205e Antimycobacterial Agents

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Agents used for the treatment of mycobacterial infections, including tuberculosis (TB), leprosy, and infections due to nontuberculous mycobacteria (NTM), are administered in multiple-drug regimens for prolonged courses. Currently, more than 160 species of mycobacteria have been identified, the majority of which do not cause disease in humans. While the incidence of disease caused by *Mycobacterium tuberculosis* has been declining in the United States, TB remains a leading cause of morbidity and mortality in developing countries—particularly in sub-Saharan Africa, where the HIV epidemic rages. Effective drug regimens are not all that is needed; without a well-organized infrastructure for diagnosis and treatment of TB, therapeutic and control efforts are severely hampered (Chaps. 2 and 13e). Infections with NTM have gained in clinical prominence in the United States and other developed countries. These largely environmental organisms often establish infection in immunocompromised patients or in persons with structural lung disease.

TUBERCULOSIS

GENERAL PRINCIPLES

The earliest recorded human case of TB dates back 9000 years. Early treatment modalities, such as bloodletting, were replaced by sanatorium regimens in the late nineteenth century. The discovery of streptomycin 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 with the regimen 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 (optimally given daily or twice weekly for 9 months), rifampin (daily for 4 months), or isoniazid plus rifapentine (weekly for 3 months) (Table 205e-1).

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. Multiple-drug regimens are used for the treatment of TB disease (Table 205e-2). Initially, an intensive phase consisting of four drugs—isoniazid, rifampin, pyrazinamide, and ethambutol—given for 2 months is followed by a continuation phase of isoniazid and rifampin for 4 months, for a total treatment duration of 6 months. The continuation phase is extended to 7 months (for a total treatment duration of 9 months) if the 2-month course of pyrazinamide is not completed or, for patients with cavitary pulmonary TB, if sputum cultures remain positive beyond 2 months of treatment (delayed culture conversion).

Treatment of TB in individuals co-infected with HIV poses significant challenges, but some progress is being made. Recent data show improved survival when antiretroviral therapy (ART) is initiated early during TB treatment. Interactions of rifampin with protease inhibitors or non-nucleoside reverse transcriptase inhibitors are significant and require close monitoring and dose adjustments. The TB immune reconstitution inflammatory syndrome (IRIS) may appear as early as 1 week after initiation of ART and manifests as paradoxical worsening or unmasking of existing TB infection. Conservative management consists of continued administration of ART and TB medications. However, severe or debilitating IRIS has been anecdotally treated with varying doses of glucocorticoids. Intermittent therapy in patients co-infected with HIV and *M. tuberculosis* has been associated with low plasma levels of several key TB drugs and with higher rates of treatment failure or relapse; therefore, intermittent twice-weekly therapy for TB in HIV-co-infected individuals is not recommended.

Adherence to medications is critical in achieving a cure with antimycobacterial therapy. Consequently, directly observed therapy (DOT) by trained staff, either in the clinic or at home, is recommended to ensure adherence. In addition, monthly dispensing of TB medicines is recommended because monthly clinical monitoring for hepatotoxicity due to these medications is essential for all patients. Discontinuation of suspected offending agents at the onset of hepatitis symptoms reduces the risk of progression to fatal hepatitis. 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 205e-3). The presence of such symptoms and signs mandates provisional discontinuation of potentially hepatotoxic agents. Biochemical testing of at least serum alanine aminotransferase and total bilirubin levels and exclusion of other causes of these abnormalities are also indicated during treatment for those at risk for hepatotoxicity (Table 205e-3). 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 available 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 nonadherence, 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 suspected, 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 TB (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 generally include a late-generation fluoroquinolone and an injectable second-line agent (such as capreomycin, amikacin, or kanamycin). Regimens of at least five drugs are recommended for the treatment of MDR-TB. Both standardized and optimized/customized regimens are in use around the world. Extensively drug-resistant TB (XDR-TB) is defined as MDR-TB with additional resistance to any fluoroquinolone and at least one of the second-line injectable agents. Treatment of XDR-TB is individualized

TABLE 205e-1 REGIMENS FOR THE TREATMENT OF LATENT TUBERCULOSIS INFECTION IN ADULTS

Regimen	Schedule	Duration	Comments
Isoniazid	300 mg/d (5 mg/kg) Alternative: 900 mg twice weekly (15 mg/kg)	9 months (6 months acceptable)	Supplement with pyridoxine (25–50 mg daily). Twice-weekly regimens require directly observed therapy.
Rifampin	600 mg/d (10 mg/kg)	4 months	Broader efficacy studies are needed.
Isoniazid plus rifapentine	900 mg (15 mg/kg) weekly + 900 mg weekly	3 months	Directly observed therapy is recommended for once-weekly treatment. This regimen may be supplemented with pyridoxine (25–50 mg/d).

Sources: D Menzies et al: Ann Intern Med 149:689, 2008; American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Am J Respir Crit Care Med 167:603, 2003; T Sterling et al: N Engl J Med 365:2155, 2011.