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and ethambutol has been successful. Therapy is prolonged, gen erally continuing for 12 months after culture conversion; typically, a course lasts for at least 18 months. Other drugs with activity against MAC organisms include IV and aerosolized aminogly cosides, fluoroquinolones, and clofazimine. In elderly patients, rifabutin can exert significant toxicity. However, with only mod est efforts, most antimycobacterial regimens are well tolerated by most patients. Resection of cavitary lesions or severely bronchi ectatic segments has been advocated for some patients, especially those with macrolide-resistant infections. The success of therapy for pulmonary MAC infections depends on whether disease is nodular or cavitary and on whether it is early or advanced, rang ing from 20 to 80%.

M. kansasii lung disease is similar to tuberculosis in many ways and is also effectively treated with isoniazid (300 mg/d), rifampin (600 mg/d), and ethambutol (15 mg/kg per day). Other drugs with very high-level activity against M. kansasii include macrolides, fluoroquinolones, and aminoglycosides. Treatment should con tinue until cultures have been negative for at least 1 year. In most instances, M. kansasii infection is easily cured. Bulky, severe, necro tizing M. kansasii lymphadenopathy, especially in the mediastinum, is strongly associated with GATA2 deficiency. Rapidly growing mycobacteria pose special therapeutic prob lems. Extrapulmonary disease in an immunocompetent host is usually due to inoculation (e.g., via surgery, injections, or trauma) or to line infection and is often treated successfully with a macrolide and another drug (with the choice based on in vitro susceptibility), along with removal of the offending focus. In contrast, pulmonary disease, especially that caused by M. abscessus, is extremely dif ficult to cure. Repeated courses of treatment are usually effective in reducing the infectious burden and symptoms. Therapy generally includes a macrolide along with an IV-administered agent such as amikacin, a carbapenem, cefoxitin, or tigecycline. Other oral agents (used according to in vitro susceptibility testing and tolerance) include fluoroquinolones, doxycycline, linezolid, and the newer tetracycline family drugs, omadacycline and eravacycline. Because nontuberculous mycobacterial infections are chronic, care must be taken in the long-term use of drugs with neurotoxicities, such as linezolid and ethambutol. Prophylactic pyridoxine has been sug gested in these cases. Durations of therapy for M. abscessus lung disease are difficult to predict because so many cases are chronic and require intermittent therapy. Expert consultation and manage ment are strongly recommended. PART 5 Infectious Diseases Once recognized, M. marinum infection is highly responsive to antimicrobial therapy and is cured relatively easily with any combination of a macrolide, ethambutol, and a rifamycin. Therapy should be continued for 1–2 months after clinical resolution of iso lated soft-tissue disease;

tendon and bone involvement may require longer courses in light of clinical evolution. Other drugs with activity against M. marinum include sulfonamides, trimethoprimsulfamethoxazole, doxycycline, and minocycline. Treatment of the other NTM is less well defined, but macrolides and aminoglycosides are usually effective, with other agents added as indicated. Expert consultation is strongly encouraged for difficult or unusual infections due to NTM. ■ ■PROGNOSIS The outcomes of nontuberculous mycobacterial infections are closely tied to the underlying condition (e.g., IFN-γ/IL-12 pathway defect, cystic fibrosis) and can range from recovery to death. With no or inad equate treatment, symptoms and signs can be debilitating, including persistent cough, fever, anorexia, and severe lung destruction. With treatment, patients typically regain strength and energy. The optimal duration of therapy when NTM persist in sputum is unknown, but treatment in this situation can be prolonged. In general, for severe underlying immunodeficiencies, hematopoietic stem cell transplanta tion is recommended and may be helpful in the resolution of severe mycobacterial disease.

■ ■GLOBAL CONSIDERATIONS In many countries, pulmonary tuberculosis is diagnosed by smear alone, which is also the method used for monitoring of response and relapse. However, examination of mycobacteria from the affected “relapsed” patients shows that a significant proportion of isolates are actually NTM. Overall, as rates of tuberculosis decline, the proportion of positive smears caused by NTM will increase. Advances in specia tion will distinguish tuberculosis from nontuberculous mycobacterial infections and thereby affect rates of assumed relapse and resistance, leading to more targeted and appropriate therapy. ■ ■FURTHER READING Blakney RA et al: Incidence of nontuberculous mycobacterial pul monary infection, by ethnic group, Hawaii, USA, 2005-2019. Emerg Infect Dis 28:1543, 2022. Daley CL et al: Treatment of nontuberculous mycobacterial pulmo nary disease: An official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline. Clin Infect Dis 71:905, 2020. Holland SM et al: Case 28-2017. A 13-month-old girl with pneumo nia and a 33-year-old woman with hip pain. N Engl J Med 377:1077, 2017. Hong GH et al: Natural history and evolution of anti-interferon-γ autoantibody-associated immunodeficiency syndrome in Thailand and the United States. Clin Infect 71:53, 2020. Lange C et al: Consensus management recommendations for less common non-tuberculous mycobacterial pulmonary diseases. Lancet Infect Dis 22:e178, 2022. Marras TK et al: Relative risk of all-cause mortality in patients with nontuberculous mycobacterial lung disease in a US managed care population. Respir Med 145:80, 2018. Marshall JE et al: Nontuberculous mycobacteria testing and culture positivity in the United States. BMC Infect Dis 24:288, 2024. Prevots DR et al: Global epidemiology of nontuberculous mycobacte rial pulmonary disease: A review. Clin Chest Med 44:675, 2023. Spinner MA et al: GATA2 deficiency: A protean disorder of hemato poiesis, lymphatics, and immunity. Blood 123:809, 2014. Szymanski EP et al: Pulmonary nontuberculous mycobacterial infec tion. A multisystem, multigenic disease. Am J Respir Crit Care Med 192:618, 2015. Divya Reddy, Sebastian G. Kurz,

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Antimycobacterial Agents Agents used for the treatment of mycobacterial infections, includ ing tuberculosis (TB), leprosy, and infections due to nontuberculous mycobacteria (NTM), are administered in multiple-drug regimens for prolonged courses. Currently, >180 species of mycobacteria have been identified, the majority of which do not cause disease in humans. While the overall incidence of disease caused by Mycobacterium tuberculosis has been declining, there has been a recent increase in incidence in the context of the COVID-19 pandemic, and TB remains

a leading cause of morbidity and mortality in low- and middle-income countries—especially in sub-Saharan Africa where TB/HIV co-infection is common. Wellorganized infrastructure for early diagnosis, treatment of TB infection and disease, and development of effective drug regimens and vaccines remain vital to the global strategies for TB control (Chaps. 183 and 485). Infections with NTM have gained in clinical prominence in the United States and other developed countries. These largely environ mental organisms often establish infection in immunocompromised patients or in persons with structural lung disease.

TABLE 186-1 Regimens for the Treatment of Latent Tuberculosis Infection in Adults REGIMEN SCHEDULE DURATION COMMENTS Isoniazid plus rifapentine 900 mg (15 mg/kg) weekly plus 900 mg (for weight >50 kg) weekly 3 months Directly observed therapy is recommended for once-weekly treatment in HIV-positive and -negative individuals. This regimen may be supplemented with pyridoxine (25–50 mg/d). Rifampin 600 mg/d (10 mg/kg) 4 months Recommended in HIV-negative individuals and in children. Data on effectiveness in HIV-positive patients are unavailable. Isoniazid plus rifampin 300 mg/d (5 mg/kg) plus 600 mg/d (10 mg/kg) 3 months Risk of hepatotoxicity may be higher with the combination regimen compared to that of the individual drugs. Isoniazid 300 mg/d (5 mg/kg) Alternative: 900 mg twice weekly (15 mg/kg) 6–9 months (6 months acceptable) Supplement with pyridoxine (25–50 mg daily) 6 months' duration strongly recommended for HIV-negative patients and conditional for

HIV-positive patients. 9 months may be more effective but with higher risk of hepatic toxicity.

Twice-weekly regimens require directly observed therapy. Source: TR Sterling et al: Guidelines for the treatment of latent tuberculosis infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep 69:1, 2020. TUBERCULOSIS ■ ■GENERAL PRINCIPLES The earliest recorded human case of TB dates back 9000 years. Early treatment modalities, such as bloodletting, were replaced by the sanatorium movement in the late nineteenth century, which focused on fresh air, nutrition, and bedrest to treat consumptive patients and came with the benefit of isolating infected individuals. The isolation of streptomycin from Streptomyces griseus in 1943 launched the era of antibiotic treatment for TB. Over subsequent decades, the discovery of additional agents and the use of multiple-drug regimens allowed progressive shortening of the treatment course from years to as little as 6 months for drug-susceptible TB. Latent TB infection (LTBI) and active TB disease are diagnosed by history, physical examination, radiographic imaging, tuberculin skin test, interferon-γ release assays, acid-fast staining, mycobacterial cultures, and/or new molecular diagnostics. LTBI is treated with isoniazid plus rifapentine (weekly for 3 months), rifampin (daily for 4 months), isoniazid plus rifampin (daily for 3 months), or isoniazid (optimally daily or twice weekly for 6−9 months) (Table 186-1). The 3-month, weekly regimen of iso niazid with rifapentine is currently the regimen of choice in children

> 2 years of age and in all adults including HIV-positive individuals. The regimen is not recommended for pregnant women and for persons with hypersensitivity reactions to isoniazid or rifampin. Shorter duration rifamycin-based regimens (rifampin alone for 4 months or for 3 months in combination with isoniazid) are currently preferred for the treatment of LTBI over isoniazid for 6−9 months in

> adults and children due to their effectiveness, safety, and tolerability. Caution is advised in HIV-positive individuals due to potential for drug interactions, lack of definitive data on effectiveness, and the possibility of subclinical TB disease that could facilitate the development of rifampin resistance. TABLE 186-2 Simplified Approach to Treatment of Active Tuberculosis (TB) in Adults CULTURE RESULTS INTENSIVE PHASE CONTINUATION PHASE EXTENSION OF TOTAL TREATMENT Culture-positive, drug-susceptible HRZE for 2 months, dailya or 3 times per week (with dose adjustment) HR for 4 months, daily or 5 days per week or HR for 4 months, 3 times per weekb

(with dose adjustment) Culture-negative HRZE for 2 months HR for 2 months, daily or 2 or 3 times per weekd Continuation phase extended to 4 months if the patient is infected with HIV Extrapulmonary, drug-susceptible HRZE for 2 months HR for 4–7 months, daily or 5 days per weeke Continuation phase extended to 10 months in TB meningitis; 7 months recommended by some authorities for bone/joint TB aDaily treatment is preferred; however, thrice-weekly therapy in the intensive phase (with or without an initial 2 weeks of daily therapy) may be considered in patients who are not infected with HIV and are at low risk of relapse (i.e., in pulmonary tuberculosis caused by drug-susceptible organisms that, at the start of treatment, is noncavitary and/or smear negative). bUse regimen with caution in HIV patients and/or those with cavitary disease, as missed doses can lead to treatment failure, relapse, and acquired drug resistance. cCulture conversion is prolonged if it occurs beyond 2 months. dTwice-weekly treatment regimens are not recommended in patients infected with HIV and those with cavitary pulmonary disease suspected to be TB. eStandard daily 6-month TB treatment regimen is considered to be adequate for most forms of extrapulmonary TB, including miliary TB. For TB meningitis, the addition of glucocorticoids is recommended. Abbreviations: E, ethambutol; H, isoniazid; R, rifampin; Z, pyrazinamide. Sources: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Clinical practice guidelines: Treatment of drug-susceptible tuberculosis. Clin Infect Dis 63:e147, 2016.

Completions rates of a self-administered, once-weekly regimen of isoniazid plus rifapentine for 3 months with monthly monitoring were found to be noninferior to those seen with directly observed therapy (DOT) in the United States, and thus, this regimen is considered an acceptable strategy for treating LTBI in countries with a focus on sec ondary prevention of TB disease. Recently, a 1-month daily regimen of rifapentine and isoniazid in HIV-positive individuals was found to be noninferior to 9 months of isoniazid; this regimen is included in the 2020 World Health Organization (WHO) LTBI treatment guidelines. For active or suspected TB disease, clinical factors, including HIV co-infection, symptom duration, radiographic appearance, and public health concerns about TB transmission, drive diagnostic testing and treatment initiation. Confirmation of active TB relies on detection of M. tuberculosis via culture or molecular testing. A combination of drugs is used for the treatment of TB disease (Table 186-2). For drugsusceptible disease, a standardized regimen is used with an intensive phase consisting of four drugs—isoniazid (H), rifampin (R), pyrazin amide (Z), and ethambutol (E)—given for 2 months, which is followed by a continuation phase of isoniazid and rifampin for 4 months, for a total treatment duration of 6 months. U.S. guidelines recommend extension of the continuation phase to 7 months (for a total treatment duration of 9 months) for

patients with cavitary disease; if the 2-month course of pyrazinamide is not completed; or if sputum cultures remain positive beyond 2 months of treatment (delayed culture conversion), which also warrants evaluation for development of drug resistance. CHAPTER 186 Antimycobacterial Agents In 2020, a large multinational randomized trial showed that a 4-month regimen composed of daily rifapentine, isoniazid, pyrazin amide, and moxifloxacin for 8 weeks, followed by rifapentine, isonia zid, and moxifloxacin for 9 weeks, was noninferior to the traditional 6-month HRZE regimen. Patients with HIV and a CD4 count >100 were included. This regimen now has conditional recommendation by Continuation phase extended to 7 months if 2 months of Z is not completed, if the patient is infected with HIV and is not receiving antiretroviral therapy, or if culture conversion is prolonged and/or cavitation is evident on chest radiography (U.S. guidelines)c

the WHO and U.S. guidelines. Remaining concerns are higher daily pill burden, potential side effects from prolonged use of moxifloxacin, and need for fluoroquinolone resistance testing in areas where resistance is prevalent.

Treatment of TB in patients co-infected with HIV poses signifi cant challenges, but some progress is being made. To improve sur vival, current recommendations include initiation of antiretroviral therapy (ART) in HIV patients co-infected with M. tuberculosis within

2 weeks of the initiation of treatment for TB (except TB meningitis) if the CD4+ T-cell count is ≤50/μL and by 8–12 weeks of TB treatment initiation if the CD4+ T-cell count is ≥50/μL. Interactions of rifampin with protease inhibitors or nonnucleoside reverse transcriptase inhibi tors can be significant and require close monitoring and dose adjust ments. Reassuringly, a recent study comparing the safety and efficacy of rifampin for 4 months in patients with LTBI showed that it was as effective as isoniazid for 9 months and was also well tolerated and safe for treatment in persons living with HIV. Rifabutin is an alternative drug of choice in HIV patients co-infected with M. tuberculosis, as it is a less potent cytochrome P3A inhibitor than rifampin. The TB immune reconstitution inflammatory syndrome (IRIS) may appear as early as 1 week after initiation of ART and manifests as paradoxical worsen ing or unmasking of existing TB infection. Conservative management consists of continued administration of ART and TB medications. However, severe or debilitating IRIS has been treated in reported case series with varying doses of glucocorticoids. A randomized, doubleblind, placebo-controlled trial showed that a 4-week course of pred nisone significantly reduced the need for hospitalization and hastened symptom improvement and quality of life in TB IRIS. Intermittent antimycobacterial therapy in patients infected with HIV and M. tuber culosis has been associated with low plasma levels of several key TB PART 5 Infectious Diseases TABLE 186-3 Monitoring and Clinical Management of Tuberculosis (TB) Treatment in Adultsa DRUG ASSESSMENT MANAGEMENT LTBI Treatment With hepatic risk factorsb, check ALT and bilirubin at baseline. If ALT is ≥3× ULN or total bilirubin is >2× ULN, defer treatment and reevaluate. Isoniazid Determine whether hepatic risk factors are present. If so, obtain baseline and periodic ALT and bilirubin values If ALT is 5× ULN (or 3× ULN with symptoms)c or if bilirubin reaches jaundice levels (usually >2× ULN), interrupt treatment. With normalization, consider an alternative agent. Rifampin Same as above Same as above TB Treatment Check ALT, bilirubin, platelets, creatinine, and hepatitis panel for all patients at baseline. If hepatic risk factors are present, check ALT and bilirubin monthly. Isoniazid If ALT is >5× ULN (or >3× ULN with hepatitis symptoms)c Obtain history of alcohol consumption and concomitant drug use. In most instances, discontinue H, Z, R, and other hepatotoxic drugs. Consider alternative agents. Obtain viral hepatitis serologies.

Rechallenge: With normalization of liver enzymes, R and H may be sequentially reintroduced. With no recurrence of hepatotoxicity, Z is not resumed in many cases. Alternative rechallenge protocols have been used. Rifampin If primary elevation is in bilirubin and alkaline phosphatase, most likely due to rifampin Discontinue R if total bilirubin reaches jaundice levels (usually >2× ULN). May try to reintroduce; if not tolerated, may substitute Q. Ethambutol Decrease in visual acuity or color vision on monthly screening Discontinue ethambutol and repeat ocular examination. Peripheral neuropathy may be a precursor of ocular toxicity; if it occurs, consider repeat ocular examination. Pyrazinamide If ALT is >5× ULN (or >3× ULN with symptoms)c Same as for H. Fluoroquinolone, bedaquiline, delamanid QTc prolongation is a concern and should be monitored, especially if drugs are used in combination Asymptomatic QTc prolongation should prompt consideration of stopping known QT-prolonging drugs and/or close monitoring, depending on the clinical situation and degree of prolongation. Symptomatic QTc prolongation (e.g., palpitations or arrhythmias) should prompt discontinuation of drugs. Linezolid Visual impairment; monitor for peripheral neuropathy and bone marrow suppression including anemia, thrombocytopenia, and leukopenia Discontinue linezolid if visual toxicity develops. Rechallenge after complete resolution, especially with a lower dose, is an option. Stop if peripheral neuropathy or bone marrow suppression develops. aAll regimens require monthly clinical monitoring. bHepatic risk factors: chronic alcohol use, viral hepatitis, preexisting liver disease, pregnancy or ≤3 months postpartum, hepatotoxic medications. cRelevant manifestations include nausea, vomiting, abdominal pain, jaundice, or unexplained fatigue. Abbreviations: ALT, alanine aminotransferase; H, isoniazid; LTBI, latent tuberculosis infection; Q, fluoroquinolone; QTc, corrected QT interval; R, rifampin; ULN, upper limit of normal; Z, pyrazinamide. Sources: JJ Saukkonen et al: An official ATS statement: Hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 174:935, 2006; American Thoracic Society/ Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med 167:603, 2003; WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. License: CC BY-NC-SA 3.0 IGO.

drugs and with higher rates of treatment failure or relapse; therefore, intermittent twice-weekly therapy for TB in HIV-co-infected individu als is not recommended. Adherence to medications is critical in achieving a cure with anti mycobacterial therapy. In addition to DOT by trained staff, either in the clinic or at home, case management interventions such as patient education/counseling, field/home visits, and patient reminders are also recommended to improve treatment adherence. Use of mobile health technologies, including video DOT, text messaging, and next-generation electronic pillboxes, shows promise in promoting TB adherence. In drug-susceptible TB, monthly dispensing of TB medications is also advised for all patients to allow essential clinical monitoring for hepa totoxicity due to these medications. Clinical monitoring includes at least monthly assessment for symptoms (nausea, vomiting, abdominal discomfort, and unexplained fatigue) and signs (jaundice, dark urine, light stools, diffuse pruritus) of hepatotoxicity, although the latter represent comparatively late manifestations (Table 186-3). The pres ence of such symptoms and signs mandates provisional discontinua tion of potentially hepatotoxic agents; discontinuation at the onset of hepatitis symptoms reduces the risk of progression to fatal hepatitis. Although biochemical monitoring is not routinely recommended, baseline assessment of liver function is recommended in adults includ ing testing of at least serum alanine aminotransferase (ALT) and total bilirubin levels (Table 186-3). (See Chap. 183 for further details.) For patients with active TB, monthly mycobacterial cultures of sputum are recommended until it is

certain that the organisms have been cleared and the patient has responded to therapy or until no sputum is avail able for culture. If significant clinical improvement does not occur or the patient's condition deteriorates over the course of therapy, possibilities include

treatment failure due to incomplete adherence, poor medication absorption, or the development of resistance. For patients co-infected with HIV and M. tuberculosis, IRIS, which is a diagnosis of exclusion, should also be a consideration. Drug susceptibility testing should be repeated at this point. If resistance is documented or strongly sus pected, at least two efficacious drugs to which the isolate is susceptible or which the patient has not already taken should be added to the therapeutic regimen. Multidrug-resistant tuberculosis (MDR-TB) is defined as disease caused by a strain of M. tuberculosis that is resistant to both isoniazid and rifampin—the most efficacious of the first-line TB drugs. The risk of MDR-TB is elevated in patients presenting from geographic areas in which ≥5% of incident cases are MDR-TB and in patients previously treated for TB. Treatment regimens for MDR-TB are rapidly evolving, and in 2019, the WHO issued a new classification of second-line agents to treat drug-resistant disease (Table 183-4). New 2022 WHO recom mendations emphasize an all-oral bedaquiline-containing regimen with the goal to limit treatment duration to 6 months compared to conventional durations of 9 months or longer (Table 186-4). Results from several recent large clinical trials have formed the basis of these recommendations. The "Bangladesh regimen" was the first shortcourse MDR-TB regimen systematically studied in the STREAM-1 trial and was able to reduce treatment duration to 9−12 months with favorable outcomes in up to 90% of patients. It consists of a seven-drug intensive phase (kanamycin, prothionamide, isoniazid, fluoroquino lone, ethambutol, pyrazinamide, and clofazimine) and a four-drug continuation phase (fluoroquinolone, ethambutol, pyrazinamide, and clofazimine). In 2018, a large meta-analysis, which pooled individual data from >12,000 patients enrolled in 50 trials, assessed the role of individual drugs to treat MDR-TB. This analysis showed an association of significantly better treatment outcomes with the use of linezolid, bedaquiline, clofazimine, carbapenems, and later generation fluoro quinolones and worse outcomes with kanamycin and capreomycin in these patients. As a result of this analysis, oral drug combinations are now prioritized, while several traditional second-line drugs, including kanamycin and capreomycin, are no longer recommended. The shift toward all-oral regimens of shortened duration has been made possible by the introduction of novel drugs, most prominently bedaquiline and pretomanid, as well as the repurposing of existing agents for MDR-TB treatment (e.g., linezolid, clofazimine). A further TABLE 186-4 Simplified Approach to Treatment of Drug-Resistant Tuberculosis (TB) in Adultsa CULTURE RESULTS INTENSIVE PHASE CONTINUATION PHASE EXTENSION OF TOTAL TREATMENT Resistant to H Lfx RZEb for 6 months … Prolonged culture conversion and/or evidence of cavitation on chest radiography. Resistant to HR (MDR)c Bdq, Pa, Lz, Mfx for 6 months (may drop Mfx if documented Q resistance) BPaLM Regimend WHO short-course regimen (9-month all-oral regimen)e Bdq plus Lfx or Mfx, Eto, E, Z, Hh, Cfz for 4–6 months At least four effective second-line agents, including all three group A and at least one group B; add group C if intolerant to A or B drugs for 5–7 months WHO extended regimenf aDrug-resistant TB treatment regimens should be constructed and care provided in close consultation with experienced drug-resistant TB clinicians. Surgical management should also be considered in appropriate cases. bProlonged pyrazinamide duration may be associated with increased risk of liver toxicity. cMonoresistance to R is rare and should be treated as MDR. The BPaLM regimen is now the preferred MDR treatment regimen for patients without significant prior exposure to Bdq, Dlm, Pa, or Lz. eThe WHO short-course regimen is recommended for patients not qualifying for BPaLM regimen (availability, medical comorbidities,

drug resistance, prior exposure to Pa or Lz) with no prior exposure to second-line drugs and documented fluoroquinolone susceptibility only. Patients with treatment intolerance to antimycobacterial agents, disseminated TB, or pregnancy should be excluded from short-course regimens. fPatients who do not qualify for WHO short-course regimens should be treated using extended MDR-TB treatment regimens. The construction of extended regimens is guided by the requirement for selection of effective antimycobacterial agents, the need to combine sufficient medicines to maximize relapse-free survival, and the need to minimize toxicity. Abbreviations: Bdq, bedaquiline; Cfz, clofazimine; E, ethambutol; Eto, ethionamide; H, isoniazid; Hh, high-dose isoniazid; Lfx, levofloxacin; Pa, Pretomanid; Dlm, Delamanid;

Lz, Linezolid; MDR, multidrug resistant; Mfx, moxifloxacin; Pa, pretomanid; Q, fluoroquinolone; R, rifampin; WHO, World Health Organization; Z, pyrazinamide. Sources: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Clinical practice guidelines: Treatment of drug-resistant tuberculosis. Am J Respir Crit Care Med 200:e93, 2019; World Health Organization consolidated guidelines on drug-resistant tuberculosis treatment. WHO 2022.

step toward a shortened all-oral regimen was the Nix-TB study, which showed that a 6-month regimen of bedaquiline, pretomanid, and linezolid (BPaL regimen) for treatment of highly drug-resistant TB was associated with favorable outcomes (absence of clinical or bac teriologic treatment failure or relapse within 6 months of treatment completion) in 89% of patients. While a major breakthrough, caution has been raised regarding the higher rate of side effects, mostly due to linezolid, and lack of a control arm. The TB PRACTECAL trial was an open-label, multicenter, randomized, controlled, noninferiority trial that evaluated the safety and efficacy of a 24-week regimen of bedaqui line, pretomanid, linezolid, and moxifloxacin (BPaLM) compared to a 9- to 20-month standard-care regimen for the treatment of rifampicinresistant TB. In this study, the 6-month BPaLM regimen was found to be noninferior in both the intention-to-treat and per-protocol analyses, with a lower percentage of serious adverse events compared to the standard-care regimen. High cost, limited access to these new drugs, and the threat of baseline and emergent resistance, especially to bedaquiline, are barriers that need to be addressed to facilitate global adaptation of these new regimens.

■ ■FIRST-LINE ANTITUBERCULOSIS DRUGS The following discussion of individual anti-TB agents focuses on treat ment of TB in adults, unless otherwise noted. Several agents are being actively investigated during the current remarkable period of drug development for TB treatment. Isoniazid Isoniazid is a critical drug for treatment of both TB dis ease and LTBI. Isoniazid has excellent bactericidal activity against both intracellular and extracellular, actively dividing M. tuberculosis. This drug is bacteriostatic against slowly dividing organisms. In treatment of LTBI, isoniazid is generally well tolerated, has well-established effi cacy, and is inexpensive. In this setting, the drug is taken daily, which is the preferred dosing schedule, or intermittently (i.e., twice weekly) using DOT for 6 months, which has been found to be equivalent to the traditional 9 months in most settings. A weekly isoniazid and rifapen tine regimen, administered over 3 months under DOT, has been shown to be noninferior to daily isoniazid given for 9 months and had a higher treatment completion rate than the single-drug regimen. More recent evidence also suggests that completion rates of a self-administered 3-month regimen of weekly isoniazid and rifapentine are noninferior CHAPTER 186 Antimycobacterial Agents Failed culture conversion at month 4–6, delayed clinical

response. Treatment interruption of >7 days is made up by adding on to the total treatment duration. Lfx or Mfx, Cfz, Z, E for 5 months At least 4 drugs for a total of

18–20 months or for 15–17 months after culture conversion

to those seen with DOT in the United States. It is expected that a 1-month daily regimen in combination with rifapentine will be added to new WHO guidelines.

For treatment of TB disease, isoniazid is used in combination with other agents to ensure killing of both actively dividing M. tuberculosis and slowly growing “persister” mycobacteria. Unless the organism is resistant, the standard regimen includes isoniazid, rifampin, ethambu tol, and pyrazinamide (Table 186-2). Isoniazid is often given together with 25–50 mg of pyridoxine daily to prevent drug-related peripheral neuropathy. MECHANISM OF ACTION Isoniazid is a prodrug activated by the mycobacterial KatG catalase-peroxidase; isoniazid is coupled with reduced nicotinamide adenine dinucleotide (NADH). The resulting isonicotinic acyl–NADH complex blocks the mycobacterial ketoenoyl reductase known as InhA through binding to its substrate and inhibit ing fatty acid synthase and ultimately mycolic acid synthesis. Mycolic acids are essential components of the mycobacterial cell wall. KatG activation of isoniazid also results in the release of free radicals that have antimycobacterial activity, including nitric oxide. The minimal inhibitory concentrations (MICs) of isoniazid for wild-type (untreated) susceptible strains are <0.1 µg/mL for M. tuber culosis and 0.5–2 µg/mL for M. kansasii. PHARMACOLOGY Isoniazid is the hydrazide of isonicotinic acid, a small, water-soluble molecule. The usual adult oral daily dose of

300 mg results in peak serum levels of 3–5 µg/mL within 30 min to 2 h after ingestion—well in excess of the MICs for most susceptible strains of M. tuberculosis. Both oral and IM preparations of isoniazid reach effective levels in the body, although antacids and high-carbohydrate meals may interfere with oral absorption. Isoniazid diffuses well throughout the body, reaching therapeutic concentrations in body cavities and fluids, with concentrations in cerebrospinal fluid (CSF) comparable to those in serum. PART 5 Infectious Diseases Isoniazid is metabolized in the liver via acetylation by N-

acetyltransferase 2 (NAT2) and hydrolysis. Both fast- and slow-acetylation phenotypes occur; patients who are “fast acetylators” may have lower serum levels of isoniazid, whereas “slow acetylators” may have higher levels and experience more toxicity. Satisfactory isoniazid levels are attained in the majority of homozygous fast NAT2 acetylators given a dose of 6 mg/kg and in the majority of homozygous slow acetylators given only 3 mg/kg. Genotyping is increasingly being used to charac terize isoniazid-related pharmacogenomic responses. Isoniazid’s interactions with other drugs are due primarily to its inhibition of the cytochrome P450 system. Among the drugs with significant isoniazid interactions are warfarin, carbamazepine, ben zodiazepines, acetaminophen, clopidogrel, maraviroc, dronedarone, salmeterol, tamoxifen, eplerenone, and phenytoin. DOSING The recommended daily dose of isoniazid for the treatment of TB is 5 mg/kg for adults and 10 mg/kg for children (U.S. guidelines recommend 10−15 mg), with a maximal daily dose of 300 mg for both. For intermittent therapy in adults (usually twice per week), the dose is 15 mg/kg, with a maximal daily dose of 900 mg. Isoniazid does not require dosage adjustment in patients with renal disease. When the 12-dose, 3-month weekly LTBI regimen is used, the dose of isoniazid is 15 mg/kg, with a maximal dose of 900 mg, and the drug is co-administered with

rifapentine. The novel 1-month regimen uses isoniazid 300 mg in conjunction with rifapentine for people aged >13 years without weight adjustment. RESISTANCE Although isoniazid, along with rifampin, is the mainstay of TB treatment regimens, ~7% of clinical M. tuberculosis isolates in the United States are resistant. Rates of primary isoniazid resistance among untreated patients are significantly higher in many populations born outside the United States. Five separate pathways for isoniazid resistance have been elucidated. Most strains have amino acid changes in either the catalase-peroxidase gene (katG) or the mycobacterial ketoenoylreductase gene (inhA). Less frequently, alterations in kasA, the gene for an enzyme involved in mycolic acid elongation, and loss of NADH dehydrogenase 2 activity confer isoniazid resistance.

In 20–30% of isoniazid-resistant M. tuberculosis isolates, increased expression of efflux pump genes, such as efpA, mmpL7, mmr, p55, and the Tap-like gene Rv1258c, has been implicated as the underlying mechanism of resistance. ADVERSE EFFECTS Although isoniazid is generally well tolerated, drug-induced liver injury and peripheral neuropathy are significant adverse effects associated with this agent. Isoniazid may cause asymp tomatic transient elevation of aminotransferase levels (often termed hepatic adaptation) in up to 20% of recipients. Other adverse reactions include rash (2%), fever (1.2%), anemia, acne, arthritic symptoms, a systemic lupus erythematosus–like syndrome, optic atrophy, seizures, and psychiatric symptoms. Symptomatic hepatitis occurs in <0.1% of persons treated with isoniazid alone for LTBI, and fulminant hepatitis with hepatic failure occurs in <0.01%. Isoniazid-associated hepatitis is idiosyncratic, but its incidence increases with age, with daily alcohol consumption, and in women who are within 3 months postpartum. In patients who have liver disorders or HIV infection, who are preg nant or in the 3-month postpartum period, who have a history of liver disease (e.g., hepatitis B or C, alcoholic hepatitis, or cirrhosis), who use alcohol regularly, who have multiple medical problems, or who have other risk factors for chronic liver disease, the risks and benefits of isoniazid treatment for LTBI should be weighed. If treatment is undertaken, these patients should have serum concentrations of ALT determined at baseline. Routine baseline hepatic ALT testing based solely on an age of >35 years is optional and depends on individual concerns. Monthly biochemical monitoring during isoniazid treat ment is indicated for patients whose baseline liver function tests yield abnormal results and for persons at risk for hepatic disease, including the groups just mentioned. Guidelines recommend that isoniazid be discontinued in the presence of hepatitis symptoms or jaundice and an ALT or AST level three times the upper limit of normal or in the absence of symptoms with an ALT or AST level five times the upper limit of normal (Table 186-3). Peripheral neuropathy associated with isoniazid occurs in up to 2% of patients given 5 mg/kg. Isoniazid appears to interfere with pyridox ine (vitamin B6) metabolism. The risk of isoniazid-related neurotoxic ity is greatest for patients with preexisting disorders that also pose a risk of neuropathy, such as HIV infection; for those with diabetes mellitus, alcohol abuse, or malnutrition; and for those simultaneously receiving other potentially neuropathic medications, such as stavudine. These patients should be given prophylactic pyridoxine (25–50 mg/d). Rifampin Rifampin is a semisynthetic derivative of Amycolatopsis rifamycinica (formerly known as Streptomyces mediterranei). The most active antimycobacterial agent available, rifampin is the keystone of first-line treatment for TB. Introduced in 1968, this drug eventually permitted dramatic shortening of the TB treatment course. Rifampin has both sterilizing and bactericidal activity against dividing and nondividing M. tuberculosis. The drug is also active against an array of other organisms, including some gram-positive and gram-negative bacteria, Legionella, M. kansasii, and Mycobacterium marinum. MECHANISM OF ACTION Rifampin exerts both intracellular and

extracellular bactericidal activities. Like other rifamycins, rifampin specifically binds to and inhibits mycobacterial DNA-dependent RNA polymerase, blocking RNA synthesis. Susceptible strains of M. tubercu losis as well as M. kansasii and M. marinum are inhibited by rifampin concentrations of 1 µg/mL. PHARMACOLOGY Rifampin is a fat-soluble, complex macrocyclic molecule readily absorbed after oral administration. Serum levels of 10–20 µg/mL are achieved 2.5 h after the usual adult oral dose of 10 mg/kg (given without food). Rifampin has a half-life of 1.5–5 h. The drug distributes well throughout most body tissues, including CSF. Rifampin turns body fluids such as urine, saliva, sputum, and tears a reddish-orange color—an effect that offers a simple means of assessing patients' adherence to this medication. Rifampin is excreted primarily through the bile and enters the enterohepatic circulation; <30% of a dose is renally excreted. As a potent inducer of the hepatic cytochrome P450 system, rifampin can decrease the half-life of some drugs, such as digoxin,

warfarin, phenytoin, prednisone, cyclosporine, methadone, oral con traceptives, clarithromycin, azole antifungal agents, quinidine, anti retroviral protease inhibitors, and nonnucleoside reverse transcriptase inhibitors. The Centers for Disease Control and Prevention (CDC) has issued guidelines for the management of drug interactions during treatment of HIV and M. tuberculosis co-infection (www.cdc.gov/tb/). DOSING The daily dosage of rifampin is 10 mg/kg for adults and 10–20 mg/kg for children, with a maximum of 600 mg/d for both. The drug is given once daily, twice weekly, or three times weekly. No adjustments of dose or frequency are necessary in patients with renal insufficiency. RESISTANCE Resistance to rifampin in M. tuberculosis, M. leprae, and other organisms is the consequence of spontaneous, mostly missense point mutations in a core region of the bacterial gene coding for the β subunit of RNA polymerase (rpoB). RNA polymerase altered in this manner is no longer subject to inhibition by rifampin. Most rapidly and slowly growing NTM harbor intrinsic resistance to rifampin, for which the mechanism has yet to be determined. ADVERSE EFFECTS Adverse events associated with rifampin are infrequent and generally mild. Hepatotoxicity due to rifampin alone is uncommon in the absence of preexisting liver disease and often con sists of isolated hyperbilirubinemia rather than aminotransferase eleva tion. Other adverse reactions include rash, pruritus, gastrointestinal symptoms, and pancytopenia. Rarely, a hypersensitivity reaction may occur with intermittent therapy, manifesting as fever, chills, malaise, rash, and—in some instances—renal and hepatic failure. Pyrazinamide A nicotinamide analogue, pyrazinamide is an important bactericidal drug used in the initial phase of TB treatment. Its administration for the first 2 months of therapy with rifampin and isoniazid allows treatment duration to be shortened from 9 to 6 months and decreases rates of relapse. MECHANISM OF ACTION Pyrazinamide's antimycobacterial activity is essentially limited to M. tuberculosis. The drug is more active against slowly replicating organisms than against actively replicating organ isms. Pyrazinamide is a prodrug that is converted by the mycobacte rial pyrimidase to the active form, pyrazinoic acid (POA). This agent is active only in acidic environments (pH <6.0), as are found within phagocytes or granulomas. The exact mechanism of action of POA is unclear, but fatty acid synthetase I may be the primary target in M. tuberculosis. Susceptible strains of M. tuberculosis are inhibited by pyra zinamide concentrations of 16–50 µg/mL at pH 5.5. PHARMACOLOGY AND DOSING Pyrazinamide is well absorbed after oral administration, with peak serum concentrations of 20–60 µg/mL at 1–2 h after ingestion of the recommended adult daily dose of 15–30 mg/kg (maximum, 2 g/d). It distributes well to various body compart ments, including CSF, and is an important component of treatment for tuberculous meningitis. The serum half-life of the drug is 9–11 h with normal renal and hepatic function. Pyrazinamide is metabolized in the liver to POA, 5-

hydroxypyrazinamide, and 5-hydroxy-POA. A high proportion of pyrazinamide and its metabolites (~70%) is excreted in the urine. The dosage must be adjusted according to the level of renal function in patients with reduced creatinine clearance. ADVERSE EFFECTS At the higher dosages used previously, hepatotox icity was seen in as many as 15% of patients treated with pyrazinamide. However, at the currently recommended dosages, hepatotoxicity now occurs less commonly when this drug is administered with isoniazid and rifampin during the treatment of TB. Older age, active liver dis ease, HIV infection, and low albumin levels may increase the risk of hepatotoxicity. The use of pyrazinamide with rifampin for the treat ment of LTBI is no longer recommended because of unacceptable rates of hepatotoxicity and death in this setting. Hyperuricemia is a common adverse effect of pyrazinamide therapy that usually can be managed conservatively. Clinical gout is rare. Although pyrazinamide is recommended by international TB orga nizations for routine use in pregnancy, it is not recommended in the United States because of inadequate teratogenicity data.

RESISTANCE The basis of pyrazinamide resistance in M. tubercu losis is a mutation in the pncA gene coding for pyrazinamidase, the enzyme that converts the prodrug to active POA. Resistance to pyra zinamide is associated with loss of pyrazinamidase activity, which pre vents conversion of pyrazinamide to POA. Of pyrazinamide-resistant

M. tuberculosis isolates, 72–98% have mutations in pncA. Conventional methods of testing for susceptibility to pyrazinamide may produce both false-negative and false-positive results because the high-acidity environment required for the drug’s activation also inhibits the growth of M. tuberculosis. There is some controversy as to the clinical signifi cance of in vitro pyrazinamide resistance.

Ethambutol Ethambutol is a bacteriostatic antimycobacterial agent first synthesized in 1961. A component of the standard first-line regi men, ethambutol provides synergy with the other drugs in the regimen and is generally well tolerated. Susceptible species include M. tubercu losis, M. marinum, M. kansasii, and organisms of the Mycobacterium avium complex (MAC); however, among first-line drugs, ethambutol is the least potent against M. tuberculosis. This agent is also used in combination with other agents in the continuation phase of treatment when patients cannot tolerate isoniazid or rifampin or are infected with organisms resistant to either of the latter drugs. MECHANISM OF ACTION Ethambutol is bacteriostatic against

M. tuberculosis. Its primary mechanism of action is the inhibition of the arabinosyltransferases involved in cell wall synthesis, which prob ably inhibits the formation of arabinogalactan and lipoarabinomannan. The MIC of ethambutol for susceptible strains of M. tuberculosis is 0.5–2 μg/mL. CHAPTER 186 PHARMACOLOGY AND DOSING From a single dose of ethambutol, 75–80% is absorbed within 2–4 h of administration. Serum levels peak at 2–4 μg/mL after the standard adult daily dose of 15 mg/kg. Etham butol is well distributed throughout the body except in the CSF; a dos age of 25 mg/kg is necessary for attainment of a CSF level half of that in serum. For intermittent therapy, the dosage is 25–35 mg/kg thrice weekly. To prevent toxicity, the dosage must be lowered and the fre quency of administration reduced for patients with renal insufficiency. Antimycobacterial Agents ADVERSE EFFECTS Ethambutol is usually well tolerated and has no significant interactions with other drugs. Optic neuritis, the most serious adverse effect reported, typically presents as reduced visual acuity, central scotoma, and loss of the ability to see green (or,

less commonly, red). The cause of this neuritis is unknown, but it may be due to an effect of ethambutol on the amacrine and bipolar cells of the retina. Symptoms typically develop several months after initiation of therapy, but ocular toxicity soon after initiation of ethambutol has been described. The risk of ocular toxicity is dose dependent, with occurrence in 1–5% of patients, and can be increased by renal insuf ficiency. The routine use of ethambutol in younger children is not recommended because monitoring for visual complications can be difficult. If drug-resistant TB is suspected, ethambutol can be used for treatment of children. All patients starting therapy with ethambutol should have a baseline test for visual acuity, visual fields, and color vision and should undergo an examination of the optic fundus. Visual acuity and color vision should be monitored monthly or less often as needed. Cessation of ethambutol in response to early symptoms of ocular toxicity usually results in reversal of the deficit within several months. Recovery of all visual function may take up to 1 year. In the elderly and in patients whose symptoms are not recognized early, deficits may be permanent. Some experts think that supplementation with hydroxycobalamin (vitamin B12) is beneficial for patients with ethambutol-related ocular toxicity. Other adverse effects of ethambutol are rare. Peripheral sen sory neuropathy occurs in rare instances. RESISTANCE Ethambutol resistance in M. tuberculosis and NTM is associated primarily with missense mutations in the embB gene that encodes for arabinosyltransferase. Mutations have been found in resis tant strains at codon 306 in 50–70% of cases. Mutations at embB306 can cause significantly increased MICs of ethambutol, resulting in clinical resistance.

■ ■OTHER RIFAMYCIN DRUGS

Rifabutin Rifabutin, a semisynthetic derivative of rifamycin S, inhibits mycobacterial DNA-dependent RNA polymerase. Rifabutin is recommended in place of rifampin for the treatment of TB in HIV-co-infected individuals who are taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors, particularly nevirap ine. A study in India showed better TB treatment outcomes in HIVco-infected patients given daily rifabutin plus atazanavir/ritonavir than in those given thrice-weekly rifabutin plus atazanavir/ritonavir. Rifabutin’s effect on hepatic enzyme induction is less pronounced than that of rifampin. Protease inhibitors may cause significant increases in rifabutin levels through inhibition of hepatic metabolism. Rifabutin is more active in vitro than rifampin against MAC organisms and other NTM, but its clinical superiority has not been established. PHARMACOLOGY Like rifampin, rifabutin is lipophilic and is absorbed rapidly after oral administration, reaching peak serum levels 2–4 h after ingestion. Rifabutin distributes best to tissues, reaching levels 5–10 times higher than those in plasma. Unlike rifampin, rifabutin and its metabolites are partially cleared by the hepatic microsomal system. Rifabutin’s slow clearance results in a mean serum half-life of 45 h— much longer than the 3- to 5-h half-life of rifampin. Clarithromycin (but not azithromycin) and fluconazole appear to increase rifabutin levels by inhibiting hepatic metabolism. ADVERSE EFFECTS The most common adverse effects of rifabutin treatment are gastrointestinal; other reactions include rash, headache, asthenia, chest pain, myalgia, and insomnia. Less common adverse reactions include fever, chills, a flulike syndrome, anterior uveitis, hepatitis, Clostridium difficile–associated diarrhea, a diffuse polymy algia syndrome, and yellow skin discoloration (“pseudo-jaundice”). Laboratory abnormalities include neutropenia, leukopenia, thrombo cytopenia, and increased levels of liver enzymes. Rifabutin appears to be better tolerated by the majority (72%) of adult TB patients who have developed rifampin-related adverse effects. Female patients, those coinfected with hepatitis B or hepatitis C, and those with rifampin-related arthralgias, dermatologic reactions, and cholestasis are more likely

to develop mild to severe rifabutin-related adverse effects. PART 5 Infectious Diseases RESISTANCE Similar to rifampin resistance, rifabutin resistance is mediated by mutations in rpoB. Rifapentine Rifapentine is a semisynthetic cyclopentyl rifamycin, sharing a mechanism of action with rifampin. Rifapentine is lipophilic and has a prolonged half-life that permits weekly or twice-weekly dosing. Therefore, rifapentine is the subject of intensive clinical inves tigation aimed at determining optimal dosing and frequency of admin istration. Currently, it is an alternative to rifampin in the continuation phase of treatment for noncavitary drug-susceptible pulmonary TB in HIV-seronegative patients who have negative sputum smears at completion of the initial phase of treatment. When administered in these specific circumstances, rifapentine (10 mg/kg, up to 600 mg) is given once weekly with isoniazid. Because of higher rates of relapse, this regimen is not recommended for patients with TB disease and HIV co-infection; moreover, it has not been approved for children <12 years of age. In a phase 2 study, substituting daily rifapentine for rifampin yielded higher rates of sputum sterilization after 2 months of intensive treatment. Higher doses of rifapentine (20 mg/kg vs 10 mg/kg) had better results and were safe and well tolerated. Regimens containing high doses of rifapentine are being evaluated to see whether they can shorten the TB treatment course to <6 months. PHARMACOLOGY Rifapentine’s absorption is improved when the drug is taken with food. After oral administration, rifapentine reaches peak serum concentrations in 5–6 h and achieves a steady state in

10 days. The half-life of rifapentine and its active metabolite, 25-desacetyl rifapentine, is ~13 h. The administered dose is excreted via the liver (70%). ADVERSE EFFECTS The adverse effects profile of rifapentine is similar to that of other rifamycins. Rifapentine is teratogenic in animal models and is relatively contraindicated in pregnancy.

RESISTANCE Rifapentine resistance is mediated by mutations in rpoB. Mutations that cause resistance to rifampin also cause resistance to rifapentine. ■ ■SECOND-LINE ANTITUBERCULOSIS DRUGS Second-line anti-TB agents are indicated for treatment of drug-resistant TB, for patients who are intolerant or allergic to first-line agents, and when first-line supplemental agents are unavailable. According to their usability, they are divided into three WHO groups. Group A • FLUOROQUINOLONES Fluoroquinolones inhibit mycobacterial DNA gyrase and topoisomerase IV, preventing cell repli cation and protein synthesis, and are bactericidal. Given their excellent activity, they have been investigated for their potential to shorten the course of treatment for drug-susceptible TB from 6 to 4 months. In contrast to prior trials, a recent large, open-label, randomized controlled trial (TBTC Study 31) yielded promising results for shortening of TB treatment. Patients with drug-susceptible TB disease were randomized to receive either a standard 6-month TB regimen or a 4-month regimen containing rifapentine (8 weeks of once-daily rifapentine, isoniazid, pyrazinamide, and ethambutol followed by 9 weeks of once-daily rifa pentine and isoniazid) or a 4-month regimen containing rifapentine and moxifloxacin (8 weeks of once-daily rifapentine, isoniazid, pyrazin amide, and moxifloxacin followed by 9 weeks of once-daily rifapentine, isoniazid, and moxifloxacin). The trial demonstrated that a 4-month regimen using daily rifapentine and moxifloxacin (but not the rifapen tine-only regimen) was noninferior to the standard 6-month TB treat ment regimen using an end point of TB-free survival 12 months after randomization. Combining once-daily rifapentine with moxifloxacin allows for synergistic action on sputum conversion in a compliancefriendly once-daily option. Current recommendations continue to be for a standard 6-month regimen, although it is anticipated that these results will inform future guidelines. Gatifloxacin has fallen out of favor because of significant dysglycemia. Ciprofloxacin

and ofloxacin are no longer recommended for the treatment of TB because of poor efficacy. Despite documented resistance to early-generation fluoroquinolones (e.g., ofloxacin and ciprofloxacin), use of a later-generation fluoroquino lone in patients with drug-resistant TB has been associated with favor able outcomes. Fluoroquinolones are also considered safe alternatives for patients who develop treatment-limiting adverse effects from first-line agents. Levofloxacin and moxifloxacin have both been used effectively in the treatment of MDR-TB. The optimal dose of levofloxacin for this indication is being actively studied, but doses of at least 750 mg are commonly used. High-dose moxifloxacin (800 mg) is recommended for standardized shorter MDR-TB regimens. The fluoroquinolones are well absorbed orally, reach high serum levels, and distribute well into body tissues and fluids. Their absorp tion is decreased by co-ingestion with products containing multivalent cations, such as antacids. Adverse effects are relatively infrequent (0.5–10% of patients) and include gastrointestinal intolerance, rashes, dizziness, and headache. Most studies of fluoroquinolone side effects have been based on relatively short-term administration for bacterial infections, but trials have now shown the relative safety and tolerability of fluoroquinolones administered for months during TB treatment in adults. Although the potential to prolong the QTc interval, leading to cardiac arrhythmias, has been a source of concern with fluoroquino lones, cessation of treatment due to this adverse effect is rare. Because the benefits may outweigh the risks in treatment of drug-resistant TB, there is increasing interest in the use of fluoroquinolones in children, which has traditionally been avoided because of the risks of tendon rupture and cartilage damage. Multiple courses of empirical fluoroquinolone therapy for presumed community-acquired pneumonia are associated with delayed diagnosis of active pulmonary TB and increased fluoroquinolone resistance in

M. tuberculosis. Mutations in the genes encoding for DNA gyrase (gyrA and gyrB) are implicated in the majority of cases—but not all cases—of clinical resistance to fluoroquinolones. DIARYLQUINOLINES Bedaquiline (TMC207 or R207910) is a dia rylquinoline with a novel mechanism of action: inhibition of the

mycobacterial ATP synthetase proton pump. Bedaquiline is bacteri cidal for M. tuberculosis. Resistance has been reported due to point mutations in the atpE gene encoding for subunit c of ATP synthetase. Clinical bedaquiline resistance has also been reported due to non target mutations in mmpR or Rv0678 (a negative repressor of the MmpS5–MmpL5 efflux pump) and PepQ (a cytoplasmic peptidase), both of which may cause cross-resistance to clofazimine. Bedaquiline is metabolized by the hepatic cytochrome CYP3A4. Rifampin lowers bedaquiline levels by 50%, and protease inhibitors also interact sig nificantly with this drug. Because efavirenz induces CYP3A4, there is concern about lower bedaquiline levels with co-administration. In a study of co-treatment with bedaquiline and efavirenz in healthy volun teers, bedaquiline levels were reduced by only 20%; however, in a study modeling chronic co-administration of these two drugs, the reduction in bedaquiline levels was estimated to be 50%, leading many national TB programs to avoid efavirenz co-administration with bedaquiline. The oral bioavailability of bedaquiline appears to be excellent. The dosage is 400 mg/d for the first 2 weeks and then 200 mg thrice weekly typically for 6 months total. The elimination half-life is long (>14 days). A single dose of this drug can inhibit the growth of M. tuberculosis for up to 1 week through a combination of long plasma half-life, high-level tissue penetration, and long tissue half-life. Bedaquiline added to a background regimen improved the 2-month sputum culture–conversion rate in multicenter, randomized, placebo-controlled trials, and these results led to approval by the U.S. Food and Drug Administration (FDA). However, the death

rate in one trial was higher in the bedaqui line arm than in the control arm (11.4 vs 2.5%); the result was a “black box” warning from the FDA, which also included QT prolongation. Subsequent studies have not found an association with significant mortality. The CDC has made a provisional recommendation for the use of bedaquiline for 24 weeks in adults with laboratory-confirmed pulmonary MDR-TB when no other effective treatment regimen can be provided. Bedaquiline is an integral part of all shorter course, oral MDR treatment regimens endorsed by the WHO. OXAZOLIDINONES Linezolid is an oxazolidinone used primarily for the treatment of drug-resistant gram-positive bacterial infections. However, this drug is active in vitro against M. tuberculosis and NTM. Several case series have suggested that linezolid may help clear mycobacteria rela tively rapidly when included in a regimen for the treatment of complex cases of drug-resistant TB. Linezolid’s mechanism of action is disruption of protein synthesis by binding to the 50S bacterial ribosome. Linezolid has nearly 100% oral bioavailability, with good penetration into tis sues and fluids, including CSF. Clinical resistance to linezolid has been reported and is typically associated with mutations in the 23S rRNA and in two ribosomal proteins, L3 (rplC) and L4 (rplD). Adverse effects may include optic and peripheral neuropathy, pancytopenia, and lactic acidosis and are usually associated with higher doses. Linezolid is a weak monoamine oxidase inhibitor and can be associated with the serotonin syndrome when given concomitantly with serotonergic drugs (primarily antidepressants such as selective serotonin reuptake inhibitors). It has been shown that ~80% of patients with MDR-TB can be successfully treated with linezolid-containing, individualized anti-TB regimens based on drug sensitivity testing. Replacement of ethambutol with linezolid for 2–4 weeks during the intensive phase of treatment of drug-susceptible TB is currently being evaluated for possible faster sputum conversion and a shorter treatment regimen. For MDR-TB treatment, linezolid is usually administered at a dose of 600 mg (or less in some cases) once daily, which appears to be effective. A single daily dose is associated with fewer adverse events than twice-a-day dosing. Sutezolid, a modified version of oxazolidinones and protein syn thesis inhibitor, is found to have higher early bactericidal activity compared to linezolid and is currently undergoing phase 2A trials. It is currently FDA approved for complex skin infections and appears to have less frequent side effects compared to linezolid; the adverse effects profile of long-term exposure compared with that of linezolid needs further investigation. Group B • CLOFAZIMINE Clofazimine is a fat-soluble rimino phenazine dye used primarily in the treatment of leprosy worldwide.

It is currently gaining popularity in the management of drug-resistant TB because of its low cost and its intracellular and extracellular activ ity. By increasing reactive oxidant species and causing membrane destabilization, clofazimine may promote killing of antibiotic-tolerant

M. tuberculosis “persister” organisms. In addition to antimicrobial activity, the drug has other pharmacologic activities, such as antiinflammatory, pro-oxidative, and immunopharmacologic properties. Clofazimine has a half-life of ~70 days in humans, and average steadystate concentrations are achieved at ~1 month. Intake with fatty meals can improve its low and variable rates of absorption (45–62%). Com mon side effects include gastrointestinal intolerance and reversible orange to brownish discoloration of skin, bodily fluids, and secretions. Dose adjustment may be necessary in patients with severe hepatic impairment. Clofazimine was studied as part of a regimen developed in Bangladesh for potential shortening of the MDR-TB treatment course. A meta-analysis suggested that inclusion of clofazimine in a multidrug regimen for treatment of MDR-TB was associated with a favorable outcome. Newer analogues with improved pharmacokinetics and alternative formulations of clofazimine (liposomal, nanosuspension, inhalational) are being

studied.

CYCLOSERINE Cycloserine is an analogue of the amino acid d-alanine and prevents bacterial cell-wall synthesis. It inhibits the action of enzymes, including alanine racemase, that are involved in the produc tion of peptidoglycans. Cycloserine is active against a range of bacteria, including M. tuberculosis. Mechanisms of mycobacterial resistance are not well understood, but overexpression of alanine racemase can confer resistance in Mycobacterium smegmatis. Cycloserine is well absorbed after oral administration and is widely distributed through out body fluids, including CSF. The usual adult dosage is 250 mg two or three times per day. Serious potential side effects include seizures and psychosis (with suicide in some cases), peripheral neuropathy, head ache, somnolence, and allergic reactions. Drug levels are monitored to achieve optimal dosing and to reduce the risk of adverse effects, especially in patients with renal failure. Cycloserine should be adminis tered as DOT only with caution and with support from experienced TB physicians to patients with epilepsy, active alcohol abuse, severe renal insufficiency, or a history of depression or psychosis. CHAPTER 186 Antimycobacterial Agents Group C • NITROIMIDAZOLES The prodrugs delamanid (OPC67683) and pretomanid (PA 824) are novel nitro-dihydro-imidaz ooxazole derivatives that are activated by M. tuberculosis–specific flavin-dependent nitroreductases and whose antimycobacterial activity is attributable to inhibition of mycolic acid biosynthesis. Delamanid was shown in a randomized, placebo-controlled, multinational clinical trial to significantly improve the culture conversion rate at 2 months. QT prolongation occurred significantly more often in delamanidtreated patients, but no clinically relevant events were reported. In a subsequent randomized phase 3 trial, there was no significant differ ence in 6-month sputum conversion between delamanid and placebo among patients with an optimized background regimen. Currently, it is part of several ongoing clinical trials including combination with beda quiline. It is recommended for use in children younger than 6 years with rifampicin-resistant TB. Usual adult dose is 100 mg twice daily. Pretomanid, the second novel agent from this class, has shown promising results in the treatment of drug-resistant TB in combination with bedaquiline. A combination of pretomanid with moxifloxacin and pyrazinamide for treatment of drug-susceptible TB was found to have higher culture conversation rates at 8 weeks compared to HRZE; how ever, a subsequent phase 3 study raised concern for higher frequency of potentially fatal hepatotoxicity. It is currently being evaluated in several phase 3 clinical trials in various combinations, including with fluo roquinolones and pyrazinamide. Based on the previously mentioned results with the BPaL regimen (Nix-TB study), the FDA has granted approval for specific highly resistant TB cases. Adult treatment dose is 200 mg administered daily. AMOXICILLIN-CLAVULANATE AND CARBAPENEMS β-Lactam agents are largely ineffective for the treatment of M. tuberculosis because of resistance conferred by a hydrolyzing class A β-lactamase, BlaC.

Carbapenems are poor substrates of BlaC, and clavulanic acid leads to irreversible inhibition. While the use of either amoxicillin-clavulanic acid or carbapenems alone for highly resistant forms of TB has been anecdotally reported with unclear results, the combination of meropenem and clavulanic acid turned out to be highly active in vitro. Recently, the combination was found to have effective early bacteri cidal activity, and in a large individual patient data meta-analysis, the combination was associated with positive outcomes. Nevertheless, the need to administer these carbapenems intravenously and the lack of information on the drugs' long-term side effects have restricted their use to certain severe cases only. Recommended daily doses are either imipenem-cilastatin 1 g (each component) IV twice daily or merope nem 1 g IV three times daily, each in combination with

clavulanic acid 125 mg oral twice daily, which is only available in combination with amoxicillin.

AMINOGLYCOSIDES Aminoglycosides have played a time-honed role in the treatment of mycobacterial infections. Amikacin and streptomy cin are aminoglycosides that exert mycobactericidal activity by bind ing to the 16S ribosomal subunit. The spectrum of antibiotic activity for amikacin and streptomycin includes M. tuberculosis, several NTM species, and aerobic gram-negative and gram-positive bacteria. Due to the need of intravenous or painful intramuscular injections and their serious side effect profile, the WHO recommends limiting their use with the increased availability of novel oral agents. Kanamycin and capreomycin, a cyclic polypeptide similar to aminoglycosides, are no longer recommended due to worse treatment outcomes and increased mortality. This recommendation is based on a large individual patientlevel meta-analysis of observational cohort studies and is likely due to increased toxicity seen with these agents. Streptomycin was the first antimycobacterial agent used for the treatment of TB. Derived from Streptomyces griseus, streptomycin is bactericidal against dividing M. tuberculosis organisms but has only low-level early bactericidal activity. In developing countries, it continues to be widely used due to its low cost. The usual daily dose of streptomycin (given IM either daily or 5 days per week) is 15 mg/kg for adults and 20–40 mg/kg for children, with a maximum of 1 g/d for both with dose reduction recommended for patients ≥60 years of age or with renal impairment. Central nervous system penetration is poor. PART 5 Infectious Diseases Amikacin resistance is less widespread, and streptomycin-resistant strains may still be susceptible. The usual daily adult dosage is 15–30 mg/kg given IM or IV (maximal daily dose, 1 g). It is frequently used to treat severe NTM infections. Mycobacterial resistance to aminoglycosides is due to mutations in the genes encoding the 16S ribosomal RNA gene (rrs). Adverse effects of both amikacin and streptomycin include ototoxicity (in up to 10% of recipients, with auditory dysfunction occurring more commonly than vestibulotoxicity), nephrotoxicity, and neurotoxicity. ETHIONAMIDE Ethionamide is a derivative of isonicotinic acid. Its mechanism of action is through inhibition of the inhA gene product enoyl–acyl carrier protein (acp) reductase, which is involved in mycolic acid synthesis. Ethionamide is bacteriostatic against metabolically active M. tuberculosis and some NTM. It is used in the treatment of drug-resistant TB, but its use is limited by severe gastrointestinal reactions (including abdominal pain, nausea, and vomiting) as well as significant central and peripheral neurologic side effects, revers ible hepatitis (in ~5% of recipients), hypersensitivity reactions, and hypothyroidism. Ethionamide should be taken with food to reduce gastrointestinal effects and with pyridoxine (50–100 mg/d) to limit neuropathic side effects. PARA-AMINOSALICYLIC ACID Para-aminosalicylic acid (PAS; 4-ami nosalicylic acid) is an oral agent used in the treatment of drug-resistant TB. Its bacteriostatic activity is due to inhibition of folate synthesis and of iron uptake. PAS has relatively little activity as an anti-TB agent. Adverse effects may include high-level nausea, vomiting, and diarrhea. PAS may cause hemolysis in patients with glucose-6-phosphate dehy drogenase deficiency. The drug should be taken with acidic foods to improve absorption. Enteric-coated PAS granules (4 g orally every

8 h) appear to be better tolerated than other formulations and produce higher therapeutic blood levels. PAS has a short half-life (1 h), and 80% of the dose is excreted in the urine. ■ ■DRUGS IN DEVELOPMENT The pipeline of novel TB drugs is rapidly changing. We direct the reader to the Working Group on New TB Drugs for the most up-todate information (https://www.newtbdrugs.org/pipeline/clinical). NONTUBERCULOUS MYCOBACTERIA More than 180 species of NTM have been identified. Only a minor ity of these environmental organisms, which are

extensively found in soil and water, are important human pathogens. NTM cause extensive disease primarily in persons with preexisting pulmonary disease or immunocompromise but can also cause nodular/bronchiectatic dis ease in otherwise seemingly healthy hosts. Disseminated infections with NTM are common in immunocompromised individuals. NTM are also important causes of skin and soft tissue infections in surgi cal settings. The two major classes of NTM are the slow-growing and rapidly growing species; subcultures of the latter grow within 1 week. The growth characteristics of NTM have diagnostic, therapeutic, and prognostic implications. The rate of growth can provide useful pre liminary information within a specific clinical context, in that growth within 2–3 weeks is much more likely to indicate an NTM than M. tuberculosis. When NTM do grow from cultures, colonization should be distinguished from active disease to optimize the risk and benefit of prolonged treatment with multiple medications. According to the recommendations of the American Thoracic Society and the Infectious Diseases Society of America, significant clinical manifestations and/ or radiographic evidence of progressive disease consistent with NTM infection as well as either reproducible sputum culture results or a single positive culture from bronchoscopy are required for the diagno sis of NTM pulmonary disease. Isolation of NTM from blood or from an infected extrapulmonary site, such as soft tissue or bone, is usually indicative of disseminated or local NTM infection (Chap. 185). Treat ment of NTM disease is prolonged and requires multiple medications. Side effects of the regimens employed are common, and intermittent therapy is often used to mitigate these adverse events. Treatment regimens depend on the NTM species, the extent or type of disease, and—to some degree—drug susceptibility test results. ■ ■THERAPEUTIC CONSIDERATIONS FOR

SPECIFIC NTM Slowly Growing Mycobacteria Slowly growing mycobacteria can be divided into three categories based on their pigment-producing capabilities and—if they do produce pigment—their requirement for light to do so. Photochromogens, including M. marinum and M. kansasii, can produce yellowish-orange pigment only when exposed to light. Scotochromogens, including Mycobacterium gordonae and Mycobac terium scrofulaceum, can make pigment regardless of light exposure. MAC organisms and Mycobacterium ulcerans are nonchromogens—i.e., are incapable of making pigment irrespective of light exposure. MYCOBACTERIUM AVIUM COMPLEX Among the NTM, MAC organisms most commonly cause human disease. In immunocompetent hosts, MAC species are most often found in conjunction with underlying significant lung disease, such as chronic obstructive pulmonary dis ease or bronchiectasis. For patients with nodular or bronchiectatic MAC lung disease, an initial regimen consisting of clarithromycin or azithromycin, rifampin or rifabutin (the latter is preferred for HIV patients receiving ART), and ethambutol is given three times per week for at least 12 months after culture conversion. A daily regimen of these three drugs, with consideration of amikacin or streptomycin in the initial treatment phase, is recommended for patients with fibrocavitary MAC lung disease or severe nodular/bronchiectatic disease. Routine initial testing for macrolide resistance is recommended, as is testing at 6 months with a failing regimen (i.e., with cultures persistently positive for NTM). Interpretation of susceptibility tests to drugs other than macrolides and aminoglycosides is hampered by poor correlation with

clinical outcomes. Amikacin has been reformulated as a liposomal sus pension for inhalation with increased penetration into airway biofilms. The CONVERT trial showed that addition of inhaled liposomal amika cin to standard three-drug regimen of azithromycin or clarithromycin, rifampin, and ethambutol in treatment-refractory (persistent sputum positivity after at least 6 months) MAC lung disease significantly increased culture conversion rates from 9 to 26% at 6 months. Respira

tory adverse events (primarily dysphonia, cough, and dyspnea) were reported in 87.4% of patients receiving inhaled liposomal amikacin compared to 50% in the standard therapy group; however, rates of seri ous adverse events were not different between the regimens. Inhaled liposomal amikacin is now approved for use in refractory pulmonary MAC infections (persistent positive cultures after at least 6 months of treatment). It is currently being evaluated as a first-line agent and as a replacement for rifampin in the treatment of MAC lung disease. Surgical resection should be considered for individuals whose infec tion is localized to one lung, who have adequate lung function to toler ate lung resection, who have had a poor response to medical therapy, and/or who have developed macrolide-resistant MAC disease. Treatment of MAC in persons living with HIV should be initiated in consultation with an infectious diseases specialist. For HIV-infected patients with well-controlled HIV disease and CD4 T-cell counts in the normal range, MAC treatment is identical to patients without HIV disease except that drug-drug interactions between antimycobacterial agents and ART should be carefully considered. HIV-infected patients with low CD4 count (CD4+ T-cell count <100/μL) are at risk for dis seminated MAC infection. MAC disease in these patients is generally treated with clarithromycin, ethambutol, and rifabutin. Azithromycin may be preferred to clarithromycin depending on adverse effects and patient tolerance. Amikacin and fluoroquinolones are often used in salvage regimens. Treatment for disseminated MAC infection in AIDS patients may be lifelong in the absence of immune reconstitution. Therapy is recommended for at least 12 months after culture conver sion and at least 6 months of effective immune reconstitution with ART (CD4+ T-cell count >100/μL). MYCOBACTERIUM KANSASII M. kansasii is the second most common NTM causing human disease in the United States. It is also the second most common cause of NTM pulmonary disease in the United States, where it is most commonly reported in the southeastern region. M. kansasii infection can be treated with rifampin, ethambutol, and either isoniazid or macrolide; therapy continues for at least 18 months or for 12 months after culture conversion. The American Thoracic Society and the Infectious Diseases Society of America recommend routine susceptibility testing to rifampin only. Resistance to isoniazid and eth ambutol can be acquired during therapy but is usually associated with rifampin resistance as well. Rifampin-resistant M. kansasii is treated with a three-drug regimen including agents such as ciprofloxacin, azithromy cin, ethambutol, rifabutin, amikacin, trimethoprim-sulfamethoxazole, and streptomycin after drug susceptibility testing. MYCOBACTERIUM MARINUM M. marinum is an NTM found in salt water and freshwater, including swimming pools and fish tanks. It is a cause of localized soft tissue infections, which may require surgical management. Combination regimens include clarithromycin and either ethambutol or rifampin. Other agents with activity against M. marinum include doxycycline, minocycline, and trimethoprim-sulfamethoxazole. Drug susceptibility testing is recommended only if the swab remains culture positive after 3 months of appropriate therapy. Rapidly Growing Mycobacteria Rapidly growing mycobacteria causing human disease include Mycobacterium abscessus, Mycobac terium fortuitum, and Mycobacterium chelonae. Treatment of these mycobacteria is complex and should be undertaken with input from experienced clinicians. It is important to note that testing rapidly growing mycobacteria for macrolide resistance is tricky, as an induc ible erm gene may confer in vivo macrolide resistance to isolates that are susceptible in vitro. M. abscessus is the third most common NTM pathogen in the United States. It is endemic in the southeastern states between Texas

and Florida. Skin, soft tissue, and bone infections occur, usually after accidental trauma or surgery. This organism appears to have a pre dilection to cause lung infections in white nonsmoking women

aged

> 60 who have no preexisting lung disease. M. abscessus isolates are usually resistant to standard anti-TB regimens. Skin and soft tissue infections are usually treated for a minimum of 4 months with a mac rolide (clarithromycin or azithromycin) and a parenteral agent such as amikacin, cefoxitin, or imipenem. Bone infections are treated for at least 6 months. This regimen can be used for the treatment of lung infections but is often unsuccessful because of drug adverse effects and toxicities. A regimen comprising a combination of at least three active drugs (amikacin, linezolid, tigecycline, imipenem, azithromycin, pro vided the organism is macrolide susceptible) is recommended based on in vitro drug susceptibility testing. A recent meta-analysis has shown that overall therapeutic efficiency rates in M. abscessus lung infection are low at ~35%; however, incorporation of amikacin, imipenem, line zolid, and/or tigecycline was associated with improved outcomes. Con versely, macrolide resistance has been associated with worse outcomes. Surgical resection should be considered in all patients with good lung reserve and a localized infection.

■ ■DRUGS FOR THE TREATMENT OF NTM Clarithromycin Clarithromycin is a macrolide antibiotic with broad activity against many gram-positive and gram-negative bacteria as well as NTM. This drug is active against MAC organisms and many other NTM species, inhibiting protein synthesis by binding to the 50S mycobacterial ribosomal subunit. NTM resistance to macrolides is probably caused by overexpression of the gene ermB, with consequent methylation of the binding site. Strains of M. abscessus subsp. abscessus harbor an inducible macrolide resistance mechanism coded by erm41, which leads to ribosomal methylation and becomes apparent after macrolide incubation of 3−5 days, significantly hampering treatment success. Twenty percent of strains have a nonfunctional erm41 gene. Clarithromycin is well absorbed orally and distributes well to tissues. It is cleared both hepatically and renally; the dosage should be reduced in renal insufficiency. Clarithromycin is a substrate for and inhibits cytochrome 3A4 and should not be administered with cisapride, pimo zide, or terfenadine because cardiac arrhythmias may occur. Numerous drugs interact with clarithromycin through the CYP3A4 metabolic pathway. Rifampin lowers clarithromycin levels; conversely, rifampin levels are increased by clarithromycin. However, the clinical relevance of this interaction does not appear to be great. CHAPTER 186 Antimycobacterial Agents For patients with nodular/bronchiectatic MAC infection, the dosage of clarithromycin is 500 mg, given morning and evening three times a week. For the treatment of fibrocavitary or severe nodular/bronchiectatic MAC infection, a dose of 500–1000 mg is given daily. Disseminated MAC infection is treated with 1000 mg daily. Clarithromycin is used in combination regimens that typically include ethambutol and a rifamy cin in order to avoid the development of macrolide resistance. Adverse effects include frequent gastrointestinal intolerance, hepatotoxicity, headache, rash, and rare instances of hypoglycemia. Clarithromycin is contraindicated during pregnancy because of its teratogenicity in animal models. Azithromycin Azithromycin is a derivative of erythromycin. Although technically an azalide and not a macrolide, it works similarly to macrolides, inhibiting protein synthesis through binding to the 50S ribosomal subunit. Azithromycin is preferred over clarithromycin due to once-daily dosing, better tolerability, fewer drug interactions, and equal efficacy. Resistance to azithromycin is almost always associated with com plete cross-resistance to

clarithromycin. Azithromycin is well absorbed orally, with good tissue penetration and a prolonged half-life (~48 h). The usual dosage for treatment of MAC infection is 250 mg daily or 500 mg three times per week. Azithromycin is used in combination with other agents to avoid the development of resistance. For prophylaxis against dis seminated MAC infection in immunocompromised individuals, a dose of 1200 mg once per week is given. Because azithromycin is not metabolized by cytochrome P450, it interacts with few drugs. Adjustment of the dos age on the basis of renal function is not necessary.

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