY

MACROLIDES

Erythromycin

- Usual doses
  - Oral: base—250 to 500 mg every 6 to 12 hours; maximum: 4 g daily
  - Ethylsuccinate: 400 to 800 mg every 6 to 12 hours; maximum: 4 g daily
  - IV: lactobionate—15 to 20 mg/kg/day divided every 6 hours, *or* 500 mg to 1 g every 6 hours, *or* given as a continuous infusion over 24 hours; maximum: 4 g daily
- Renal or hepatic failure
  - In renal failure, slightly dialyzable (5%–20%); supplemental dose is not necessary in hemodialysis or peritoneal dialysis or in continuous arteriovenous or venovenous hemofiltration
  - No dose adjustment in hepatic failure
- Cerebrospinal fluid (CSF) penetration
  - CSF-to–blood level ratio: normal meninges—2% to 13%; inflamed meninges—7% to 25%
- Adverse effects
  - Cardiovascular corrected QT (QTc) interval prolongation, torsades de pointes, gastrointestinal (GI) upset, pruritis, erythema multiforme, cholestatic jaundice
- Contraindications
  - Caution for patients with underlying heart disease or for those taking other drugs that may prolong the QT interval regarding potential for inducing fatal ventricular arrhythmias
  - Hypersensitivity to erythromycin, any macrolide antibiotics, or any component of the formulation
  - Concomitant use with cisapride, ergotamine, terfenadine, lovastatin, or simvastatin
- Drug-drug interactions
  - Major inhibitor of cytochrome P-450 isoenzyme 3A (CYP3A4)
- Indications
  - *Bartonella* spp. infections, chancroid, granuloma inguinale, legionnaires' disease, lymphogranuloma venereum, nongonococcal urethritis, pertussis

Azithromycin

- Usual dose
  - 500 mg on day 1, followed by 250 mg once daily on days 2 to 5
- Renal or hepatic failure
  - No dosage adjustment required; use with caution in patients with severe renal impairment (glomerular filtration rate <10 mL/min)
- CSF penetration
  - Poor central nervous system (CNS) penetration
- Adverse effects
  - Cardiovascular (QTc) prolongation, torsades de pointes, GI upset, pruritis, erythema multiforme, vaginitis, cholestatic jaundice
- Contraindications
  - Caution for patients with underlying heart disease or for those taking other drugs that may prolong the QT interval regarding potential for inducing fatal ventricular arrhythmias
  - Hypersensitivity to azithromycin, any macrolide antibiotics, or any component of the formulation
  - History of cholestatic jaundice/hepatic dysfunction associated with prior azithromycin use
- Drug-drug interactions
  - Amiodarone and other QTc-prolonging agents, quinine
- Indications
  - Treatment of acute otitis media; pharyngitis/tonsillitis; community-acquired pneumonia; pelvic inflammatory disease; genital ulcer disease (in men) due to *Haemophilus ducreyi* (chancroid); acute bacterial exacerbations of chronic obstructive pulmonary disease; acute bacterial sinusitis; prevention of *Mycobacterium avium* complex (alone or in combination with rifabutin) in patients with advanced human immunodeficiency virus (HIV) infection; treatment of disseminated *M. avium* complex (in combination with ethambutol) in patients with advanced HIV infection; skin and skin structure infections (uncomplicated) due to *Staphylococcus aureus, Streptococcus pyogenes,* or *Streptococcus agalactiae;* urethritis and cervicitis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*

Clarithromycin

- Usual dose
  - Oral: 250 to 500 mg every 12 hours or 1000 mg (two 500-mg extended-release tablets) once daily for 7 to 14 days
- Renal or hepatic failure
  - Creatinine clearance <30 mL/min: decrease clarithromycin dose by 50%
  - Hemodialysis: administer after hemodialysis session is completed; in hepatic failure, no dosing adjustment is necessary as long as renal function is normal
- CSF penetration
  - Poor CNS penetration
- Adverse effects
  - Cardiovascular (QTc) prolongation, torsades de pointes, hypersensitivity reactions
- Contraindications
  - Caution for patients with underlying heart disease or for those taking other drugs that may prolong the QT interval regarding potential for inducing fatal ventricular arrhythmias
  - Hypersensitivity to azithromycin, any macrolide antibiotics, or any component of the formulation
  - History of cholestatic jaundice/hepatic dysfunction associated with prior azithromycin use
- Drug-drug interactions
  - Colchicine toxicity, major inhibitor of CYP3A4
- Indications
  - Pharyngitis/tonsillitis; acute maxillary sinusitis; acute exacerbation of chronic bronchitis; community-acquired pneumonia; uncomplicated skin/skin structure infections due to susceptible *S. aureus, S. pyogenes;* disseminated mycobacterial infections due to *M. avium* or *Mycobacterium intracellulare;* prevention of disseminated mycobacterial infections due to *M. avium* complex disease (e.g., patients with advanced HIV infection); duodenal ulcer disease due to *Helicobacter pylori* in regimens with other drugs, including amoxicillin and lansoprazole or omeprazole

KETOLIDES

- No longer manufactured

CLINDAMYCIN

- Usual doses
  - Oral: 150 to 450 mg/dose every 6 to 8 hours; maximum dose: 1800 mg daily
  - IM, IV: 1.2 to 2.7 g/day in 2 to 4 divided doses; maximum dose: 4800 mg daily
- Renal or hepatic failure
  - Renal failure: no adjustment required
- CSF penetration
  - Poor
- Adverse effects
  - Diarrhea, abdominal pain, vaginitis

SHORT VIEW SUMMARY—cont'd

- Contraindications
  - Hypersensitivity to clindamycin, lincomycin, or any component of the formulation
- Drug-drug interactions
  - Lincosamide antibiotics may diminish the therapeutic effects of erythromycin
- Indications
  - Treatment of susceptible bacterial infections, mainly those caused by anaerobes, streptococci, pneumococci, and staphylococci; pelvic inflammatory disease (IV)

The macrolide antibiotics (erythromycin, azithromycin, and clarithromycin) and the lincosamide antibiotics (lincomycin and clindamycin) are chemically unrelated but possess many similar biologic properties in terms of mechanisms of action and resistance, antimicrobial activity, and clinical pharmacology. Erythromycin, the macrolide in longest use, is sometimes useful as an alternative to penicillin G and other antibiotics. Azithromycin and clarithromycin have some advantages over erythromycin related to their antimicrobial activity, pharmacokinetics, fewer gastrointestinal side effects, and effectiveness in certain infections. Although more expensive, they have largely replaced erythromycin in clinical use. Azithromycin is noteworthy among the macrolides for fewer drug interactions and antiinflammatory activities. Dirithromycin, a semisynthetic derivative of erythromycin, is not available in the United States, is not widely used in Europe, but is prescribed in China; it is not included in this chapter but reviews of its use are available.[1,2] All of the macrolide antibiotics in clinical use have the potential for inducing cardiac arrhythmias. Telithromycin, the first member of the ketolide class, exhibited increased activity against many bacterial strains that were resistant to macrolides. It was associated with rare, yet severe hepatic toxicity that substantially limited its clinical usefulness, and manufacturing has therefore been discontinued. Clindamycin has been restricted in use by its association with *Clostridioides difficile* (formerly *Clostridium difficile*) colitis; it remains mostly as an alternative-choice antibiotic in the treatment of several infections, especially certain anaerobic infections. Lincomycin is now mainly of historic interest.

ERYTHROMYCIN

Derivation, Chemistry, and Preparations

Erythromycin was derived in 1952 from a strain of *Saccharopolyspora erythraea* (originally named *Streptomyces erythreus*) obtained from soil from the Philippines. It consists of a mixture of antibiotics in which erythromycin A is the active component. The structure (Fig. 29.1) of erythromycin A consists of a 14-member macrocyclic lactone ring—therefore the class name *macrolide*—attached to two sugar moieties, desosamine and L-cladinose. Erythromycin base is poorly soluble in water, has a pKa of 8.8, is rapidly inactivated by gastric acid, and is often inconsistently absorbed after oral administration. Pharmaceutical preparations for oral use have been made with an aim to diminish destruction by gastric acid and to promote better absorption. Oral preparations available include (1) enteric-coated tablets, enteric-coated pellets in capsules for delayed release, and "film"-coated tablets of the base; (2) the stearate salt (formed in association with the amino group on desosamine), available as film-coated tablets; and (3) the ethylsuccinate ester (formed with the hydroxyl group on desosamine), available in tablet, chewable, and liquid forms. The water-soluble salt of erythromycin prepared for intravenous use is erythromycin lactobionate. Erythromycin lactobionate is not given intramuscularly due to injection site pain. Erythromycin base is also available in 0.5%, 2%, and 3% topical solutions, gels, and creams for treatment of acne vulgaris and in an ophthalmic ointment for treatment of bacterial conjunctivitis and prevention of neonatal gonococcal and chlamydial conjunctivitis.

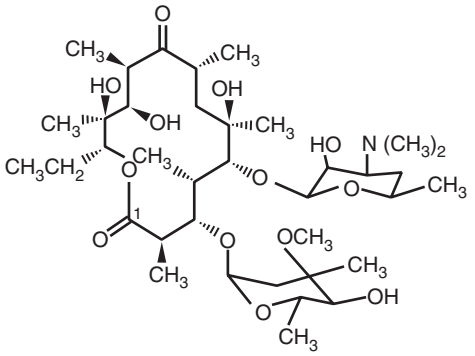

FIG. 29.1 **Erythromycin base.**

Mechanisms of Action

Erythromycin inhibits RNA-dependent protein synthesis at the step of chain elongation in susceptible organisms. X-ray crystallography studies indicate that several functional groups on erythromycin A bind to sequences on domain V of the 23S ribosomal RNA (rRNA) that is a component of the 50S subunit of the bacterial ribosome.[3,4] That binding site is near the peptidyl transferase center, and peptide chain elongation is thereby prevented by blocking of the polypeptide exit tunnel.[3–5] As a result, peptidyl transfer RNA (peptidyl-tRNA) is dissociated from the ribosome.[3,4] Data provided by macrolide-resistant mutants indicate that there are also important interactions between macrolides and specific ribosomal proteins or bases of the 50S subunit near the peptidyl transferase center.[5,6]

Studies in *Escherichia coli* and *Staphylococcus aureus* have demonstrated that erythromycin also inhibits the formation of the 50S ribosomal subunit.[3,5,7] In some bacteria, erythromycin interferes with the ribosomal binding of other macrolides, lincomycin, and chloramphenicol, suggesting common or overlapping binding sites for these antibiotics.

Mechanisms of Resistance

Decreased Microbial Entry or Export of Drug

Enterobacteriaceae exhibit decreased permeability of the outer cell envelope to macrolides.[8–10] This intrinsic resistance is also exhibited by *Pseudomonas* spp. and *Acinetobacter* spp. In addition, chromosomally encoded efflux pumps of several families can provide macrolide and, in some cases, lincosamide and streptogramin resistance.[6] A different efflux system for erythromycin and other 14- and 15-member macrolides (but not 16-member macrolides, lincosamides, or analogues of streptogramin B), called the *M phenotype,* has been elucidated in erythromycin-resistant strains of *Streptococcus pyogenes, Streptococcus pneumoniae,* group C streptococci, and enterococcal species. This efflux system is encoded by the *mef*(A) gene, is carried on a transposable element, and consists of transmembrane domains across the cytoplasmic membrane.[3] The M phenotype resistance is expressed by *S. pneumoniae* at moderate levels with erythromycin minimal inhibitory concentrations (MICs) of 1 to 64 μg/mL.[11]

Target Site Alterations

Mutations in genes for 50S ribosomal proteins or bases of critical domains of the 23S rRNA receptor site confer resistance to erythromycin and sometimes to other macrolides (M), lincosamides (L), and streptogramin type B (S_B); in some but not all strains, this is associated with a decreased binding affinity for erythromycin in *S. pneumoniae, Helicobacter pylori, Mycobacterium avium, Bacillus subtilis, S. pyogenes, Campylobacter* spp., *Mycoplasma pneumoniae, E. coli,* and *S. aureus.*[3,5,6,12–16] This pattern of resistance, referred to as the MLS_B phenotype, is mediated by the *erm* (erythromycin ribosome methylation) genes on plasmids or transposons on chromosomes, which are self-transferable. There are many identified classes of *erm* genes, the most important of which are the *ermA, ermB, ermC,* and *ermF* classes. The resistance results from decreased binding of the antibiotics to their overlapping targets on the ribosome. It is the most widespread mechanism of resistance to the macrolides and the lincosamides and can be exhibited by strains of *S. aureus* (particularly having *ermA* or *ermC* genes), *S. pyogenes* (with *ermA* or *ermB* genes), *S. pneumoniae, Enterococcus* spp., *Corynebacterium*

diphtheriae, Campylobacter spp., *Bacteroides fragilis* (*ermF* gene), *Clostridium perfringens, Listeria* spp., *M. pneumoniae,* and *Legionella* spp. The MLS_B resistance phenotype may be constitutive or inducible by subinhibitory concentrations of erythromycin or other macrolides that bring about induction of the methylating enzyme. Lincosamides are not inducers of this system. When of the inducible type, macrolide resistance is manifest, but clindamycin susceptibility is often found in vitro; however, in that latter case, resistance will often emerge in vivo by selection of mutants that are constitutively producing a methylating enzyme, especially in infections with high bacterial density.[14] Strains of *S. pyogenes* with the *ermB* gene are constitutive producers of methylase and therefore are usually resistant to the macrolides and clindamycin.[17] Strains of *S. pyogenes* with the *ermA* gene are usually inducible producers of methylase that consistently exhibit macrolide resistance and both macrolide and clindamycin resistance when the strain is exposed to those antibiotics.[14,17]

Drug Inactivation

Enzymatic inactivation of erythromycin and some other 14-, 15-, and 16-member ring macrolides by phosphotransferases has been described in strains of *S. aureus, E. coli,* and *Nocardia* spp. and is encoded by genes designated *mph*(A), *mph*(B), and *mph*(C).[6] Esterase genes (*ere*[A] and *ere*[B]) on plasmids encode for the hydrolysis of the macrocyclic lactone of erythromycin and have been found in strains of *E. coli, Klebsiella* spp., *Citrobacter* spp., *Proteus* spp., *Enterobacter* spp., and rare strains of *S. aureus.*[6]

Polymerase chain reaction methods that allow for relatively rapid detection of the different mechanisms of macrolide resistance among clinical isolates (genotypic testing) have been developed.[18] A given bacterial strain may possess more than one type of macrolide resistance mechanism, resulting in complex resistant phenotypes.

Antimicrobial Activity

The antimicrobial activity of erythromycin is broad in spectrum, being exhibited against gram-positive and gram-negative bacteria, including actinomycetes and mycobacteria, as well as against treponemes, mycoplasmas, *Chlamydia,* and rickettsiae. Depending on drug concentration, bacterial species, phase of growth, and density of the inoculum, erythromycin is essentially bacteriostatic. Bacterial killing is favored by higher antibiotic concentrations, higher pH, lower bacterial density, and rapid growth.[19] The activity of erythromycin, which is a weak base, increases markedly with increasing pH over the range of 5.5 to 8.5 for both gram-positive and gram-negative bacteria,[20,21] possibly reflecting increased entry into the bacterial cell of the un-ionized drug that is more plentiful at the higher pH.

The in vitro susceptibilities of potential pathogens to erythromycin are listed in Table 29.1.[6,16,22–33] Erythromycin shows high activity against the majority of pneumococci and group A streptococci isolated in the United States; however, resistant clinical isolates have been increasingly encountered worldwide, especially in *S. pneumoniae* and particularly among penicillin-resistant group A streptococci.[22,34–37] In the United States (1998–2011), the prevalence of erythromycin resistance among *S. pneumoniae* strains was approximately 45% by 2011.[38] In another study of *S. pneumoniae* strains from the United States, approximately 37% of strains with intermediate resistance to penicillin (MIC, 0.12–1.0 μg/mL) and 69% of strains showing high-level resistance to penicillin (MIC, >2.0 μg/mL) were resistant to erythromycin.[39] *S. pneumoniae* strains demonstrate complete cross-resistance among the macrolides,[40,41] but cross-resistance extending from the macrolides to clindamycin is variable, depending on whether the resistance mechanism is of the MLS_B or M phenotype.[41,42] The M phenotype had been the predominant one for *S. pneumoniae* in the United States, accounting for 83% of isolates and usually associated with low levels of erythromycin resistance, which typically does not extend to clindamycin.[35,43] Recent surveillance data from the United States, however, demonstrate a decrease in prevalence of the M phenotype and an increase in prevalence of clones with both MLS_B and M phenotypes.[44,45] The MLS_B phenotype is the predominant one in most of Europe[46] and Asia[47] for *S. pneumoniae,* and it is associated with a high level of erythromycin resistance (MIC, 128 to >1024 μg/mL)[43] and generally with clindamycin resistance.

Worldwide, erythromycin resistance in *S. pyogenes* is demonstrated in approximately 7% to 39% of isolates,[48–50] with lower rates of macrolide resistance of 5% to almost 7% reported in the United States.[17,51,52] As with *S. pneumoniae,* there is cross-resistance among the macrolides in *S. pyogenes;* however, resistance does not extend to clindamycin if resistance is due to the M phenotype.[50,53] A survey of 1885 clinical strains isolated in 2002 to 2003 from 45 medical centers in the United States showed that almost 7% were macrolide resistant, with 56% of them demonstrating the MLS_B phenotype and 44% having the M phenotype.[17]

Resistance to erythromycin by *S. aureus* may be selected by its use in hospitals.[54] Most methicillin-resistant strains and many methicillin-sensitive clinical isolates are now resistant to this agent.[55,56] Analyses of staphylococcal isolates from pediatric and adult patients revealed that across all ages, strains that were methicillin sensitive were on average 35% resistant to erythromycin, whereas strains that were methicillin resistant were 88% resistant.[57] In addition, there is a potential for the emergence, during treatment in an individual patient, of erythromycin resistance by *S. aureus.*[58,59] These strains may demonstrate the emergence of high-level resistance to erythromycin alone, or they may show cross-resistance to other macrolides and to lincomycin and clindamycin[14] due to the inducible type of MLS_B resistance, described earlier.

The viridans group of streptococci has traditionally been considered generally susceptible to erythromycin. However, macrolide resistance may be increasing in some areas, with 57.8% susceptible in North America, 62.7% in Asia and the Pacific, and 73.7% in Europe.[48,60]

Other susceptible gram-positive organisms include the majority of strains of *Listeria monocytogenes* and *C. diphtheriae.*[61,62] Appreciable in vitro activity has been demonstrated against *Nocardia asteroides* when combined with ampicillin.[63]

Erythromycin displays activity against a wide range of gram-positive anaerobes, including *Actinomyces israelii,*[64] *Peptostreptococcus* spp., *Propionibacterium, Lactobacillus, Eubacterium, Bifidobacterium,* and many strains of *Peptococcus.*[65] *Clostridium tetani* and *C. perfringens* are generally susceptible[66]; however, many strains of *C. perfringens* may be only moderately sensitive[67] due to erythromycin target-site alterations.[68] Resistance among *C. difficile* strains has increased over time, with resistance rates ranging from 27% to 63%[69,70] primarily due to the increase in prevalence of certain ribotypes, such as polymerase chain reaction ribotype 001.[70]

With gram-negative bacteria, erythromycin displays activity against *Bordetella pertussis,* for which reports of resistance are rare,[71] and *Moraxella catarrhalis*[72]; moderate activity against *Neisseria meningitidis*[73] and *Neisseria gonorrhoeae*[74,75]; and relatively poor activity against *Haemophilus influenzae.*[74] Enterobacteriaceae are resistant to erythromycin.[76] However, erythromycin activity against gram-negative organisms is affected by pH: as the pH rises to 8.5, so does erythromycin's activity against organisms such as *E. coli* and *Klebsiella pneumoniae.*[21] In 2004, only 0.3% of *Campylobacter jejuni* isolates tested in the United States were resistant (MIC, ≥32 μg/mL) to erythromycin.[77]

Breakpoint interpretive criteria for macrolide activity against anaerobic bacteria has not been established, but erythromycin generally has moderate activity against some species of gram-negative anaerobes, such as *Prevotella* and *Porphyromonas,* but *B. fragilis* strains are usually resistant.[78] Erythromycin also demonstrates clinically useful activity against such diverse organisms as *Legionella pneumophila,*[30] *M. pneumoniae,*[30] *Ureaplasma urealyticum,*[79] *Chlamydia trachomatis,*[28] and *Chlamydia pneumoniae.*[80] Extracellular and intracellular *L. pneumophila* strains show substantial susceptibility to erythromycin.[30,81] Erythromycin is about 30 times more potent against *M. pneumoniae* than is levofloxacin[30] and 50 times more potent than tetracycline.[82] Macrolide-resistant variants of *M. pneumoniae* range in incidence between 2% and 26% in European countries,[83,84] 13.2% in the United States,[85] and up to 90% in some areas of Japan and China.[86,87]

Atypical mycobacteria are erythromycin sensitive; however, both clarithromycin and azithromycin are more active than erythromycin against mycobacteria.[88] *Mycobacterium tuberculosis* is resistant to erythromycin.[89]

Clinical Pharmacology

The peak serum levels obtained after single doses of various erythromycin preparations are given in Table 29.2.[90–92] Erythromycin base is subject

TABLE 29.1 In vitro Susceptibilities to Erythromycin, Azithromycin, and Clarithromycin

	ERYTHROMYCIN		AZITHROMYCIN		CLARITHROMYCIN	
ORGANISM	**MIC_{50}**	**MIC_{90}**	**MIC_{50}**	**MIC_{90}**	**MIC_{50}**	**MIC_{90}**
Streptococcus pneumoniae						
Penicillin-susceptible (MIC ≤0.06 μg/mL)	0.03	1.0	0.125	1.0	0.016	0.25
Penicillin-intermediate (MIC = 0.12–1.0 μg/mL)	0.03	>64.0	0.125	>64.0	0.03	>64.0
Penicillin-resistant (MIC ≥2.0 μg/mL)	1.0	>64.0	1.0	>64.0	0.5	>64.0
Streptococcus pyogenes	≤0.06	0.06	0.12	0.25	0.03	0.06
Streptococcus agalactiae	0.06	8	0.06	0.12	0.03	0.06
Viridans streptococci	0.12	>128	2.0	8.0	0.5	8
Enterococcus spp.						
Vancomycin-sensitive	1	2	>8	>8	0.5	1
Vancomycin-resistant	>128	>128	>8	>8	>128	>128
Staphylococcus aureus						
Methicillin-sensitive	0.25	>128	—	—	0.06	>128
Methicillin-resistant	>128	>128	>128	>128	>128	>128
Staphylococcus epidermidis	32	>128	16	128	16	>128
Corynebacterium diphtheriae	0.015	0.026	0.044	0.058	0.006	0.008
Listeria monocytogenes	0.125	0.25	1	1	0.06	0.125
Moraxella catarrhalis	≤0.25	≤0.25	≤0.06	0.06	≤0.25	≤0.25
Haemophilus influenzae	4	8	1	2	8	16
Bordetella pertussis	0.03	0.06	0.03	0.06	0.06	0.06
Neisseria gonorrhoeae	0.5	2	0.12	0.25	0.25	1
Neisseria meningitidis	1	1	0.5	1	0.12	0.5
Campylobacter jejuni	0.5–2	1–4	0.25	0.12–0.5	0.5–2	1–8
Helicobacter pylori	0.12	0.25	0.25	0.5	0.008	0.015
Mycoplasma pneumoniae	≤0.015	≤0.015	≤0.015	0.015	≤0.015	≤0.015
Chlamydia trachomatis	—	≤0.25[b]	—	0.25[b]	—	≤0.015[b]
Chlamydia pneumoniae	0.125	0.25	0.125	0.25	NA	0.03
Legionella pneumophila	0.125	0.5	0.12	0.5	0.032	0.046
Bacteroides fragilis	32	>32	>32	>32	4	8
Peptococcus, Peptostreptococcus	2	16	1	>64	1	4
Clostridium perfringens	2	2	4	4	0.125	0.125
Propionibacterium spp.	≤0.06	0.5	0.125	2	≤0.06	≤0.06
Mycobacterium avium complex	—	≥64	8[c]	—	2[c]	—

[a] *MIC_{50} (MIC_{90})*, Minimal inhibitory concentration for 50% (90%) of isolates (μg/mL); values are ranges reported in referenced publications.[6,16,22–32,61,67,74,201,388–390]
[b] Reported as MIC_{100}.
[c] Reported as median MIC.

TABLE 29.2 Serum Levels of Erythromycin in Adults

			PEAK SERUM LEVELS	
PREPARATION	**DOSE (mg)**	**ROUTE**	**Hours After Dose**	**Concentration (μg/mL)**
Base	250	Oral	4	0.3–1.0[a]
	500		4	0.3–1.9
Stearate	250 (fasting)	Oral	3	0.2–1.3
	500 (fasting)		3	0.4–1.8
	500 (after food)		3	0.1–0.4[b]
Ethylsuccinate	500	Oral	0.5–2.5	1.5[c] (0.6[d])
Estolate	250	Oral	2–4	1.4–1.7
	500		3.5–4	4.2[c] (1.1[d])
Lactobionate	200	Intravenous	Immediately	3–4
	500		1	9.9

[a] Somewhat higher levels reported with some enteric-coated preparations after repeated doses.[62]
[b] One study demonstrated higher levels (to 2.8 μg/mL) with dose taken during a meal.
[c] Total drug (inactive ester and free base).
[d] Free base.

to destruction by gastric acid, and preparations of the base have been made with an acid-resistant coating to delay dissolution of the drug until it reaches the small bowel. The esters and ester salts of erythromycin used in the liquid suspension are more acid stable, form a stable suspension in water, and are tasteless. Erythromycin base (absorbed intact), stearate (absorbed as the base), and ethylsuccinate (absorbed both as the intact ester and as the free base after hydrolysis in the intestine) are usually absorbed more completely in the fasting state, although one study demonstrated increased absorption of a stearate preparation when it was taken with a meal.[93] After absorption, about 45% of the ethylsuccinate preparation is present in the serum as the inactive ester and about 55% as the active base.

Average serum levels achieved under fasting conditions with these preparations are similar; however, results with the base may be erratic. Erythromycin base has become available in a capsule containing enteric-coated granules; this preparation is promoted as giving more uniform absorption,[93,94] but some enteric-coated tablets may provide similar blood levels.[95] The level of base achieved is similar to that achieved by the other oral preparations taken in comparable doses in the fasting state. The clinical significance of the much less active esterified form of the drug that is present in serum in appreciable concentration is controversial. It would seem that in treatment of infections of only moderate severity by organisms highly sensitive to erythromycin, differences in therapeutic results using the various oral preparations would be insignificant. Limited clinical comparisons confirm that suspicion.[96]

Intravenous preparations of erythromycin achieve appreciably higher serum levels and should be used to treat serious infections requiring erythromycin.

Erythromycin is distributed through total body water.[97] Values given for protein binding vary from 40% to 90%. The drug persists in tissues longer than in the blood. The ratios of tissue or body fluid concentrations to simultaneous serum concentrations (usually at peak) are as follows: aqueous humor, 0.3; ascites, 0.4; bile, 28; middle ear exudate in otitis media, 0.3 to 0.7; pleural fluid, 0.7; prostatic fluid, 0.4; cerebrospinal fluid (CSF) without meningitis, 0 to 0.02, and with meningitis, 0.05 to 0.1; infected maxillary paranasal sinus, 0.4 to 0.8; and tonsil, 0.3. Concentrations achieved in the middle ear in otitis media are adequate to treat pneumococcal and group A streptococcal infections involving sensitive strains of these species but are not adequate to consistently eradicate *H. influenzae*.[98,99] High concentrations of erythromycin are achieved in alveolar macrophages[100] and polymorphonuclear leukocytes[101] compared with those in extracellular fluid.

Erythromycin does not enter the CSF in the setting of normal (uninflamed) meninges.[102] However, concentrations of erythromycin achieved in the CSF of patients with meningitis suggest that large parenteral doses may be effective against highly susceptible organisms such as *S. pneumoniae*.[103] Limited data from patients with septic arthritis suggest poor penetration of synovial fluid. Erythromycin is transferred across the placenta; fetal serum concentrations are about 2% of those in maternal serum, but higher concentrations accumulate in fetal tissue and amniotic fluid.[104] The drug is excreted in breast milk with a ratio of 0.41 between maternal milk and plasma levels, but it is considered safe if the infant is of an age to receive erythromycin directly.[105]

Up to 4.5% of an oral dose and 15% of a parenteral dose of erythromycin are recoverable in the urine. Urine concentrations after oral doses are often high but quite variable. Erythromycin is concentrated by the liver and excreted into the bile in high concentrations; however, only about 1.5% of the dose of the base and 0.2% of the ester can be recovered from bile in the first 8 hours, and some of this is reabsorbed from the intestine.[106] After an oral dose, large concentrations of the antibiotic are found in feces, probably representing ingested drug that was never absorbed as well as some that was excreted in bile. A large proportion of absorbed drug cannot be accounted for by urinary or biliary excretion or by tissue binding and may be inactivated in the liver by demethylation.[107]

The normal serum half-life of erythromycin is 1.4 hours, and appreciable serum levels are maintained for 6 hours. In anuric patients, the half-life is prolonged to about 5 hours, but dosage reduction in patients with renal failure is generally not necessary.[108,109] Erythromycin is not removed by peritoneal dialysis or hemodialysis.

Adverse Reactions

Although frequently used specifically for its motility effects, gastrointestinal adverse effects (30%) are the most common adverse effects caused by erythromycin. Symptoms including abdominal pain (16%), nausea and vomiting (14%), and diarrhea occur more commonly in children and young adults than in older persons and may be associated with either intravenous or oral administration.[110] Pseudomembranous colitis caused by overgrowth of toxin-producing *C. difficile* occurs rarely with the use of erythromycin.[111,112]

Thrombophlebitis with intravenous use can be decreased by appropriate dilution of the dose in at least 250 mL of solution and by avoidance of rapid infusions. Infusion should take place over 45 to 60 minutes.

Allergic reactions including skin rash, fever, and eosinophilia are rare. Severe reactions such as Stevens-Johnson syndrome have been reported.[113] Cholestatic hepatitis occurs rarely,[114] and chiefly in adults.[115] The syndrome typically begins after 20 days of therapy, but more rapidly in those previously treated, and consists of nausea, vomiting, and abdominal pain followed by jaundice, fever, and abnormal liver function tests consistent with cholestatic hepatitis. These findings are sometimes accompanied by rash, leukocytosis, and eosinophilia. The abnormalities usually clear within days to a few weeks after the drug is stopped but may return rapidly on rechallenge. However, hepatocyte toxicity induced by the drug or its metabolites, as well as allergy to altered hepatocyte components, may be contributory.[116] Reversible hepatotoxicity, including jaundice, has occurred with the stearate salt and with the ethylsuccinate ester of erythromycin.[117]

Ototoxicity has been reported rarely in association with the use of large intravenous doses of erythromycin lactobionate or large doses of oral erythromycin.[118,119] This may occur more commonly in older adults, in patients with hepatic or renal insufficiency, with receipt of higher doses, and with concurrent use of ototoxic medications.[120,121] Symptoms are usually reversible; however, irreversible tinnitus and hearing loss have been reported.[113,122]

Mitochondrial toxicities have also been reported with the use of macrolides. When simulating concentrations of locally applied antibiotics in a cell culture model of primary human osteoblasts, erythromycin inhibited mitochondrial energetics, namely, proliferation and metabolic activity, of the osteoblasts, but to a lesser degree than azithromycin.[123] Mitochondria isolated from rat cardiomyocytes have also been affected by exposure to macrolide antibiotics. The resulting induced cascade of reactive oxygen species formation, mitochondrial membrane permeability, mitochondrial swell, and cytochrome *c* release within the cardiomyocytes with exposure to azithromycin, clarithromycin, and erythromycin has been proposed as a starting point for cardiotoxicities, including arrhythmias, QT prolongation, and torsades de pointes.[124]

Polymorphic ventricular tachycardia (torsades de pointes) with QT prolongation has been reported in association with treatment with intravenous and oral erythromycin.[125–127] The drug has been shown to affect repolarization in the isolated heart and to block electrical current in guinea pig ventricular myocytes in a way consistent with the observed arrhythmia.[128] The possibility for interaction with potential-lengthening drugs (classes IA and III antiarrhythmics) and for increased risk in the presence of electrolyte abnormality or prolonged QT interval should be kept in mind. Other major contributing factors to macrolide-associated torsades de pointes include the coadministration of cytochrome P-450 isoenzyme 3A4 (CYP3A4) inhibitors (resulting in increased drug exposure). One study reported that coadministration of CYP3A4 inhibitors and erythromycin led to a fivefold greater risk of cardiac sudden death.[127] (See further discussion of the potential for macrolide-induced arrhythmias and sudden death in the "Adverse Effects" section under "Azithromycin and Clarithromycin".)

Superinfection, especially of the gastrointestinal tract or vagina, with *Candida* species or gram-negative bacilli may occur, as with other antibiotics.

Infantile hypertrophic pyloric stenosis has been epidemiologically linked to early exposure to erythromycin in children. It has been hypothesized that erythromycin interacts with motilin receptors, inducing

strong gastric and pyloric contractions leading to pyloric hypertrophy.[129,130] There is no substantive evidence of a risk associated with prenatal exposure.[131] Erythromycin is classified as pregnancy category B.

Drug Interactions

Incompatibility during administration between intravenous preparations of erythromycin and other drugs has been reported; the latter include vitamin B complex and vitamin C, cephalothin, tetracycline, chloramphenicol, colistin, and heparin.

Erythromycin may produce interactions with other drugs by interfering with their hepatic metabolism through the CYP3A subclass of the cytochrome P-450 enzyme system.[132,133] The resulting increased drug levels may result in serious toxicity (Table 29.3).[134] For example, elevations of midazolam serum concentrations have led to unconsciousness. The reverse of that process, in which drugs that elevate levels of erythromycin may promote its proarrhythmic effects, has been discussed earlier (see the "Adverse Reactions" section under "Erythromycin").

Erythromycin can increase the bioavailability of digoxin, possibly by interfering with its inactivation by gut flora.[132] Erythromycin may inhibit the assay organism used in some determinations of serum folic acid. Sequential use of erythromycin and clindamycin should be avoided when possible because of the potential for the development of cross-resistance or dissociated resistance.

Uses of Erythromycin

Erythromycin has few indications for use as the drug of choice due to the availability of other macrolides with improved pharmacokinetic profiles, in addition to fewer side effects and drug interactions (Table 29.4).[6,75,109,135–146]

Although erythromycin continues to be useful in the treatment of community-acquired respiratory infections, its utility has become limited to an alternative to penicillin G for group A β-hemolytic streptococci

TABLE 29.3 Potentially Clinically Significant Drug Interactions Produced by Macrolides

DRUG	INTERACTIONS
Erythromycin	Alfentanil, alprazolam, amiodarone, bromocriptine, buspirone, carbamazepine, cilostazol, cisapride, clomipramine plus risperidone, clozapine, colchicine, cyclosporine, diazepam, digoxin, disopyramide, dofetilide, ergot alkaloids, felodipine, lidocaine, levofloxacin, loratadine, lovastatin, methylprednisolone, midazolam, moxifloxacin, phenytoin, pimozide, quinidine, repaglinide, rifabutin, rifampin, ropivacaine, saquinavir, sertraline, sildenafil, simvastatin, sirolimus, sotalol, tacrolimus, terfenadine, theophylline, triazolam, valproate, verapamil, warfarin
Clarithromycin	Alprazolam, amiodarone, amprenavir, atazanavir, atorvastatin, carbamazepine, cisapride, colchicine, cyclosporine, darunavir, diazepam, digoxin, disopyramide, disulfiram, dofetilide, efavirenz, ergot alkaloids, fluoxetine, itraconazole, lidocaine, loratadine, lovastatin, methylprednisolone, midazolam, phenytoin, pimozide, quinidine, repaglinide, rifabutin, rifampin, ritonavir, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, theophylline, verapamil, warfarin, zidovudine
Azithromycin	Cyclosporine (one case), digoxin, phenytoin, rifampin, tacrolimus, warfarin

[a]Interactions generally lead to increased levels of the listed drugs caused by interaction of the macrolide with cytochrome P-450 hepatic metabolism. Exceptions are digoxin, in which the raised levels are caused by interference with digoxin inactivation by gut flora, and zidovudine, in which serum concentrations may be decreased by unknown mechanisms. Rifampin and rifabutin may lower the levels of clarithromycin, and clarithromycin may raise the levels of rifampin and rifabutin. Ritonavir may raise clarithromycin levels. Clarithromycin may produce modest reduction of zidovudine levels.
Modified from Kim RB and the Editors of the Medical Letter. The Medical Letter Handbook of Adverse Drug Interactions. *New Rochelle, NY: The Medical Letter on Drugs and Therapeutics; 2003.*

TABLE 29.4 Major Indications for Use of Macrolides

INFECTIONS IN WHICH MACROLIDES ARE THE DRUGS OF CHOICE

INFECTION	MACROLIDE	ADULT DOSAGES[a]
Bartonella henselae (cat-scratch disease bacillus)	Azithromycin Clarithromycin[b]	500 mg PO on day 1, then 250 mg PO on days 2–5 500 mg PO bid for 7–10 d
Bartonella henselae or *B. quintana* (bacillary angiomatosis, trench fever)	Erythromycin Azithromycin	0.5 g qid PO for 12 wk 500 mg qd PO for 4–6 wk (patients with endocarditis should receive treatment for 4–6 mo)
Bordetella pertussis	Erythromycin Azithromycin Clarithromycin[b]	0.5 g qid PO for 14 d 500 mg PO on day 1, then 250 mg PO on days 2–5 500 mg PO bid for 7 d
Campylobacter jejuni[c]	Azithromycin Erythromycin	500 mg daily PO for 3–7 d 250 mg qid PO for 5–7 d
Chlamydia pneumoniae (TWAR strain)	Azithromycin Clarithromycin[b] Erythromycin	500 mg qd PO/IV for 1–2 d, then 500 mg PO qd to complete 7–10 d[d] 250–500 mg bid PO for 7–10 d 0.5 g tid–qid PO for 7–10 d
Chlamydia trachomatis (inclusion conjunctivitis)[e]	Erythromycin Azithromycin	Erythromycin base or ethylsuccinate 50 mg/kg/d PO divided into 4 doses daily for 14 d Single dose of 20 mg/kg up to a maximum dose of 1 g
Chlamydia trachomatis (pneumonia)[e]	Erythromycin	Erythromycin base or ethylsuccinate 50 mg/kg/d PO divided into 4 doses daily for 14 d
Chlamydia trachomatis (trachoma)	Azithromycin	1 g PO, single dose
Chlamydia trachomatis (urethritis or cervicitis)	Azithromycin	1 g PO, single dose
Diphtheria[f]	Infection: erythromycin Carrier: erythromycin	125–500 mg qid PO for 14 d 250 mg qid PO for 7–10 d
Haemophilus ducreyi (chancroid)	Azithromycin	1 g, single dose
Helicobacter pylori	Clarithromycin[b] (+amoxicillin, *or* metronidazole + proton pump inhibitor)	500 mg bid PO for 10–14 d
Legionella spp. pneumonia	Azithromycin ± rifampin (or a fluoroquinolone ± rifampin)	1 g IV or PO on day 1, then 500 mg qd for 7–10 d total duration

TABLE 29.4 Major Indications for Use of Macrolides—cont'd

INFECTIONS IN WHICH MACROLIDES ARE THE DRUGS OF CHOICE		
INFECTION	**MACROLIDE**	**ADULT DOSAGES[a]**
Mycobacterium avium complex disseminated disease	Clarithromycin[b] (+ethambutol ± rifabutin) Azithromycin (+ethambutol ± rifabutin)	500 mg PO bid for variable periods[g] 500–600 mg qd PO for variable periods[g]
Mycobacterium avium complex prophylaxis	Azithromycin Clarithromycin[b]	1200 mg once weekly PO until initiation of effective antiretroviral therapy 500 mg bid PO until initiation of effective antiretroviral therapy
Mycobacterium avium complex pulmonary infiltrative disease	Clarithromycin[b] (+ethambutol ± rifabutin) Azithromycin (+ethambutol ± rifabutin)	500 mg bid PO for 1 yr after sputum cultures are negative 500–600 mg qd PO for 1 yr after sputum cultures are negative
Mycobacterium fortuitum/chelonae complex	Clarithromycin[b] (+amikacin)	500 mg bid PO for 4–6 mo
Mycoplasma pneumoniae	Azithromycin Clarithromycin[b] Erythromycin	500 mg PO qd for 5–10 d 250 mg PO bid for 14 d 0.5 g tid–qid PO for 14–21 d
Nongonococcal urethritis in men (*C. trachomatis* or *Ureaplasma urealyticum*)	Azithromycin	1 g PO, single dose
INFECTIONS IN WHICH MACROLIDES ARE AN IMPORTANT ALTERNATIVE DRUG		
INFECTION	**MACROLIDES AND ADULT DOSAGES[a]**	**DRUG OF CHOICE**
Groups A, C, G streptococcal infection	Erythromycin 250–500 mg qid PO[h] Azithromycin 500 mg PO on day 1, then 250 mg PO on days 2–5 Clarithromycin[b] 250 mg bid PO[h]	Penicillin G or V
Streptococcus pneumoniae infection	Erythromycin 250–500 mg qid PO[i] Azithromycin 500 mg qd[i] Clarithromycin[b] 250–500 mg bid[i]	Penicillin G, ceftriaxone, or cefotaxime
Moraxella catarrhalis	Azithromycin 500 mg PO on day 1, then 250 mg PO on days 2–5 Erythromycin 250–500 mg qid PO Clarithromycin[b] 250–500 mg bid PO	Cefuroxime; a fluoroquinolone
Haemophilus influenzae (upper respiratory infection and bronchitis)	Azithromycin 500 mg PO on day 1, then 250 mg PO on days 2–5 Clarithromycin[b] 250–500 mg bid PO	Trimethoprim-sulfamethoxazole
Shigella	Azithromycin 500 mg PO on day 1, then 250 mg PO on days 2–5	Fluoroquinolone
Prevention of infection after colorectal surgery	1 g PO each of neomycin and erythromycin base at 1, 2, and 11 PM on the day before 8 AM surgery (combined with vigorous purgation over second day before surgery)	Cefoxitin or cefotetan
Rheumatic fever prophylaxis	Erythromycin 250 mg bid PO	Penicillin G
Anthrax	Erythromycin 500 mg qid PO for 10 d[j]	Ciprofloxacin, doxycycline
Lymphogranuloma venereum	Erythromycin 500 mg qid PO for 21 d	A tetracycline
Acne vulgaris	Erythromycin 250 mg qid PO or topical preparation	A tetracycline PO and a number of topical drugs
Borrelia burgdorferi (Lyme disease)	Azithromycin 500 mg PO for 7–10 d[k]	Doxycycline, amoxicillin, cefuroxime axetil PO[k]
Babesia microti	Azithromycin 500 mg on day 1 and 250 mg on days 2–7 + atovaquone 750 mg q12h	Clindamycin + quinine

[a]Intravenous therapy should be used in serious illness or when oral therapy is not possible or reliable.
[b]Not recommended for use in pregnancy.
[c]In some areas, such as in Thailand, macrolide- and fluoroquinolone-resistant strains have become common.
[d]Mild-to-moderate severity: azithromycin 500 mg PO on day 1, then 250 mg PO on days 2–5.
[e]Diseases of infants.
[f]Antitoxin is essential primary therapy for disease.
[g]May be discontinued after >1 yr with *M. avium* complex treatment, when CD4 cell count >100 cells/mm^3 for 3–6 mo on highly active antiretroviral therapy (HAART), and patient is asymptomatic.
[h]Treatment should be continued for 10 days for group A.
[i]Resistance to macrolides is increasing and is particularly frequent in penicillin-resistant strains.
[j]Therapy may need to be continued for prolonged periods until vaccination is completed in those infected by the pulmonary route.
[k]For treatment of erythema migrans, uncomplicated facial nerve palsy, mild cardiac disease, and arthritis, oral therapy is satisfactory. For other neurologic or more serious cardiac disease, intravenous therapy with ceftriaxone, cefotaxime, or penicillin G is recommended.

in the setting of penicillin hypersensitivity. Use is further limited in areas in which the incidence of penicillin-resistant pneumococci is high, and thus resistance to erythromycin is common.[44,147] Erythromycin is also effective for the treatment of *M. catarrhalis*. Erythromycin is not consistently effective in treatment of infections caused by *H. influenzae*.[98,99] Treatment of *M. pneumoniae* infection with erythromycin, as with tetracycline, shortens the clinical course of the infection, even if started late in the course of illness; radiologic clearing of pulmonary lesions occurs earlier with erythromycin.[148,149] Clinical experience and studies in vitro and in guinea pigs suggest that erythromycin is effective in treating pneumonia caused by *L. pneumophila* or *Legionella micdadei*[150]; however, its use has been superseded by the newer macrolides, azithromycin and clarithromycin.[151] The US Food and Drug Administration has approved azithromycin and levofloxacin for the treatment of

legionellosis, and they are now considered preferable to erythromycin, especially when given orally.[140,152]

Early treatment of pertussis with erythromycin is associated with clinical improvement, a rapid clearance of *B. pertussis* from the nasopharynx, and a reduction in secondary transmission in households. Erythromycin is also recommended for postexposure prophylaxis of pertussis.[153,154] Treatment of infants with erythromycin for pneumonia or conjunctivitis caused by *C. trachomatis* is approximately 80% effective, although a second course of antimicrobial therapy may be required.[155] Because of reports of an association between oral erythromycin and infantile hypertrophic pyloric stenosis, monitoring for its signs and symptoms should be implemented in treated infants who are younger than 6 weeks of age.[130]

Erythromycin treatment of patients with gastroenteritis caused by *C. jejuni* hastens the eradication of the organism from the feces but does not appear to alter the clinical course of uncomplicated infection when therapy begins 4 days or more after the onset of symptoms.[156] However, earlier treatment of young children with acute dysentery associated with *C. jejuni* has been shown to shorten the course of diarrhea and fecal excretion of susceptible organisms.[157,158]

Erythromycin base given orally together with neomycin on the day before colorectal surgery and combined with vigorous purgation is about as effective as parenteral cephalosporin administration just before surgery in decreasing the incidence of septic complications.[159] No advantage has been demonstrated for the use of a combination of oral and intravenous antibiotics.[160] In the presence of bowel obstruction or when there is need for emergency surgery, the parenteral antibiotic regimen should be used.[109]

Erythromycin given orally for up to 3 months remains the drug of choice in treating certain visceral or angioproliferative *Bartonella* infections (bacillary angiomatosis and bacillary peliosis hepatis in immunocompromised patients), but might be difficult to tolerate.[109,161,162] Relapses have been described, especially of lesions in bone and skin and when antibiotics are given for a shorter duration (<3 months), particularly in severely immunosuppressed patients.[163]

A comparative study involving a small number of children with cholera, who were all treated with rehydration solutions, showed that erythromycin or trimethoprim-sulfamethoxazole was effective and superior to treatment without an antimicrobial agent.[164] Erythromycin may be used as an alternative antibiotic in the treatment of anthrax. In view of the availability of more effective alternative drugs, erythromycin should not be used alone in the treatment of deep-seated staphylococcal infections because of the potential for the emergence of resistant strains during therapy.[59,165] Erythromycin may occasionally be useful in treating urinary tract infections caused by gram-negative bacilli that might otherwise require the use of more toxic agents.[166] Urine pH must generally be raised to 8.0 or above to achieve effective activity at urinary concentrations against the gram-negative bacilli.

Erythromycin and other 14-member ring macrolides have a gastrointestinal motility–stimulating effect. In this regard, erythromycin acts as a motilin receptor agonist in the gut and gallbladder.[167] Erythromycin lactobionate 3 mg/kg IV every 8 hours has been effective for the treatment of gastroparesis in hospitalized diabetic patients.[168] When given orally, erythromycin may improve gastric emptying for several weeks but is often associated with tachyphylaxis due to downregulation of the motilin receptor when given for longer than 4 weeks.[169] These prokinetic effects have also been studied for the treatment of postvagotomy gastroparesis,[170] gastroparesis in critically ill patients receiving mechanical ventilation,[171] and intestinal dysmotility in young infants.[172]

There has been interest in the antiinflammatory activities of low-dose erythromycin (600 mg/day) and other macrolides, first suggested due to the beneficial effect of erythromycin treatment of patients with diffuse panbronchiolitis.[173,174] Those activities include interference with oxidant production by neutrophils (in which the cladinose moiety of erythromycin was found to be the key structure[175]), acceleration of neutrophil apoptosis, suppression of the release of proinflammatory cytokines, and promotion of the release of nitric oxide from endothelial cells.[175,176] At the molecular level, macrolides appear to modulate inflammation in some cells, such as human bronchial epithelial cells, by inhibiting transcription factors,[177,178] which regulate the expression of interleukin-8, among others, a chemokine that acts as a major recruiter of neutrophils in chronic airway disease.[179] The antiinflammatory protective effects of erythromycin appear to be a slow process as demonstrated by the requirement of at least a 28-day pretreatment with erythromycin to suppress an inflammatory response in zymosan-induced peritonitis in rats.[180] The 14-member ring macrolides have been effective in animal models in preventing the acute exacerbation of interstitial pneumonia and acute lung injury, such as after the use of bleomycin.[23,181] In vitro studies have demonstrated that erythromycin and other macrolides at subinhibitory concentrations reduce the adherence of various pathogenic bacterial species, such as *Pseudomonas aeruginosa,* to host cells.[182]

AZITHROMYCIN AND CLARITHROMYCIN

Azithromycin and clarithromycin were developed to improve the qualities of erythromycin. They have better oral absorption, longer half-lives, fewer gastrointestinal side effects, and a greater antimicrobial spectrum of activity than erythromycin.

Derivation, Chemistry, and Preparations

Azithromycin is derived from erythromycin, differing in having a methyl-substituted nitrogen in its 15-member lactone ring (Fig. 29.2). It is therefore an azalide antibiotic. Clarithromycin, having a 14-member ring structure, is produced by modifying position C6 of the lactone ring of erythromycin to possess a methoxy group (Fig. 29.3). These changes increase the stability of these compounds in gastric acid, improving absorption by the oral route.[183]

Azithromycin is available in capsules for oral use as azithromycin dihydrate equivalent to 250 mg of azithromycin; in film-coated tablets of 250 mg, 500 mg, and 600 mg; as a powder for oral suspension (1 g/packet, 100 mg/5 mL, 200 mg/5 mL, and 2000 mg/60 mL as a single dose); and as IV powder for solution (500 mg). The 2000-mg/60-mL formulation of azithromycin is incorporated into sustained-release microspheres that release the drug slowly, allowing for most of the drug to be released into the lower gastrointestinal tract, thereby potentially

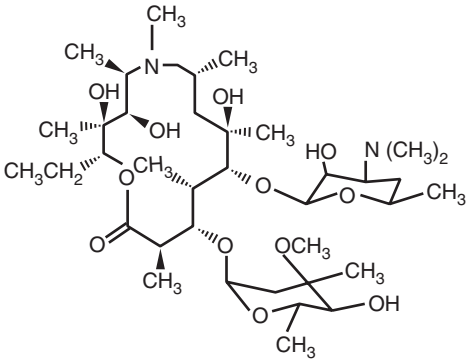

FIG. 29.2 **Azithromycin base.**

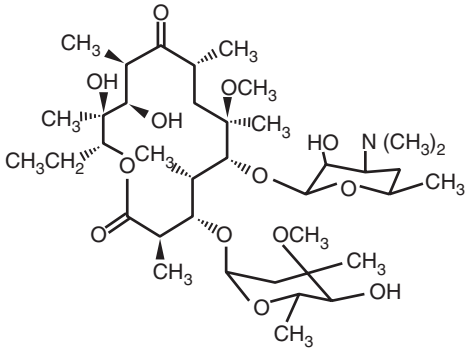

FIG. 29.3 **Clarithromycin base.**

reducing gastrointestinal side effects, and allowing for a higher dose to be administered as a single dose.

Clarithromycin is provided in 250- or 500-mg film-coated tablets, extended-release 500-mg tablets, and as granules for oral suspension (125 mg/5 mL and 250 mg/5 mL). Clarithromycin 500 mg is also available for intravenous administration in some countries.

Mechanisms of Action and Resistance

Limited studies suggest that azithromycin, clarithromycin, and erythromycin bind to the same receptor on the bacterial 50S ribosomal subunit and inhibit RNA-dependent protein synthesis by the same mechanism.[4,184] Azithromycin has greater activity than the 14-member macrolides erythromycin and clarithromycin against gram-negative bacteria (especially for *M. catarrhalis* and *H. influenzae*) and therefore appears to better penetrate the outer envelope of those organisms.[185] Like other macrolides, azithromycin and clarithromycin are generally considered to be bacteriostatic agents; however, bactericidal activity is demonstrated in vitro against such species as *S. pyogenes, S. pneumoniae,* and *H. influenzae.*[184,185] In vitro activity of the newer macrolides increases with rising pH, as with erythromycin.

Mechanisms of resistance to azithromycin or clarithromycin are the same as or similar to those for erythromycin.[3,5,6] There is complete cross-resistance among erythromycin, azithromycin, and clarithromycin for gram-positive organisms showing resistance to erythromycin by the MLS_B phenotype because the methylation mechanism already described operates for all of the 14- and 15-member macrolides.[15] Cross-resistance among the 14- and 15-member macrolides is also characteristic of the M phenotype and is the result of an efflux system for the drugs. Macrolide-resistant strains of *H. pylori* with point mutations in the 23S rRNA genes are increasing and are thought to be due to prior macrolide exposure.[186,187] Further studies with such strains suggest that horizontal transfer of the mutated gene can occur.[188] Similar point mutations in the 23S rRNA gene associated with macrolide resistance in *M. avium* complex have been selected in patients undergoing clarithromycin or azithromycin monotherapy for disseminated infections.[189]

Antimicrobial Activity

Although the most widely prescribed antibiotic in the United States, azithromycin is about two- to fourfold less active than erythromycin against *S. pneumoniae* and *S. pyogenes.*[183,184,190] Clarithromycin is highly active against gram-positive bacteria, being two- to fourfold more active than erythromycin against most streptococci, including *S. pneumoniae* and *S. pyogenes,* and methicillin-sensitive *S. aureus.*[34,183,184] Streptococci and staphylococci that are resistant to erythromycin are resistant to clarithromycin and azithromycin.[40,41,184,191] Selection for penicillin and multidrug-resistant *S. pneumoniae* appears to be associated with macrolide, as well as cephalosporin, use.[190] Additional information regarding the emergence of macrolide resistance in clinical isolates of *S. pneumoniae* and *S. pyogenes* was discussed earlier under "Erythromycin". Most methicillin-resistant staphylococci are resistant to the newer macrolides.[55,56] An active metabolite of clarithromycin, 14-hydroxyclarithromycin, has slightly greater activity than the parent compound against *S. aureus* and *S. pneumoniae* and is additive in vitro to the activity of clarithromycin.[6,191]

The activity of clarithromycin against many gram-negative bacteria is similar to that of erythromycin,[6,184] although it is slightly more active against *M. catarrhalis.* 14-Hydroxyclarithromycin also has slightly greater activity for *M. catarrhalis* and *H. influenzae* than the parent compound.[191] Azithromycin is more active than erythromycin or clarithromycin against gram-negative bacteria, especially against *H. influenzae* and *M. catarrhalis,* likely because of its higher penetration into the bacteria due to higher lipophilicity.[183,192,193] The greater activity of azithromycin against the Enterobacteriaceae is of questionable clinical significance. However, it is of interest that prolonged incubation of *P. aeruginosa* strains with macrolides at clinically achievable concentrations is associated with decreased viability and diminished protein synthesis.[194] Azithromycin is the most potent in that regard. Furthermore, macrolides have been shown to inhibit the expression of quorum sensing of *P. aeruginosa,* thereby downregulating quorum sensing–regulated genes that encode virulence factors such as adhesion molecules and those that bring about cytotoxicity and inflammation.[195] Azithromycin is more active than erythromycin against *N. meningitidis* and *N. gonorrheae;* however, azithromycin resistance among *N. gonorrheae* isolates has increased up to 4% and 7.9% as of 2014 in the United States and European countries.[196,197]

Azithromycin and clarithromycin have equal or slightly better in vitro activities than erythromycin against *L. pneumophila.*[30,81] All three macrolides generally have good activity against *M. pneumoniae* and *C. pneumoniae,*[30,79,191] although *M. pneumoniae* macrolide-resistant isolates have been detected sporadically in recent years, especially in Japan, as discussed earlier in the "Antimicrobial Activity" section under "Erythromycin". Azithromycin and clarithromycin have significantly greater activity than erythromycin against *C. trachomatis* and *U. urealyticum*[28,79] and somewhat greater activity against *Borrelia burgdorferi.*[184,185] The small in vitro differences in potency among these macrolides may not have any clinical significance with regard to efficacy.[198] Both azithromycin and clarithromycin also have significant and approximately equal activity against *Toxoplasma gondii* in tissue culture systems.[199]

The macrolides show little activity against *M. tuberculosis.*[200] In contrast, clarithromycin shows substantial activity against *Mycobacterium leprae* and is superior in this respect to erythromycin and azithromycin.[191,200] Clarithromycin and azithromycin have appreciable activities against *M. avium* complex. Clarithromycin is about fourfold more active than azithromycin against this organism in vitro[201] and is somewhat more active in slowing its replication in infected human macrophages.[202]

Azithromycin and clarithromycin demonstrate activity against *Mycobacterium abscessus* complex species; however, this organism produces an inducible 23S rRNA methylase encoded by *erm*(41), which promotes macrolide resistance. Overall, clarithromycin induces greater *erm*(41) expression leading to higher macrolide resistance compared to azithromycin, but levels of inducible clarithromycin resistance are distinguishable among the subspecies of *M. abscessus.*[203] *M. abscessus* subspecies *bolletii* demonstrate inducible resistance, as do *M. abscessus* subspecies *abscessus,* if the *erm*(41) sequevar T28 is present. Conversely, *erm*(41) sequevar C28 is associated with clarithromycin susceptibility among *M. abscessus* subspecies *abscessus. M. abscessus* subspecies *massiliense* may also harbor *erm*(41) but remain susceptible to clarithromycin.[204,205]

Clinical Pharmacology

The oral bioavailability of azithromycin after a single 500-mg dose is 37%.[206] Food increases the maximum serum concentration by approximately 50%,[207] but absorption is unaffected by magnesium- or aluminum-containing antacids.[208] The maximum serum concentration achieved after a single 500-mg oral dose was 0.41 μg/mL within 2 to 4 hours.[184] The maximum concentration and 24-hour area under the curve after a single 2-g dose of the sustained-release formulation are two and three times higher than those achieved with a total treatment dose of 1.5 g of conventional, immediate-release azithromycin.[209]

Protein binding of azithromycin in serum varies between 7% and 50% depending on the drug concentration.[184] Azithromycin is widely distributed in tissues, and for most tissues the drug concentration exceeds that in serum by 10- to 100-fold,[206] particularly in sputum and lung. Very high concentrations were found in alveolar macrophages and neutrophils.[210] The extensive tissue uptake of azithromycin has been attributed to cell uptake of this basic compound into relatively acidic lysosomes because of ionic trapping.[210] Very low concentrations were noted in CSF in patients without meningitis and in the aqueous humor of the uninflamed eye.[211] However, appreciable concentrations of azithromycin have been detected in the brains of patients undergoing resections of brain tumors after they received 500 mg orally.[211] The average half-life in many tissues is between 2 and 4 days,[206] so it is estimated that significant antibacterial activity against many pathogens persists in tissue for at least 5 days after a 5-day course of treatment.[206] The average terminal half-life is 68 hours, consistent with a slow release of drug from tissues, followed by elimination from the vascular compartment. About 6% of an oral dose appears as unchanged drug in the urine within 1 week of administration, and another small proportion is metabolized to inactive compounds, particularly by demethylation.[206] Most of the drug that is absorbed remains unmetabolized and is probably