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major or sole pathogen infecting a joint, the duration of treatment should be similar to that used for arthritis caused by aerobic bacteria (Chap. 135).

Although not every anaerobe needs to be covered with pathogendirected therapy in most polymicrobial infections, several studies of Bacteroides bacteremia have clearly demonstrated that patients receiving effective therapy have lower mortality rates and more rapid sterilization of blood cultures than patients receiving ineffec tive therapy. FAILURE OF THERAPY Anaerobic infections that fail to respond to treatment or that relapse should be reassessed. Potential causes include an uncontrolled source of infection (e.g., ongoing intestinal leak into the perito neum), superinfection with a new organism, and/or antibiotic fail ure. Additional imaging may be useful to discern whether surgical drainage or debridement is warranted. Obtaining additional culture specimens will help identify whether an organism resistant to the antibiotics being used is present. Strong consideration should be given to obtaining susceptibility profiles for the isolates. ■ ■FURTHER READING Cooley L, Teng J: Anaerobic resistance: Should we be worried? Curr Opin Infect Dis 32:523, 2019. Debreuil LJ: Fifty years devoted to anaerobes: Historical, lessons, and highlights. Eur J Clin Microbiol Infect Dis 43:1, 2024. Finegold SM: Anaerobes: Problems and controversies in bacteriology, infections, and susceptibility testing. Rev Infect Dis 12:S223, 1990. Reissier S et al: Recent trends in antimicrobial resistance among PART 5 Infectious Diseases anaerobic clinical isolates. Microorganisms 11:1474, 2023. Styrt B, Gorbach SL: Recent developments in the understanding of the pathogenesis and treatment of anaerobic infections (2). N Engl J Med 321:240, 1989. Wexler HM: Bacteroides: The good, the bad, and the nitty-gritty. Clin Microbiol Rev 20:593, 2007. Section 8 Mycobacterial Diseases Mario C. B. Raviglione, Andrea Gori

Tuberculosis Tuberculosis (TB), which is caused by bacteria of the Mycobacterium tuberculosis complex, is one of the oldest diseases known to affect humans. In 2023, after being replaced by COVID-19 during the three previous years, TB probably returned to be the top cause of infectious death from a single infectious agent. Population genomic studies suggest that M. tuberculosis may have emerged ~70,000 years ago in Africa and subsequently disseminated along with anatomi cally modern humans, expanding globally during the Neolithic Age as human density started to increase. This disease most often affects the lungs, although other organs are involved in up to one-third of cases. If properly treated, TB caused by drug-susceptible strains is curable in the vast majority of cases. If untreated, the disease may be fatal in more than 70% of people. Transmission usually takes place through the airborne spread of droplet nuclei produced by patients with infectious pulmonary TB. Through pharmacologic prophylaxis, the development of the disease can be prevented in those who have contracted TB infection.

ETIOLOGIC AGENT Mycobacteria belong to the family Mycobacteriaceae and the order Actinomycetales. Of the pathogenic species belonging to the M. tuber culosis complex, which comprises eight distinct subgroups, the most common and important agent of human disease by far is M. tuberculosis (sensu stricto). A closely related organism isolated from cases in West, Central, and East Africa is M. africanum. The complex includes some zoonotic members, such as M. bovis (the bovine tubercle bacillus— characteristically resistant to pyrazinamide, once an important cause of TB transmitted by unpasteurized milk, and currently responsible for 140,000 human cases worldwide in 2020, half of them in Africa) and M. caprae (related to M. bovis). In addition, other organisms that have been reported rarely as causing TB include M. pinnipedii (a bacillus infecting seals and sea lions in the southern hemisphere and recently isolated from humans), M. mungi (isolated from banded mongooses in southern Africa), M. orygis (described in oryxes and other Bovidae in Africa and Asia and a potential cause of infection in humans), and

M. microti (the “vole” bacillus, a less virulent organism). Finally, M. canetti is a rare isolate from East African cases that produces unusual smooth colonies on solid media and is considered closely related to a supposed progenitor type. There is no known environmen tal reservoir for any of these organisms. M. tuberculosis is a rod-shaped, non-spore-forming, thin aero bic bacterium measuring 0.5 µm by 3 µm. Mycobacteria, including M. tuberculosis, are often neutral on Gram staining. However, once stained, the bacilli cannot be decolorized by acid alcohol; this charac teristic justifies their classification as acid-fast bacilli (AFB; Fig. 183-1). Acid fastness is due mainly to the organisms’ high content of mycolic acids, long-chain cross-linked fatty acids, and other cell-wall lipids. Microorganisms other than mycobacteria that display some acid fast ness include species of Nocardia and Rhodococcus, Legionella micdadei, and the protozoa Isospora and Cryptosporidium. In the mycobacterial cell wall, lipids (e.g., mycolic acids) are linked to underlying ara binogalactan and peptidoglycan. This structure results in very low FIGURE 183-1 Acid-fast bacillus smear showing M. tuberculosis bacilli. (Courtesy of the Centers for Disease Control and Prevention, Atlanta.)

permeability of the cell wall, thus reducing the effectiveness of most antibiotics. The complete genome sequence of M. tuberculosis comprises 4.4 million base pairs, 4043 genes encoding 3993 proteins, and 50 genes encoding stable RNAs; its high guanine-plus-cytosine content (65.6%) is indicative of an aerobic “lifestyle.” A large propor tion of genes are devoted to the production of enzymes involved in cell wall metabolism. Substantial genetic variability exists among the innu merable M. tuberculosis strains from different parts of the world. Based on such genetic variability it is possible to distinguish and compare different strains. Their distinction is important to study transmission dynamics and identify outbreaks. Starting in the 1990s, reproducible genotyping methods were developed to type the bacterium. Initially, they included insertion sequence 6110 (IS6110), restriction fragment length polymorphism (RFLP) typing, and spoligotyping. Lately, most studies utilize mycobacterial interspersed repetitive unit variable num ber tandem repeats (MIRU-VNTRs) and whole genome sequencing analysis. EPIDEMIOLOGY In 2023, 8.2 million new cases of TB (all forms, both pulmonary and extrapulmonary) were reported to the World Health Organization (WHO), around 97% of which were reported from low- and middleincome countries. However, because of insufficient case detection and incomplete notification, reported cases represent only about two-thirds of the total estimated cases. The WHO estimated that 10.8 million (range, 10.1–11.7 million, rate 134 per 100,000 persons) new (incident) cases of TB occurred worldwide in 2023. Eight countries accounted for two thirds of all cases: India (26%), Indonesia (10%), China

(6.8%), the Philippines (6.8%), Pakistan (6.3%), Nigeria (4.6%), Bangladesh (3.5%) and the Democratic Republic of the Congo (3.1%). Of all cases, 55% occurred in male patients, 33% in female patients, and 12% in children. It is further estimated that 1.25 million (range 1.13–1.37 million) deaths from TB, including 160,000 among persons with HIV co-infection, occurred in 2023; 98% of these deaths were in low- and middle-income countries. Estimates of TB incidence and mortality FIGURE 183-2 Estimated tuberculosis (TB) incidence rates (per 100,000 population) in 2022. The designations used and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization (WHO) concerning the legal status of any country, territory, city, or area or of its authorities or concerning the delimitation of its frontiers or boundaries. Dotted, dashed, and white lines represent approximate border lines for which there may not yet be full agreement. (Reproduced with permission from Global Tuberculosis Report 2023. Geneva, World Health Organization; 2023.)

rates (per 100,000 population) in 2022 are depicted in Figs. 183-2 and 183-3, respectively).

During the past few years, numbers of reported cases have stabilized or are slowly declining in most high-income countries. In the United States, TB cases and incidence rates steadily decreased from 1992 to 2021. In 2022, 8300 cases of TB (2.5 cases per 100,000 population) were reported to the U.S. Centers for Disease Control and Prevention (CDC), a slight increase from the 7882 cases reported in 2021. In the United States, TB is uncommon among young white adults of European descent, who have only rarely been exposed to M. tuberculosis infection during recent decades. In contrast, because of a high risk of transmission in the past, the prevalence of M. tuberculosis infection is relatively high among elderly whites; overall, 13 million persons are estimated to be “latently” infected. In general, adults ≥65 years of age have the highest incidence rate per capita and children <14 years of age the lowest. Of the total 7882 cases in 2021, 28% were among U.S.-born persons and 71% among non-U.S.-born persons. Non-Hispanic Black or African American persons accounted for the highest proportion of cases (34%), followed by non-Hispanic White persons (29%), and Hispanic/Latinos (24%). Among non-U.S.-born persons in the United States in 2021, 48% occurred in persons born in Asia, 33% among Hispanic/Latino persons, and 12% among African American persons. Overall, the high est rates per capita were among non-U.S.-born persons of more than one ethnicity (30 cases per 100,000 population). In 2020 in the United States 600 deaths were caused by TB, the highest number since 2006. In 2021 in Canada, TB cases and rates per 100,000 population were 1829 and 4.8, respectively. Of these cases, 76% occurred in foreignborn persons. However, the highest rates per 100,000 population were among Inuit (135) and First Nation persons (16). Similarly, in Europe, TB has reemerged as an important public health problem, mainly as a result of cases among immigrants from high-incidence countries and among marginalized populations, often in large urban settings. In most Western European countries, there are more cases annually among foreign-born than native populations. CHAPTER 183 Tuberculosis In 2023 TB incidence was decreasing in Africa, resuming a slow decline in the European, Eastern Mediterranean, and Southeast Asia Incidence per 100,000 population per year 0–9.9 10–99 100–199 200–299 300–499 ≥500 No data Not applicable

FIGURE 183-3 Estimated tuberculosis (TB) mortality rates in HIV-negative persons in 2022. (See disclaimer in Fig. 183-2. Reproduced with permission from Global Tuberculosis Report 2023. Geneva, World Health Organization; 2023.) PART 5 Infectious Diseases regions following the COVID-19 pandemic, and still increasing in the Americas and the Western Pacific. Globally, TB incidence

has increased by nearly 5% since 2020 as a result of essential service disrup tions during the worst period of the pandemic. Of the estimated 10.8 million new cases of TB in 2023, 6.1% were in people living with HIV, with the majority of them occurring in Africa. Furthermore, an estimated 400,000 (range, 360,000-440,000) cases of rifampin-resistant (also called rifampicin-resistant) TB (RR-TB) and multidrug-resistant TB (MDR-TB)—a form of the disease caused by bacilli resistant at least to isoniazid and rifampin—occurred in 2023, representing 3.2% and 16%, respectively, of all new and previously treated cases. Only 189,000 MDR/RR-TB cases were enrolled on treatment in 2023 because of a lack of culture and drug susceptibility testing (DST) capacity in many settings worldwide. The countries of the former Soviet Union remain those with the highest proportions of MDR/RR disease among new TB cases, reaching up to one-third of the total. Overall, more than 50% of all MDR/RR-TB cases occur in India (27%), the Russian Federation (7.4%), Indonesia (7.4%), China (7.3%) and the Philippines (7.2%). Cases of extensively drug-resistant TB (XDR-TB), in which MDR-TB is compounded by additional resis tance to any fluoroquinolones and at least one additional group A drug (e.g., bedaquiline and linezolid), and cases of pre-XDR-TB, a form in which MDR/RR-TB strains are also resistant to any fluoroquinolone, occur worldwide. However, the vast majority of XDR-TB cases remain undiagnosed because reliable methods for DST are still lacking and laboratory capacity in low-income countries is limited. ■ ■FROM EXPOSURE TO INFECTION M. tuberculosis is most commonly transmitted from a person with infectious pulmonary TB by droplet nuclei containing M. tuberculosis bacteria, which are aerosolized by coughing, sneezing, or speaking. The tiny droplets dry rapidly; the smallest (<5–10 μm in diameter) may remain suspended in the air for several hours and may reach the terminal air passages when inhaled. Other routes of transmission of tubercle bacilli (e.g., through the skin or the placenta) are uncommon and of no epidemiologic significance. The risk of transmission and of subsequent acquisition of M. tuberculosis infection is determined mainly by exogenous factors, although endogenous factors also may

Mortality per 100,000 population per year 0–0.9 1–4.9 5–19 20–39 ≥40 No data Not applicable play a role. The probability of contact with a person who has an infec tious form of TB, the intimacy and duration of that contact, the degree of infectiousness of the case, and the shared environment in which the contact takes place are all important determinants of the likelihood of transmission. The most infectious patients whose sputum contains AFB visible by microscopy have cavitary pulmonary disease or, much less commonly, laryngeal TB and produce sputum containing as many as 105–107 AFB/mL. Patients with sputum smear–negative/culture-pos itive TB are less infectious, although they have been responsible for up to 20% of transmission in some studies in the United States. Those with culture-negative pulmonary TB and extrapulmonary TB are essentially noninfectious. Because persons with both HIV infection and TB are less likely to have cavitations, they may be less infectious than those without HIV co-infection. Crowding in poorly ventilated rooms is one of the most important factors in the transmission of tubercle bacilli because it increases the intensity of contact with a case. The virulence of the transmitted organism is also an important factor in establishing infection. Endogenous factors such as the degree of immune compe tence also are important. In particular, HIV-infected patients, persons undergoing cancer treatment, or those administered immunosuppres sive drugs may be at higher risk of TB infection acquisition. Attempts to estimate the basic reproductive number R0 for TB have resulted in a wide range of values depending on environmental conditions and social behaviors of populations: from 0.24 in the Netherlands during the period 1933−2007 to 4.3 in China in 2012, reflecting the status of disease control. ■ ■FROM INFECTION TO DISEASE Unlike the risk of acquiring infection with M.

tuberculosis, the risk of developing disease after being infected depends largely on endogenous factors, such as the individual’s innate immunologic and nonimmu nologic defenses and the level at which the individual’s cell-mediated immunity is functioning. Clinical illness directly following infection is classified as primary TB and is common among children in the first few years of life and among immunocompromised persons. Although primary TB may be severe and disseminated, it generally is not asso ciated with high-level transmissibility. When infection is acquired later in life, the chance is greater that the mature immune system will

TABLE 183-1 Risk Factors for Active Tuberculosis in Persons Who Have Been Infected with Tubercle Bacilli FACTOR RELATIVE RISK/ODDSa Recent infection (<1 year) 12.9 Fibrotic lesions (spontaneously healed) 2–20 Comorbidities and iatrogenic causes HIV infection 21–>30 Silicosis

Chronic renal failure/hemodialysis 10–25 Diabetes 2–4 IV drug use 10–30 Excessive alcohol use

Immunosuppressive treatment

Tumor necrosis factor α inhibitors 4–5 Gastrectomy 2–5 Jejunoileal bypass 30–60 Posttransplantation period (renal, cardiac) 20–70 Tobacco smoking 2–3 Malnutrition and severe underweight

aOld infection = 1. contain it at least temporarily. Bacilli, however, may persist for years before reactivating to produce secondary (or postprimary) TB, which, because of frequent cavitation, is more often infectious than is primary disease. Overall, it is estimated that up to 10% of infected persons will eventually develop active TB in their lifetime—half of them during the first 18 months after infection. The risk is much higher among immu nocompromised individuals and, particularly, HIV-infected persons. Reinfection of a previously infected individual, which is common in areas with high rates of TB transmission, may also favor the develop ment of disease. At the height of the TB resurgence in the United States in the early 1990s, molecular typing and comparison of strains of

M. tuberculosis suggested that up to one-third of cases of active TB in some inner-city communities were due to recent transmission rather than to reactivation of old infection. Age is an important determinant of the risk of disease after infection. Among infected persons, the incidence of TB is highest during late adolescence and early adulthood; the reasons are unclear. The incidence among women peaks at 25–34 years of age. In this age group, rates among women may be higher than those among men, whereas at older ages the opposite is true. The risk increases in the elderly, possibly because of waning immunity and comorbidity. A variety of diseases and conditions favor the development of active TB (Table 183-1). In absolute terms, the most potent risk factor for TB among infected individuals is HIV co-infection, which suppresses cellular immunity. The risk that infection will proceed to active disease is directly related to the patient’s degree of immunosuppression. In a study of people living with HIV (PLWH), those who were tuberculin skin test (TST)–positive had risks varying from 2.6 to 13.3 cases per 100 person-years, which increased as the CD4+ T cell count decreased. ■ ■NATURAL HISTORY OF DISEASE Studies conducted in various countries before the advent of antimi crobial TB therapy showed that untreated TB is often fatal. About one-third of patients died within 1 year after diagnosis. Historic data also show that 55% of sputum smear-positive cases were dead within 5 years and up to 86% (weighted mean, 70%) within 10 years. A lower case fatality rate, around 20%, was estimated for untreated

paucibacil lary smear-negative cases at 5 years. Of the survivors at 5 years, ~60% had undergone spontaneous remission, while the remainder were still excreting tubercle bacilli. With effective, timely, and proper antimi crobial TB treatment, patients have a very high chance of being cured. However, improper use of anti-TB drugs, while reducing mortality rates, may also result in large numbers of chronic infectious cases, often with drug-resistant bacilli.

PATHOGENESIS AND IMMUNITY

■ ■INFECTION AND MACROPHAGE INVASION

The interaction of M. tuberculosis with the human host begins when droplet nuclei containing viable microorganisms, propelled into the air by infectious patients, are inhaled by a close bystander. Although the majority of inhaled bacilli are trapped in the upper airways and expelled by ciliated mucosal cells, a fraction (usually <10%) reach the alveoli, a unique immunoregulatory environment. There, in the very early phases of infection, the predominant cells infected by M. tuber culosis are myeloid dendritic cells. Subsequently, alveolar macrophages that have not yet been activated (prototypic alternatively activated macrophages) phagocytose the bacilli. Adhesion of mycobacteria to macrophages results largely from binding of the bacterial cell wall to a variety of macrophage cell-surface receptor molecules, including complement receptors, the mannose receptor, the immunoglobulin G Fcγ receptor, and type A scavenger receptors. Surfactants may also play a role in the early phase of interaction between the host and the pathogen, and surfactant protein D can prevent phagocytosis. Phago cytosis is enhanced by complement activation, leading to opsonization of bacilli with C3 activation products such as C3b and C3bi. Con comitantly, binding of certain receptors, such as the mannose receptor, regulates postphagocytic events like phagosome–lysosome fusion and inflammatory cytokine production. After a phagosome forms, the sur vival of M. tuberculosis in the cell seems to depend in part on reduced acidification due to lack of assembly of a complete vesicular protonadenosine triphosphatase. A complex series of events is generated by the bacterial cell-wall lipoglycan lipoarabinomannan, which inhibits the intracellular increase of Ca^{2+}. Thus, the Ca^{2+}/calmodulin pathway (leading to phagosome–lysosome fusion) is impaired, and the bacilli survive within the phagosomes by blocking fusion. The M. tuberculosis phagosome inhibits the production of phosphatidylinositol 3-phosphate, which normally earmarks phagosomes for membrane sorting and mat uration (including phagolysosome formation), which would destroy the bacteria. Bacterial factors block the host defense of autophagy, in which the cell sequesters the phagosome in a double-membrane vesicle (autophagosome) that is destined to fuse with lysosomes. If the bacilli are successful in arresting phagosome maturation, then bacterial rep lication begins and the macrophage eventually ruptures and releases its bacillary contents. This process is mediated by the ESX-1 secretion system that is encoded by genes contained in the region of difference 1 (RD1). Other uninfected phagocytic cells are then recruited to con tinue the infection cycle by ingesting dying macrophages and their bacillary content, thus, in turn, becoming infected themselves and expanding the infection. CHAPTER 183 Tuberculosis ■ ■VIRULENCE OF TUBERCLE BACILLI M. tuberculosis must be viewed as a complex formed by a multi tude of strains that differ in virulence and are capable of produc ing a variety of manifestations of disease. Since the elucidation of the M. tuberculosis genome in 1998, large mutant collections have been generated, and many bacterial genes that contribute to M. tuberculosis virulence have been found. Moreover, different patterns of virulence defects have been defined in various animal models—predominantly mice but also guinea pigs, rabbits, and nonhuman primates. The katG gene encodes for a catalase/peroxidase enzyme that protects against oxidative stress and is required for

isoniazid activation and subsequent bactericidal activity. RD1 is a 9.5-kb locus that encodes two key small protein antigens—the 6-kDa early secretory antigen (ESAT-6) and culture filtrate protein 10 (CFP-10)—as well as a putative secretion apparatus that may facilitate their egress; the absence of this locus in the vaccine strain M. bovis bacille Calmette-Guérin (BCG) is a key attenuating mutation. Mutants lacking key enzymes of bacterial bio synthesis become auxotrophic for the missing substrate and often are totally unable to proliferate in animals; these include the leuCD and panCD mutants, which require leucine and pantothenic acid, respec tively. The isocitrate lyase gene (icl1) encodes a key step in the glyoxyl ate shunt that facilitates bacterial growth on fatty acid substrates; this gene is required for long-term persistence of M. tuberculosis infection

in mice with chronic TB. M. tuberculosis mutants in regulatory genes such as sigma factor C and sigma factor H (sigC and sigH) are associ ated with normal bacterial growth in mice, but they fail to elicit full tissue pathology. Finally, the mycobacterial protein CarD (expressed by the carD gene) seems essential for the control of rRNA transcription that is required for mycobacterial replication and persistence in the host cell. Its loss exposes mycobacteria to oxidative stress, starvation, DNA damage, and ultimately sensitivity to killing by a variety of host mutagens and defense mechanisms.

■ ■INNATE RESISTANCE TO INFECTION Several observations suggest that genetic factors play a key role in innate resistance to infection with M. tuberculosis and the devel opment of disease. The existence of this resistance, which is poly genic in nature, is suggested by the differing degrees of susceptibility to TB in different populations. This mechanism of elimination of the pathogen may be accompanied by negative results in the TST and interferon γ (IFN-γ) release assays (IGRAs). In mice, a gene called Nramp1 (natural resistance–associated macrophage protein 1) plays a regulatory role in resistance/susceptibility to mycobacteria. The human homologue NRAMP1, which maps to chromosome 2q, may play a role in determining susceptibility to TB, as is suggested by a study among West Africans. Studies of mice identified a novel host resistance gene, ipr1, that is encoded within the sst1 locus; ipr1 encodes an IFN-induc ible nuclear protein that interacts with other nuclear proteins in mac rophages primed with IFNs or infected by M. tuberculosis. In addition, polymorphisms in multiple genes, such as those encoding for various major histocompatibility complex alleles, IFN-γ, T cell growth factor β, interleukin (IL) 10, mannose-binding protein, IFN-γ receptor, Toll-like receptor 2, vitamin D receptor, and IL-1, have been associated with susceptibility to TB. PART 5 Infectious Diseases ■ ■THE HOST RESPONSE, GRANULOMA FORMATION, AND “LATENCY” In the initial stage of host–bacterium interaction, prior to the onset of an acquired cell-mediated immune (CMI) response, M. tuberculosis disseminates widely through the lymph vessels, spreading to other sites in the lungs and other organs, and undergoes a period of extensive growth within naïve inactivated macrophages; additional naïve macro phages are recruited to the early granuloma. How the bacillus accesses the parenchymal tissue still needs to be elucidated: it may directly infect epithelial cells or transmigrate through infected macrophages across the epithelium. Infected dendritic cells or monocytes then begin to transport bacilli to the lymphatic system. Studies suggest that

M. tuberculosis uses specific virulence mechanisms to subvert host cellular signaling and to elicit an early regulated proinflammatory response that promotes granuloma expansion and bacterial growth during this key early phase. A study of M. marinum infection in zebraf ish has delineated one molecular mechanism by which mycobacteria induce granuloma formation. The mycobacterial

protein ESAT-6 induces secretion of matrix metalloproteinase 9 (MMP9) by nearby epithelial cells that are in contact with infected macrophages. MMP9 in turn stimulates recruitment of naïve macrophages, thus inducing gran uloma maturation and bacterial growth. Disruption of MMP9 function results in reduced bacterial growth. Another study has shown that M. tuberculosis–derived cyclic AMP is secreted from the phagosome into host macrophages, subverting the cell's signal transduction path ways and stimulating an elevation in the secretion of tumor necrosis factor α (TNF-α) as well as further proinflammatory cell recruitment. Ultimately, the chemoattractants and bacterial products released dur ing the repeated rounds of cell lysis and infection of newly arriving macrophages enable dendritic cells to access bacilli; these cells migrate to the draining lymph nodes and present mycobacterial antigens to T lymphocytes. At this point, the development of cell-mediated and humoral immunity begins. These initial stages of infection are usually asymptomatic. About 2–4 weeks after infection, two host responses to M. tuber culosis develop: a macrophage-activating CMI response and a tis sue-damaging response. The macrophage-activating response is a

T cell–mediated phenomenon resulting in the activation of macrophages that are capable of killing and digesting tubercle bacilli. The tissuedamaging response is the result of a delayed-type hypersensitivity reac tion to various bacillary antigens; it destroys inactivated macrophages that contain multiplying bacilli but also causes caseous necrosis of the involved tissues (see below). Although both of these responses can inhibit mycobacterial growth, it is the balance between the two that determines the forms of TB that will develop subsequently. With the development of specific immunity and the accumulation of large numbers of activated macrophages at the site of the primary lesion, granulomatous lesions (tubercles) are formed. These lesions consist of accumulations of lymphocytes and activated macrophages that evolve toward epithelioid and giant cell morphologies. Initially, the tissue-damaging response can limit mycobacterial growth within mac rophages. As stated above, this response, mediated by various bacterial products, not only destroys macrophages but also produces early solid necrosis in the center of the tubercle. Although M. tuberculosis can survive, its growth is inhibited within this necrotic environment by low oxygen tension and low pH. At this point, some lesions may heal by fibrosis, with subsequent calcification, whereas inflammation and necrosis occur in other lesions. Some observations have challenged the traditional view that any encounter between mycobacteria and macrophages results in chronic infection. It is possible that an immune response capable of eradicating early infection may sometimes develop as a consequence, for instance, of disabling mutations in mycobacterial genomes rendering their replication ineffective. Individual granulomas that are formed during this phase of infection can vary in size and cell composition; some can contain the spread of mycobacteria, while others cannot. TB infection ensues as a result of this dynamic balance between the microorganism and the host. For many years, TB infection has been called "latent TB infection (LTBI)." This terminology was used to define a state of persistent immune response to stimulation by M. tuberculosis antigens with no evidence of clinically manifest, active TB. The qualification "latent" may offer some convenience of distin guishing infection from disease, albeit an inaccurate description of a process that encompasses bacterial generations that are not dormant. Latency may be an inaccurate term because bacilli may remain active during this "latent" stage, forming biofilms in necrotic areas within which they temporarily hide. Therefore, some have proposed the term persister as a more accurate descriptor of the behavior of the bacilli in this phase. It is important to recognize that infection and disease do not represent a binary state but rather a continuum along which infection will eventually move in the direction of full containment

or disease. The ability to predict, through systemic biomarkers, which infected individuals will progress toward disease would be of immense value in devising prophylactic interventions at scale. ■ ■MACROPHAGE-ACTIVATING RESPONSE Cell-mediated immunity is critical at this early stage. In the majority of infected individuals, local macrophages are activated when bacillary antigens processed by macrophages stimulate T lymphocytes to release a variety of lymphokines. These activated macrophages aggregate around the lesion's center and effectively neutralize tubercle bacilli without causing further tissue destruction. In the central part of the lesion, the necrotic material resembles soft cheese (caseous necrosis)— a phenomenon that may also be observed in other conditions, such as neoplasms. Even when healing takes place, viable bacilli may remain within macrophages or in the necrotic material for many years. These "healed" lesions in the lung parenchyma and hilar lymph nodes may later undergo calcification. ■ ■DELAYED-TYPE HYPERSENSITIVITY In a minority of cases, the macrophage-activating response is weak, and mycobacterial growth can be inhibited only by intensified delayed hypersensitivity reactions, which lead to lung tissue destruction. The lesion tends to enlarge further, and the surrounding tissue is progres sively damaged. At the center of the lesion, the caseous material lique fies. Bronchial walls and blood vessels are invaded and destroyed, and cavities are formed. The liquefied caseous material, containing large

amounts of bacilli, is drained through bronchi. Within the cavity, tubercle bacilli multiply, spill into the airways, and are discharged into the environment through expiratory maneuvers such as coughing and talking. In the early stages of infection, bacilli are usually transported by macrophages to regional lymph nodes, from which they gain access to the central venous return; from there they reseed the lungs and may also disseminate beyond the pulmonary vasculature throughout the body via the systemic circulation. In young children with poor natural immunity, hematogenous dissemination may result in fatal miliary TB or tuberculous meningitis. ■ ■ROLE OF MACROPHAGES AND MONOCYTES While cell-mediated immunity confers partial protection against M. tuberculosis, humoral immunity plays a less well-defined role in protection (although evidence is accumulating on the existence of antibodies to lipoarabinomannan, which may prevent dissemination of infection in children). In cell-mediated immunity, two types of cells are essential: macrophages, which directly phagocytose tubercle bacilli, and T cells (mainly CD4+ T lymphocytes, although the role of CD8+ T cells has recently been the subject of much research), which induce protection through the production of cytokines, especially IFN-γ. After infection with M. tuberculosis, alveolar macrophages secrete various cytokines responsible for several events (e.g., the formation of granulo mas) as well as systemic effects (e.g., fever and weight loss). However, alternatively activated alveolar macrophages may be particularly sus ceptible to M. tuberculosis growth early on, given their more limited proinflammatory and bactericidal activity, which is related in part to being bathed in surfactant. New monocytes and macrophages attracted to the site are key components of the immune response. Their primary mechanism is probably related to production of oxidants (such as reac tive oxygen intermediates or nitric oxide) that have antimycobacterial activity and increase the synthesis of cytokines such as TNF-α and IL-1, which in turn regulate the release of reactive oxygen intermediates and reactive nitrogen intermediates. In addition, macrophages can undergo apoptosis—a defensive mechanism to prevent the release of cytokines and bacilli via their sequestration in the apoptotic cell. Recent work also describes the involvement of neutrophils in the host response, although the timing of their appearance and their effectiveness remain uncertain. ■ ■ROLE OF T LYMPHOCYTES Alveolar macrophages, monocytes, and dendritic cells are also critical in processing and presenting antigens to T lymphocytes,

primarily CD4+ and CD8+ T cells; the result is the activation and proliferation of CD4+ T lymphocytes, which are crucial to the host's defense against M. tuberculosis. Qualitative and quantitative defects of CD4+ T cells explain the inability of HIV-infected individuals to contain mycobacte rial proliferation. Activated CD4+ T lymphocytes can differentiate into cytokine-producing TH1 or TH2 cells. TH1 cells produce IFN-γ—an activator of macrophages and monocytes—and IL-2. TH2 cells produce IL-4, IL-5, IL-10, and IL-13 and may also promote humoral immunity. The interplay of these various cytokines and their cross-regulation determine the host's response. The role of cytokines in promoting intracellular killing of mycobacteria, however, has not been entirely elucidated. IFN-γ may induce the generation of reactive oxygen and nitrogen intermediates and regulate genes involved in bactericidal effects. TNF-α also is important. Although its precise mechanisms are complex and not yet fully clarified, there is a suggested model that foresees an ideal setting for TNF-α between excessive activation—with consequent worsening of immunopathologic reactions—and insuf ficient activation—with resulting lack of containment—in the control of TB infection. Observations made originally in transgenic knockout mice and more recently in humans suggest that other T cell subsets, especially CD8+ T cells, may play an important role. CD8+ T cells have been associated with protective activities via cytotoxic responses and lysis of infected cells as well as with production of IFN-γ and TNF-α. Finally, natural killer cells act as co-regulators of CD8+ T-cell lytic activities, and γδ T cells are increasingly thought to be involved in protective responses in humans.

■ ■MYCOBACTERIAL LIPIDS AND PROTEINS Lipids are involved in mycobacterial recognition by the innate immune system, and lipoproteins (such as 19-kDa lipoprotein) trigger potent signals through Toll-like receptors present in blood dendritic cells. M. tuberculosis possesses various protein antigens. Some are present in the cytoplasm and cell wall; others are secreted. That the latter are more important in eliciting a T lymphocyte response is suggested by experiments documenting the appearance of protective immunity in animals after immunization with live, protein-secreting mycobacteria. Among the antigens that may play a protective role are some proteins of the antigen 85 complex are the 30-kDa major secretory protein (85B) and ESAT-6 antigens. Protective immunity is probably the result of reactivity to many different mycobacterial antigens. These antigens are being incorporated into newly designed vaccines on various platforms.

■ ■SKIN-TEST REACTIVITY Coincident with the appearance of immunity, delayed-type hypersensi tivity to M. tuberculosis develops. This reactivity is the basis of the TST, which is used primarily for the diagnosis of M. tuberculosis infection in persons without symptoms. The cellular mechanisms responsible for TST reactivity are related mainly to previously sensitized CD4+ T lymphocytes, which are attracted to the skin-test site. There, they proliferate and produce cytokines. Although delayed hypersensitivity is associated with protective immunity (TST-positive persons are less susceptible to a new M. tuberculosis infection than are TST-negative persons), it by no means guarantees protection against reactivation. In fact, cases of active TB are often accompanied by strongly positive skintest reactions. There is also evidence of reinfection with new strains of M. tuberculosis in patients previously treated for active disease. This evidence underscores the fact that previous infection or active TB does not necessarily confer fully protective immunity. CHAPTER 183 CLINICAL MANIFESTATIONS TB is classified as pulmonary, extrapulmonary, or both. Depending on several factors linked to host immunologic status and bacterial strains, extrapulmonary TB may occur in 10–40% of patients. Furthermore, up to two-thirds of HIV-infected patients with TB may have both pulmo nary and extrapulmonary TB or extrapulmonary TB alone. Tuberculosis ■

■PULMONARY TB Pulmonary TB is traditionally categorized as primary or postprimary (adult-type, secondary). This distinction has been challenged by molecular evidence from TB-endemic areas indicating that a large percentage of cases of adult pulmonary TB result from recent infection (either primary infection or reinfection) and not from reactivation. Primary Disease Primary pulmonary TB occurs soon after the initial infection. It may be asymptomatic or may present with fever and occasionally pleuritic chest pain. In areas of high TB transmission, this form of disease is often seen in children. Because most inspired air is distributed to the middle and lower lung zones, these areas are most commonly involved in primary TB. The lesion forming after initial infection (Ghon focus) is usually peripheral and accompanied by transient hilar or paratracheal lymphadenopathy, which may or may not be visible on standard chest radiography (CXR) (Fig. 183-4). Some patients develop erythema nodosum on the legs (see Fig. A1-39) or phlyctenular conjunctivitis. In the majority of cases, the lesion heals spontaneously and becomes evident only as a small calcified nodule. Pleural reaction overlying a subpleural focus also is common. The Ghon focus, with or without overlying pleural reaction, thickening, and regional lymphadenopathy, is referred to as the Ghon complex. In young children with immature cell-mediated immunity and in persons with impaired immunity (e.g., those with malnutrition or HIV infection), primary pulmonary TB may progress rapidly to clinical illness. The initial lesion increases in size and can evolve in different ways. Pleural effusion, which is found in up to two-thirds of cases, results from the penetration of bacilli into the pleural space from an adjacent subpleural focus. In severe cases, the primary site rapidly enlarges, its central portion undergoes necrosis, and cavitation develops (progressive primary TB). TB in young children is almost

FIGURE 183-4 Chest radiograph showing right hilar lymph node enlargement with infiltration into the surrounding lung tissue in a child with primary tuberculosis. (Courtesy of Prof. Robert Gie, Department of Paediatrics and Child Health, Stellenbosch University, South Africa; with permission.) invariably accompanied by hilar or paratracheal lymphadenopathy due to the spread of bacilli from the lung parenchyma through lymphatic vessels. Enlarged lymph nodes may compress bronchi, causing total obstruction with distal collapse, partial obstruction with large-airway wheezing, or a ball-valve effect with segmental/lobar hyperinflation. Lymph nodes may also rupture into the airway with development of pneumonia, often including areas of necrosis and cavitation, distal to the obstruction. Bronchiectasis (Chap. 301) may develop in any segment/lobe damaged by progressive caseating pneumonia. Occult hematogenous dissemination commonly follows primary infection. However, in the absence of a sufficient acquired immune response, which usually contains the infection, disseminated or miliary disease may result (Fig. 183-5). Small granulomatous lesions develop in multiple organs and may cause locally progressive disease or result in tuberculous meningitis; this is a particular concern in very young children and immunocompromised persons (e.g., PLWH). PART 5 Infectious Diseases FIGURE 183-5 Chest radiograph showing bilateral miliary (millet-sized) infiltrates in a child. (Courtesy of Prof. Robert Gie, Department of Paediatrics and Child Health, Stellenbosch University, South Africa; with permission.)

FIGURE 183-6 Chest radiograph showing a right-upper-lobe infiltrate and a cavity with an air-fluid level in a patient with active tuberculosis. (Courtesy of Dr. Andrea Gori, Infectious Diseases Unit, Fondazione IRCCS Ca’ Granda Ospediale Maggiore Policlinico, University of Milan, Milan, Italy; with permission.) Postprimary (Adult-Type) Disease Also referred to as reacti vation or secondary TB, postprimary TB is probably most accurately termed adult-type TB because it may result from

endogenous reac tivation of distant or recent infection (primary infection or reinfec tion). It is usually localized to the apical and posterior segments of the upper lobes, where the substantially higher mean oxygen tension (compared with that in the lower zones) favors mycobacterial growth. The superior segments of the lower lobes also are frequently involved. The extent of lung parenchymal involvement varies greatly, from small infiltrates to extensive cavitary disease. With cavity formation, lique fied necrotic contents are ultimately discharged into the airways and may undergo bronchogenic spread, resulting in satellite lesions within the lungs that may in turn undergo cavitation (Figs. 183-6 and 183-7). Massive involvement of pulmonary segments or lobes, with coales cence of lesions, produces caseating pneumonia. While up to one-third of untreated patients reportedly succumb to severe pulmonary TB FIGURE 183-7 CT scan showing a large cavity in the right lung of a patient with active tuberculosis. (Courtesy of Dr. Elisa Busi Rizzi, National Institute for Infectious Diseases, Spallanzani Hospital, Rome, Italy; with permission.)

within a few months after onset (the classic “galloping consumption” of the past), others may undergo a process of spontaneous remission or proceed along a chronic, progressively debilitating course (“consump tion” or phthisis). Under these circumstances, some pulmonary lesions become fibrotic and may later calcify, but cavities persist in other parts of the lungs. Individuals with such chronic disease continue to discharge tubercle bacilli into the environment. Most patients respond to treatment, with defervescence, decreasing cough, weight gain, and a general improvement in well-being within several weeks. Early in the course of disease, symptoms and signs are often non specific and insidious, consisting mainly of fever, often diurnal, and night sweats due to defervescence, weight loss, anorexia, general mal aise, and weakness. However, in up to 90% of cases, cough eventually develops—often initially nonproductive and limited to the morning and subsequently accompanied by the production of purulent sputum, sometimes with blood streaking. Hemoptysis develops in 20–30% of cases, and massive hemoptysis may ensue as a consequence of the erosion of a blood vessel in the wall of a cavity. Hemoptysis, however, may also result from rupture of a dilated vessel in a cavity (Rasmussen’s aneurysm) or from aspergilloma formation in an old cavity. Pleuritic chest pain sometimes develops in patients with subpleural parenchy mal lesions or pleural disease. Extensive disease may produce dyspnea and, in rare instances, adult respiratory distress syndrome. Physical findings are of limited use in pulmonary TB. Many patients have no abnormalities detectable by chest examination, whereas others have detectable rales in the involved areas during inspiration, especially after coughing. Occasionally, rhonchi due to partial bronchial obstruction and classic amphoric breath sounds in areas with large cavities may be heard. Systemic features include fever (often low-grade and intermit tent) in up to 80% of cases and wasting. Absence of fever, however, does not exclude TB. In some recurrent cases and among patients with low Karnofsky score, finger clubbing has been reported. The most common hematologic findings are mild anemia, leukocytosis, and thrombocytosis with a slightly elevated erythrocyte sedimentation rate and/or C-reactive protein level. None of these findings is consistent or sufficiently accurate for diagnostic purposes. Hyponatremia due to the syndrome of inappropriate secretion of antidiuretic hormone also has been reported. ■ ■EXTRAPULMONARY TB In descending order of frequency, the extrapulmonary sites most involved in TB are the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, peritoneum, and pericardium. However, virtu ally any organ system may be affected. As a result of hematogenous dissemination in PLWH, extrapulmonary TB is seen more commonly today than in the past in settings of high HIV prevalence. Lymph Node TB (Tuberculous Lymphadenitis) The most common presentation of extrapulmonary TB in both HIV-seronegative individuals and PLWH (35% of cases worldwide and

>40% of cases in the United States in recent series), lymph node disease is particularly frequent among PLWH and among children (Fig. 183-8). In the United States, besides children, women (particularly non-Caucasians) seem to be especially susceptible. Once caused mainly by M. bovis, tuberculous lymphadenitis today is due largely to M. tuberculosis. Lymph node TB presents as painless swelling of the lymph nodes, most commonly at posterior cervical and supraclavicular sites (a condition historically referred to as scrofula). Lymph nodes are usually discrete in early dis ease but develop into a matted nontender mass over time; a fistulous tract draining caseous material may result. Associated pulmonary disease is present in fewer than 50% of cases, and systemic symptoms are uncommon except in HIV-infected patients. The diagnosis is established by fine-needle aspiration biopsy (with a yield of up to 80%) or surgical excision biopsy. Bacteriologic confirmation is achieved in most cases, granulomatous lesions with or without visible AFBs are typically seen, and cultures are positive in 70–80% of cases. Among PLWH, granulomas are less well organized and are frequently absent entirely, but bacterial loads are heavier than in HIV-seronegative patients, with higher yields from microscopy and culture. Differential

FIGURE 183-8 Tuberculous lymphadenitis affecting the cervical lymph nodes in a 2-year-old child from Malawi. (Courtesy of Prof. S. Graham, Centre for International Child Health, University of Melbourne, Australia; with permission.) diagnosis includes a variety of infectious conditions, neoplastic dis eases such as lymphomas or metastatic carcinomas, and rare disorders like Kikuchi disease (necrotizing histiocytic lymphadenitis), Kimura disease, and Castleman disease. CHAPTER 183 Pleural TB Involvement of the pleura accounts for ~20% of extra pulmonary cases in the United States and elsewhere. Isolated pleural effusion usually reflects recent primary infection, and the collection of fluid in the pleural space represents a hypersensitivity response to mycobacterial antigens. Pleural disease may also result from con tiguous parenchymal spread, as in many cases pleurisy accompanies postprimary disease. Depending on the extent of reactivity, the effusion may be small, remain unnoticed, and resolve spontaneously or may be sufficiently large to cause symptoms such as fever, pleuritic chest pain, and dyspnea. Physical findings are those of pleural effusion: dullness to percussion and absence of breath sounds. CXR reveals the effusion and, in up to one-third of cases, also shows a parenchymal lesion. Thoracentesis is required to ascertain the nature of the effusion and to differentiate it from manifestations of other etiologies. The fluid is straw-colored and at times hemorrhagic; it is an exudate with a protein concentration >50% of that in serum (usually ~4–6 g/dL), a normal to low glucose concentration, a pH of ~7.3 (occasionally <7.2), and detectable white blood cells (usually 500–6000/μL). Neutrophils may predominate in the early stage, but lymphocyte predominance is typical later. Mesothelial cells are generally rare or absent. AFBs are rarely seen on direct smear, and cultures often may be falsely negative for M. tuber culosis; positive cultures are more common among postprimary cases. An elevated pleural concentration of adenosine deaminase is consistent with TB, while TB may be excluded if the value is very low. Lysozyme also is present in the pleural effusion. Measurement of IFN-γ, either directly or through stimulation of sensitized T cells with mycobacterial antigens, can be diagnostically helpful. Needle biopsy of the pleura is often required for diagnosis and is recommended over pleural fluid analysis; it reveals granulomas and/or yields a positive culture in up to 80% of cases. Pleural biopsy can yield a positive result in ~75% of cases when real-time automated nucleic acid amplification is used (the Xpert MTB/RIF assay [Cepheid; Sunnyvale, CA]; see “Nucleic Acid Ampli fication Technology,” below); testing of pleural fluid with this assay is not recommended because of low sensitivity. This form of pleural TB responds rapidly to chemotherapy and may resolve spontaneously. Concurrent glucocorticoid administration may reduce the duration of fever and/or

chest pain but is not of proven benefit. Tuberculosis Tuberculous empyema is a less common complication of pulmonary TB. It is usually the result of the rupture of a cavity, with spillage of a large number of organisms into the pleural space. This process may create a bronchopleural fistula with evident air in the pleural space.

CXR shows hydropneumothorax with an air-fluid level. The pleural fluid is purulent and thick and contains large numbers of lymphocytes. Acid-fast smears and mycobacterial cultures are often positive. Surgical drainage is usually required as an adjunct to chemotherapy. Tubercu lous empyema may result in severe pleural fibrosis and restrictive lung disease. Removal of the thickened visceral pleura (decortication) is occasionally necessary to improve lung function.

TB of the Upper Airways Nearly always a complication of advanced cavitary pulmonary TB, TB of the upper airways may involve the larynx, pharynx, and epiglottis. Symptoms include hoarseness, dys phonia, and dysphagia in addition to chronic productive cough. Find ings depend on the site of involvement, and ulcerations may be seen on laryngoscopy. Acid-fast smear of the sputum is often positive, but biopsy may be necessary in some cases to establish the diagnosis. Car cinoma of the larynx may have similar features but is usually painless. Genitourinary TB Genitourinary TB, which accounts for ~10– 15% of all extrapulmonary cases in the United States and elsewhere, may involve any portion of the genitourinary tract. Clinical manifesta tions are cryptic and protean. Patients may be asymptomatic and their disease discovered only after destructive lesions of the kidneys have developed. Symptoms are often nonspecific and include those of uri nary tract infection with frequency, dysuria, nocturia and hematuria, and abdominal or flank pain. Without a high index of suspicion, this form of TB may result in delayed diagnosis with irreversible organ damage. Up to 75% of patients have abnormalities on CXR suggesting previous or concomitant pulmonary disease. Urinalysis gives abnormal results in 90% of cases, revealing pyuria and hematuria. The docu mentation of culture-negative pyuria in acidic urine should raise the suspicion of TB. IV pyelography, abdominal CT, or MRI (Fig. 183-9) may show deformities and obstructions; calcifications and ureteral strictures are suggestive findings. Culture of three morning urine specimens yields a definitive diagnosis in nearly 90% of cases. Severe ureteral strictures may lead to hydronephrosis, serious renal damage, and, ultimately, renal failure. Genital TB is diagnosed more commonly in female than in male patients. In female patients, it affects the fallo pian tubes and the endometrium and may cause infertility, pelvic pain, and menstrual abnormalities. Diagnosis requires biopsy or culture of specimens obtained by dilation and curettage. In male patients, genital TB preferentially affects the epididymis, producing a slightly tender mass that may drain externally through a fistulous tract; orchitis and PART 5 Infectious Diseases FIGURE 183-9 MRI of culture-confirmed renal tuberculosis. T2-weighted coronary plane: coronal sections showing several renal lesions in both the cortical and the medullary tissues of the right kidney. (Courtesy of Dr. Alberto Matteelli, Department of Infectious Diseases, University of Brescia, Italy; with permission.)

FIGURE 183-10 CT scan demonstrating destruction of the right pedicle of T10 due to Pott’s disease. The patient, a 70-year-old Asian woman, presented with back pain and weight loss and had biopsy-proven tuberculosis. (Courtesy of Charles L. Daley, MD, University of California, San Francisco; with permission.) prostatitis also may develop. In almost half of cases of genitourinary TB, urinary tract disease is also present. Genitourinary TB responds well to chemotherapy. Skeletal TB In the United States, TB of the bones and joints is responsible for ~10% of extrapulmonary cases. In bone and

joint dis ease, pathogenesis is related to reactivation of hematogenous foci or to spread from adjacent paravertebral lymph nodes. Weight-bearing joints (the spine in 40% of cases, the hips in 13%, and the knees in 10%) are most commonly affected. Spinal TB (Pott's disease or tuberculous spondylitis; Fig. 183-10) often involves two or more adjacent vertebral bodies. Whereas the upper thoracic spine is the most common site of spinal TB in children, the lower thoracic and upper lumbar vertebrae are usually affected in adults. From the anterior superior or inferior angle of the vertebral body, the lesion slowly reaches the adjacent body, later affecting the intervertebral disk. With advanced disease, collapse of vertebral bodies results in kyphosis (gibbus). A paravertebral "cold" abscess also may form. In the upper spine, this abscess may track to and penetrate the chest wall, presenting as a soft tissue mass; in the lower spine, it may reach the inguinal ligaments or present as a psoas abscess. CT or MRI reveals the characteristic lesion and suggests its etiology. The differential diagnosis includes tumors and other infec tions. Pyogenic bacterial osteomyelitis involves the disk very early and produces rapid sclerosis. Aspiration of the abscess or bone biopsy confirms the tuberculous etiology, as cultures are usually positive and histologic findings highly typical. A catastrophic complication of Pott's disease is paraplegia, which is usually due to an abscess or a lesion compressing the spinal cord. Paraparesis due to a large abscess is a medical emergency and requires rapid drainage. TB of the hip joints, usually involving the head of the femur, causes pain; TB of the knee produces pain and swelling. If the disease goes unrecognized, the joints may be destroyed. Diagnosis requires examination of the synovial fluid, which is thick in appearance, with a high protein concentration and a variable cell count. Although synovial fluid culture is positive in a high percentage of cases, synovial biopsy and tissue culture may be neces sary to establish the diagnosis. Skeletal TB responds to chemotherapy, but severe cases may require surgery. Tuberculous Meningitis and Tuberculoma TB of the central nervous system (CNS) accounts for ~5% of extrapulmonary cases in the United States. It is seen most often in young children but also devel ops in adults, especially those infected with HIV. Tuberculous menin gitis results from the hematogenous spread of primary or postprimary pulmonary TB or from the rupture of a subependymal tubercle into the subarachnoid space. In more than half of cases, evidence of old pulmonary lesions or a miliary pattern is found on CXR. The disease

often presents subtly as headache and slight mental changes after a prodrome of weeks of low-grade fever, malaise, anorexia, and irritabil ity. If not recognized, tuberculous meningitis may evolve acutely with severe headache, confusion, lethargy, altered sensorium, and neck rigidity. Typically, the disease evolves over 1–2 weeks, a course longer than that of typical bacterial meningitis. Because meningeal involve ment is pronounced at the base of the brain, paresis of cranial nerves (ocular nerves in particular) is a frequent finding, and the involvement of cerebral arteries may produce focal ischemia. The ultimate evolution is toward coma, with hydrocephalus and intracranial hypertension. Lumbar puncture is the cornerstone of diagnosis. In general, exami nation of cerebrospinal fluid (CSF) reveals a high leukocyte count (up to 1000/μL), usually with a predominance of lymphocytes but some times with a predominance of neutrophils in the early stage; a protein content of 1–8 g/L (100–800 mg/dL); and a low glucose concentration. However, any of these three parameters can be within the normal range. AFBs are infrequently seen on direct smear of CSF sediment, but repeated lumbar punctures increase the yield. Culture of CSF is diag nostic in up to 80% of cases and remains the gold standard. Real-time automated nucleic acid amplification (the Xpert MTB/RIF assay) has a sensitivity of up to 80% and is the preferred initial diagnostic option. Treatment should be initiated immediately upon a positive Xpert MTB/ RIF result. A negative result does not exclude a diagnosis of TB and requires further diagnostic workup.

Imaging studies (CT and MRI) may show hydrocephalus and abnormal enhancement of basal cisterns or ependyma. If unrecognized, tuberculous meningitis is uniformly fatal. This disease responds to chemotherapy; however, neurologic sequelae are documented in 25% of treated cases, in most of which the diagnosis has been delayed. Clinical trials have demonstrated that patients given adjunctive glucocorticoids may experience faster resolu tion of CSF abnormalities and elevated CSF pressure, resulting in lower rates of death or severe disability and relapse. In one study, adjunctive dexamethasone significantly enhanced the chances of survival among persons >14 years but did not reduce the frequency of neurologic sequelae. The dexamethasone schedule was (1) 0.4 mg/kg per day given intravenously with tapering by 0.1 mg/kg per week until the fourth week, when 0.1 mg/kg per day was administered, followed by (2) 4 mg/d given by mouth with tapering by 1 mg per week until the fourth week, when 1 mg/d was administered. The WHO now recommends that adjuvant glucocorticoid therapy with either dexamethasone or pred nisolone, tapered over 6–8 weeks, should be used in CNS TB. However, among PLWH, a recent placebo-controlled study demonstrated no benefit with respect to survival or secondary endpoints from a 6- to 8-week tapering course of adjunctive dexamethasone. Tuberculoma, an uncommon manifestation of TB of the CNS, presents as one or more space-occupying lesions and usually causes seizures and focal signs. CT or MRI reveals contrast-enhanced ring lesions, but biopsy is necessary to establish the diagnosis. Gastrointestinal TB Gastrointestinal TB is uncommon, making up only 3.5% of extrapulmonary cases in the United States. Various pathogenetic mechanisms are involved: swallowing of sputum with direct seeding, hematogenous spread, or (largely in developing areas) ingestion of milk from cows affected by bovine TB. Although any por tion of the gastrointestinal tract may be affected, the terminal ileum and the cecum are the sites most commonly involved. Abdominal pain (at times similar to that associated with appendicitis) and swell ing, obstruction, hematochezia, and a palpable mass in the abdomen are common findings at presentation. Fever, weight loss, anorexia, and night sweats also are common. With intestinal wall involvement, ulcerations and fistulae may simulate Crohn disease; the differential diagnosis of this entity is always difficult. Anal fistulae should prompt an evaluation for rectal TB. Because surgery is required in most cases, the diagnosis can be established by histologic examination and culture of specimens obtained intraoperatively. Tuberculous peritonitis follows either the direct spread of tubercle bacilli from ruptured lymph nodes and intraabdominal organs (e.g., genital TB in women) or hematogenous seeding. Nonspecific abdomi nal pain, fever, and ascites should raise the suspicion of tuberculous

peritonitis. The coexistence of cirrhosis (Chap. 355) in patients with tuberculous peritonitis complicates the diagnosis. In tuberculous peritonitis, paracentesis reveals an exudative fluid with a high protein content and leukocytosis that is usually lymphocytic (although neutro phils occasionally predominate). The yield of direct smear and culture is relatively low; culture of a large volume of ascitic fluid can increase the yield, but peritoneal biopsy (with a specimen best obtained by lapa roscopy) is often needed to establish the diagnosis.

Pericardial TB (Tuberculous Pericarditis) Due either to direct extension from adjacent mediastinal or hilar lymph nodes or to hematogenous spread, pericardial TB has often been a disease of the elderly in countries with low TB prevalence. However, it also develops frequently in PLWH. Case fatality rates are as high as 40% in some series. The onset may be subacute, although an acute presentation, with dyspnea, fever, dull retrosternal pain, and a pericardial friction rub, is possible. An effusion eventually develops in many cases; cardiovascu lar symptoms and signs of cardiac

tamponade may ultimately appear (Chap. 281). In the presence of effusion, TB must be suspected if the patient belongs to a high-risk population (HIV-infected, originating in a high-prevalence country); if there is evidence of previous TB in other organs; or if echocardiography, CT, or MRI shows effusion and thickness across the pericardial space. A definitive diagnosis can be obtained by pericardiocentesis under echocardiographic guidance. The pericardial fluid must be submitted for biochemical, cytologic, and microbiologic evaluation. The effusion is exudative in nature, with a high count of lymphocytes and monocytes. Hemorrhagic effusion is common. Direct smear examination is very rarely positive. Culture of pericardial fluid reveals M. tuberculosis in up to two-thirds of cases, whereas pericardial biopsy has a higher yield. High levels of adenosine deaminase, lysozyme, and IFN-γ may suggest a tuberculous etiology. CHAPTER 183 Without treatment, pericardial TB is usually fatal. Even with treat ment, complications may develop, including chronic constrictive peri carditis with thickening of the pericardium, fibrosis, and sometimes calcification, which may be visible on a chest radiograph. Systematic reviews and meta-analyses show a trend toward benefit from gluco corticoid treatment with regard to death and constrictive pericarditis. However, the largest and most recent study—the IMPI study—failed to show such a benefit. Of the patients enrolled in this trial, 67% were PLWH, and only a fraction was receiving antiretroviral treatment (ART). A supplemental analysis among HIV-negative patients showed a small mortality benefit, as did another small study among PLWH. The WHO currently recommends that, in patients with tuberculous pericarditis, initial adjuvant glucocorticoid therapy may be used. The 2016 guidelines of the American Thoracic Society (ATS), the CDC, and the Infectious Diseases Society of America (IDSA), on the other hand, suggest that glucocorticoid therapy should not be routinely administered. Tuberculosis Caused by direct extension from the pericardium or by retrograde lymphatic extension from affected mediastinal lymph nodes, tubercu lous myocarditis is extremely rare. Usually, it is fatal and is diagnosed postmortem. Miliary or Disseminated TB Miliary TB is due to hematogenous spread of tubercle bacilli. Although in children it is often the conse quence of primary infection, in adults it may be due to either recent infection or reactivation of old disseminated foci. The lesions are usu ally yellowish granulomas 1–2 mm in diameter that resemble millet seeds (thus the term miliary, coined by nineteenth-century patholo gists). Clinical manifestations are nonspecific and protean, depending on the predominant site of involvement. Fever, night sweats, anorexia, weakness, and weight loss are presenting symptoms in the majority of cases. At times, patients have a cough and other respiratory symp toms due to pulmonary involvement as well as abdominal symptoms. Physical findings include hepatomegaly, splenomegaly, and lymphade nopathy. Eye examination may reveal choroidal tubercles, which are pathognomonic of miliary TB, in up to 30% of cases. Meningismus occurs in fewer than 10% of cases. A high index of suspicion is required for the diagnosis of miliary TB. Frequently, CXR (Fig. 183-5) reveals a miliary reticulonodular pattern

(more easily seen on underpenetrated film), although no radiographic abnormality may be evident early in the course and among PLWH. Other radiologic findings include large infiltrates, interstitial infiltrates (especially in PLWH), and pleural effusion. Sputum-smear microscopy is negative in most cases. Various hematologic abnormalities may be seen, including anemia with leukopenia, lymphopenia, neutrophilic leukocytosis and leukemoid reactions, and polycythemia. Dissemi nated intravascular coagulation has been reported. Elevation of alka line phosphatase levels and other abnormal liver function tests are detected in patients with severe hepatic involvement. TST results may be negative in up to half of cases, but reactivity may be restored during chemotherapy. Bronchoalveolar lavage and transbronchial biopsy are more likely to provide bacteriologic

confirmation, and granulomas are evident in liver or bone-marrow biopsy specimens from many patients. If it goes unrecognized, miliary TB is lethal; with proper early treat ment, however, it is amenable to cure. Glucocorticoid therapy has not proved beneficial.

A rare presentation seen in the elderly, cryptic miliary TB has a chronic course characterized by mild intermittent fever, anemia, and—ultimately—meningeal involvement preceding death. An acute septicemic form, nonreactive miliary TB, occurs very rarely and is due to massive hematogenous dissemination of tubercle bacilli. Pancy topenia is common in this form of disease, which is rapidly fatal. At postmortem examination, multiple necrotic but nongranulomatous ("nonreactive") lesions are detected. Less Common Extrapulmonary Forms TB may cause chorio retinitis, uveitis, panophthalmitis, and painful hypersensitivity-related phlyctenular conjunctivitis. Tuberculous otitis is rare and presents as hearing loss, otorrhea, and tympanic membrane perforation. In the nasopharynx, TB may simulate granulomatosis with polyangiitis. Cutaneous manifestations of TB include primary infection due to direct inoculation, abscesses and chronic ulcers, scrofuloderma, lupus vulgaris (a smoldering disease with cutaneous nodules, plaques, and fissures), miliary lesions, and erythema nodosum. Tuberculous mas titis results from retrograde lymphatic spread, often from the axillary lymph nodes. Adrenal TB is a manifestation of disseminated disease presenting rarely as adrenal insufficiency. Finally, congenital TB results from transplacental spread of tubercle bacilli to the fetus or from PART 5 Infectious Diseases FIGURE 183-11 Estimated HIV prevalence in new and relapse tuberculosis (TB) cases in 2022. (See disclaimer in Fig. 183-2. Reproduced with permission from Global Tuberculosis Report 2022. Geneva, World Health Organization; 2023.)

ingestion of contaminated amniotic fluid. This rare disease affects the liver, spleen, lymph nodes, and various other organs. Post-TB Lung Disease and Complications A substantial proportion of TB survivors considered cured experience chronic impairment of lung function, dyspnea, residual cough, bronchiectasis, and pulmonary hypertension. In addition, aspergillomas and chronic pulmonary aspergillosis (Chap. 223) have been seen post-TB. Chronic pulmonary aspergillosis may manifest as simple aspergilloma (fungal ball) or chronic cavitary aspergillosis. In the presence of large residual cavities, Aspergillus fumigatus may colonize the lesion and produce symptoms such as respiratory impairment, hemoptysis, persistent fatigue, and weight loss, often resulting in the erroneous diagnosis of TB recurrence. The detection of Aspergillus precipitins (IgG) in the blood suggests chronic pulmonary aspergillosis, as do radiographic abnormalities such as thickening of the pleura and cavitary walls or the presence of a fungal ball inside the cavity. Treatment is difficult. Recent preliminary studies on the use of triazoles for ≥6 months indicate improvement or stabilization of 60–75% of the radiologic and clinical manifestations. Surgical removal of lesions is risky except in simple aspergilloma. HIV-Associated TB (See also Chap. 208) TB is one of the most common diseases among PLWH worldwide. Responsible for up to a quarter of all HIV-related mortality (167,000 deaths per year), TB is still one of the main causes of death in this population, especially in Africa (Fig. 183-11). Classic studies showed that a person with a positive TST who acquires HIV infection has a 3–13% annual risk of developing active TB, with the exact risk depending on the degree of immunosuppression when observation begins. Furthermore, a new TB infection acquired by a PLWH may evolve into active disease in a matter of weeks rather than months or years. TB can appear at any stage of HIV infection, and its presentation varies with the stage. When cell-mediated immunity is only partially compromised, pulmonary TB presents in a typical man ner (Figs. 183-6 and 183-7), with upper-lobe infiltrates and cavitation and without

significant lymphadenopathy or pleural effusion. In later stages of HIV infection, when the CD4+ T-cell count is <200/μL, a primary TB–like pattern, with diffuse interstitial and subtle infiltrates, HIV prevalence in new and relapse TB cases, all ages (%) 0–4.9 5–9.9 10–19 20–49 ≥50 No data Not applicable

little or no cavitation, pleural effusion, and intrathoracic lymphade nopathy, is more common. However, these forms are becoming less common because of the expanded use of ART. Extrapulmonary TB is common among PLWH. In various series, extrapulmonary TB—alone or in association with pulmonary disease—has been documented in 40–60% of all cases in PLWH. The most common forms are lymphatic, disseminated, pleural, and pericardial. Mycobacteremia and meningitis also are common, particularly in advanced HIV disease. The diagnosis of TB in PLWH can be complicated. The Xpert MTB/RIF assay is the preferred initial diagnostic option for pulmonary TB, ensuring a sen sitivity of more than 80% and a specificity of 98%; therapy should be started on the basis of a positive result because treatment delays may be fatal. A negative Xpert MTB/RIF result, however, does not exclude a diagnosis of TB. Culture remains the gold standard. Detection of myco bacterial lipoarabinomannan antigen in urine has shown favorable results in assisting with the diagnosis of TB in PLWH (see “Additional Diagnostic Procedures,” below). The immune reconstitution inflammatory syndrome (IRIS) or TB immune reconstitution disease consists of exacerbations in systemic manifestations (lymphadenopathy, fever) or respiratory signs (worsen ing of pulmonary infiltrations, pleural effusion) as well as laboratory or radiographic manifestations of TB. This syndrome is rarely seen among non-HIV-infected persons, is associated with the administration of ART, and occurs in ~10% of HIV-infected TB patients. Usually devel oping 1–3 months after initiation of ART, IRIS is more common among patients with advanced immunosuppression and extrapulmonary TB. “Unmasking IRIS” may develop after the initiation of ART in patients with undiagnosed subclinical TB. The earlier ART is started after TB treatment is initiated and the lower the baseline CD4+ T-cell count, the greater the risk of IRIS. Death due to IRIS is relatively infrequent and occurs mainly among patients who have a high preexisting mor tality risk. The presumed pathogenesis of IRIS consists of an immune response that is rapidly improved by HIV suppression and is stimulated by antigens released as bacilli are killed during effective chemotherapy. There is no diagnostic test for IRIS, and its confirmation relies heav ily upon case definitions incorporating clinical and laboratory data; a variety of case definitions have been suggested. The first priority in the management of a possible case of IRIS is to ensure that the clinical syndrome does not represent a failure of TB treatment or the develop ment of another infection. Mild paradoxical reactions can be managed with symptom-based treatment and do not worsen outcomes of treat ment for TB. However, IRIS can result in serious neurologic complica tions or death in patients with CNS TB. Therefore, ART should not be initiated during the first 8 weeks of TB treatment in patients with TB meningitis. Glucocorticoids have been used for severe paradoxical reactions; prednisolone given for 4 weeks at a low dosage (1.5 mg/kg

per day for 2 weeks and half that dose for the remaining 2 weeks) has reduced the need for hospitalization and therapeutic procedures and has hastened alleviation of symptoms, as reflected by Karnofsky per formance scores, quality-of-life assessments, radiographic response, and C-reactive protein levels. The effectiveness of glucocorticoids in alleviating the symptoms of IRIS is probably linked to suppression of proinflammatory cytokine concentrations, as these medications reduce serum concentrations of IL-6, IL-10, IL-12p40, TNF-α, IFN-γ, and IFN-γ-inducible protein 10. Recommendations for the prevention and treatment of TB in PLWH are provided below. DIAGNOSIS

The key to the early diagnosis of TB is a high index of suspicion. Diag nosis is not difficult in persons belonging to high-risk populations who present with typical symptoms and a classic chest radiograph showing upper-lobe infiltrates with cavities (Fig. 183-6). On the other hand, the diagnosis can easily be missed in an elderly nursing-home resident or a teenager with a focal infiltrate. Often, the diagnosis is first entertained when the chest radiograph of a patient being evaluated for respiratory symptoms is abnormal. If the patient has no complicating medical con ditions that cause immunosuppression, the chest radiograph may show typical upper-lobe infiltrates with cavitation (Fig. 183-6). The longer the delay between the onset of symptoms and the diagnosis, the more

likely is the finding of cavitary disease. In contrast, immunosuppressed patients, including PLWH, may have “atypical” findings on CXR—e.g., lower-zone infiltrates without cavity formation—or interstitial disease only.

The several approaches to the diagnosis of TB require, above all, a well-organized microbiology laboratory network with an appropriate distribution of tasks at different levels of the health care system. Besides clinical assessment and radiography, screening and referral are the principal tasks at the peripheral and community levels. Diagnosis at a secondary level (e.g., a traditional district hospital in a high-incidence setting) can be accomplished nowadays through real-time automated nucleic acid amplification technology (e.g., the Xpert MTB/RIF assay, which also allows detection of drug resistance) or through traditional AFB microscopy where new tools have not yet been introduced. At a tertiary level, molecular tests, rapid culture, and DST should be applied. ■ ■NUCLEIC ACID AMPLIFICATION TECHNOLOGY Several test systems based on amplification of mycobacterial nucleic acid have become available in the past few years and are now the pre ferred first-line diagnostic tests. These tests are progressively replacing smear microscopy, as they ensure rapid confirmation of all types of TB. One system that permits rapid diagnosis of TB with high speci ficity and sensitivity (approaching that of liquid culture) is the fully automated, real-time nucleic acid amplification technology known as the Xpert MTB/RIF assay. Xpert MTB/RIF can simultaneously detect TB and rifampin resistance in <2 h and has minimal biosafety and training requirements. Therefore, it can be housed in nonconventional laboratory settings as long as a stable and uninterrupted power supply can be assured. The WHO recommends its use worldwide as the firstline diagnostic test in all adults and children with signs or symptoms of active TB. Given the test’s high sensitivity, the WHO also recom mends its use as the initial diagnostic test for PLWH in whom TB is suspected. In the diagnosis of pulmonary TB, this test has an overall sensitivity of 85% reaching 98% among AFB-positive cases and ~70% among AFB-negative specimens; its specificity is 98%. When compared with phenotypic drug susceptibility testing for simultaneous detection of rifampin resistance, Xpert MTB/RIF has an overall sensitivity of 96% and a specificity of 98%. The newer Xpert MTB/RIF Ultra assay (Ultra), which uses the same GeneXpert diagnostic platform, has an overall sensitivity of 90% including “trace calls” (i.e., the “noise” produced by detection of DNA from nonviable bacilli) as positive with the greatest increases among smear-negative, culture-positive cases (+17%) and among PLWH (+12%). If “trace calls” are excluded, sensitivity decreases to 86%. Because of this greater sensitivity and the capacity to also detect nonviable bacilli, the new Ultra cartridge has 2% lower specificity than the original test. However, excluding “trace calls,” specificity increases to 98%. Among PLWH Ultra sensitivity is 88% and specificity 95%. Sensitivity and specificity for detection of rifampin resistance by Ultra are 94% and 99%, respectively, similar to those by the Xpert MTB/RIF assay. CHAPTER 183 Tuberculosis In the

diagnosis of extrapulmonary TB, Xpert MTB/RIF or Ultra should be the initial tests applied to CSF from patients in whom TB meningitis is suspected as well as a replacement test (preferable to con ventional microscopy, culture, and histopathology) for selected non respiratory specimens—those obtained by gastric lavage, fine-needle aspiration, or pleural or other biopsies. Sensitivity varies according to specimen type with the lowest in pleural fluid (50% with Xpert MTB/ RIF and 71% with Ultra) and the highest in synovial fluid (97%) and lymph node biopsy (100% with Ultra). “Trace calls” in specimens from persons with extrapulmonary TB, as well as for PLWH and children, should be considered true positives, given the high risk of severe mor bidity and premature death, while among other cases they warrant additional tests to confirm the diagnosis of TB and prevent overtreat ment. Among patients with a recent history of TB, “trace calls” may represent DNA from dead bacilli under degradation. Truenat MTB and MTB Plus are two other newly introduced rapid adopted rapid molecular tests with sensitivities of 73% and 80%, respectively, if compared with bacteriological culture, and specificities of 98% and 96%, respectively. Truenat MTB-Rif Dx detects

rifampin resistance with a sensitivity of 84% and a specificity of 97%. These rapid tests, being portable and battery-operated, can be used in peripheral care settings rather than smear microscopy, culture, and phenotypic DST. New high-throughput automated platforms for TB diagnosis and drug-resistant variants are now available (Abbott Real Time MTB and RIF/INH, FluoroType MTBDR and MTB, BD Max MDR-TB, cobas MTB and MTB-RIF/INH). These platforms are suit able for centralized laboratories and have the advantage of processing a large number of samples in a reasonable time. Sensitivity is higher than 91% and specificity ranges from 97 to 100%. Head-to-head studies with Xpert MTB/RIF have shown comparable performance. Another available molecular test for detection of M. tuberculosis is based on loop-mediated isothermal amplification (LAMP), a temperature-inde pendent technology that amplifies DNA, is relatively simple to use, and is interpreted through a visual display. It may be used as a replacement for sputum-smear microscopy for the diagnosis of adult pulmonary TB and as a follow-up test to smear microscopy for the further inves tigation of smear-negative specimens from adults with suspected pul monary TB. The TB-LAMP assay should not replace rapid molecular tests that detect both TB and rifampin resistance, and its usefulness in PLWH in whom TB is suspected remains unclear.

■ ■AFB MICROSCOPY In some low- and middle-income settings, a presumptive diagnosis is still often based on the finding of AFB on microscopic examination, such as a smear of expectorated sputum or of tissue (e.g., a lymph node biopsy). Although inexpensive, AFB microscopy has relatively low sensitivity (40–60%) in culture-confirmed cases of pulmonary TB and does not distinguish TB from nontuberculous mycobacteria. The traditional method—light microscopy of specimens stained with ZiehlNeelsen basic fuchsin dyes—is satisfactory, although time consuming and operator dependent. Most modern laboratories processing large numbers of diagnostic specimens use auramine–rhodamine staining and fluorescence microscopy; this approach is more sensitive than the Ziehl-Neelsen method. However, it is expensive because it requires high-cost mercury vapor light sources and a darkroom. Less expensive light-emitting diode (LED) fluorescence microscopes are now recom mended by the WHO as the microscopy tool of choice. They are as sensitive as—or more sensitive than—traditional fluorescence micro scopes. As a result, conventional light and fluorescence microscopes are being replaced with this more recent technology, especially in developing countries. For patients with signs or symptoms of pulmo nary TB, it has been recommended that one or two sputum specimens, preferably collected early in the morning, should be submitted to the laboratory for AFB smear and mycobacterial culture. If tissue

is obtained, it is critical that the portion of the specimen intended for culture not be put in preservation fluid such as formaldehyde. The use of AFB microscopy in examining urine or gastric lavage fluid is lim ited by the low numbers of organisms, which can cause false-negative results, or the presence of commensal mycobacteria, which can cause false-positive results. PART 5 Infectious Diseases ■ ■MYCOBACTERIAL CULTURE Definitive diagnosis depends on the isolation and identification of M. tuberculosis from a clinical specimen. Commercial liquid-culture systems are recommended by the WHO as the reference standard for culture. The MGIT (mycobacteria growth indicator tube) system uses a fluorescent compound sensitive to the presence of oxygen dissolved in the liquid medium. The appearance of fluorescence, detected by fluo rometric technology, indicates active growth of mycobacteria. MGIT cultures usually become positive after a period ranging from 10 days to 2–3 weeks; the tubes are read weekly until the eighth week of incuba tion before the result is declared to be negative. Specimens may also be inoculated onto egg- or agar-based medium (e.g., Löwenstein-Jensen or Middlebrook 7H10 or 7H11) and incubated at 37°C (under 5% CO_2 for Middlebrook medium). Because most species of mycobacteria, includ ing M. tuberculosis, grow slowly, 4–8 weeks may be required before growth is detected on these conventional culture media. Although M. tuberculosis may be identified presumptively on the basis of growth

time and colony pigmentation and morphology, a variety of biochemi cal tests have traditionally been used to speciate mycobacterial isolates. In modern, well-equipped laboratories, commercial liquid culture for isolation and species identification by molecular methods or highpressure liquid chromatography of mycolic acids has replaced isolation on solid media and identification by biochemical tests. A low-cost, rapid immunochromatographic lateral-flow assay based on detection of MTP64 antigen may also be used for species identification of the M. tuberculosis complex in culture isolates. These new methods, which are increasingly used in limited-resource settings, have decreased the time required for bacteriologic confirmation of TB to 2–3 weeks. ■ ■DRUG SUSCEPTIBILITY TESTING Universal DST is considered by the WHO as the current standard of care for all TB patients and should consist of DST to at least rifampin for all initial isolates of M. tuberculosis, as rifampin resistance is an excellent proxy for MDR-TB diagnosis. Expanded and rapid suscep tibility testing for isoniazid and key second-line anti-TB drugs (espe cially the fluoroquinolones and the injectable drugs) is mandatory when RR-TB is found in order to guide selection of the appropriate treatment regimens. Susceptibility testing may be conducted directly by molecular techniques (with the clinical specimen) or indirectly (with mycobacterial cultures) on solid or liquid medium. Results are obtained rapidly by direct susceptibility testing on liquid medium, with an average reporting time of 3 weeks. With indirect testing on solid medium, results may not be available for ≥8 weeks. Highly reliable genotypic methods for the rapid identification of genetic mutations in gene regions known to be associated with resistance to rifampin (such as those in rpoB) and isoniazid (such as those in katG and inhA) have been developed and are being widely implemented for screening of patients at increased risk of drug-resistant TB. Apart from the Xpert MTB/RIF, Xpert MTB/RIF Ultra, and Truenat MTB-Rif Dx assays, which effectively detect rifampin resistance, the most widely used tests are molecular line probe assays (LPAs). LPAs are a family of DNA strip-based tests capable of detecting bacterial DNA and identifying drug resistance–associated mutations. After extraction of DNA from M. tuberculosis isolates or from clinical specimens, the resistance gene regions are amplified by polymerase chain reaction (PCR) and labeled and probe-hybridized PCR products are detected by colorimetric development. This assay confirms the presence of M. tuberculosis as well as mutations in target resistance-gene

regions. Given the rapidity and accuracy of commercially available LPAs, the WHO recommends that they are used to detect resistance to isoniazid and rifampin when patients have sputum smear–positive specimens or a cultured isolate of M. tuberculosis. These recommendations do not eliminate the need for conventional phenotypic culture-based DST to identify resistance to other drugs and to monitor emergence of additional drug resistance. A similar approach has been developed for second-line anti-TB drugs, such as the fluoroquinolones. Therefore, second-line LPAs (instead of phenotypic culture-based DST) are now recommended by the WHO as the initial test for rapid detection of resistance to the fluoroquino lones or the second-line injectable drugs in isolates from patients with confirmed RR-TB or MDR-TB. As with first-line LPAs, these recom mendations do not eliminate the need for conventional phenotypic, culture-based DST to identify resistance to other drugs and to monitor for the emergence of additional resistance. Detection of pyrazinamide resistance is important among persons with MDR/RR-TB. The WHO has recently recommended the use of a LPA with reverse hybridizationbased technology in culture isolates rather than phenotypic culturebased DST. Whole genome sequencing (WGS) of M. tuberculosis can provide comprehensive information on mutations conferring resistance, but it has been hampered by the requirement for a culture sample before DNA processing. Amplification and sequencing of relevant genomic targets directly from sputum samples have been successfully tested, and targeted new-generation sequencing (tNGS) is now recommended by the WHO to detect drug resistance after TB diagnosis in order to guide decisions on treatment. This class of diagnostics is particularly useful for patients requiring comprehensive DST with faster results

than phenotypic DST. However, its suboptimal sensitivity for some new and repurposed drugs still requires confirmation by phenotypic DST. ■ ■RADIOGRAPHIC PROCEDURES CXR is a rapid imaging technique that has historically been used as a primary tool to detect pulmonary TB. CXR has high sensitivity but poor specificity. Although TB may often present with typical patterns strongly suggesting the disease, some abnormalities seen in TB are also present in several other lung conditions. The initial suspicion of pulmonary TB is often based on abnormal CXR findings in a patient with respiratory symptoms. The presence of lesions suggestive of TB should prompt bacteriologic investigations in all cases, without excep tion. Although the “classic” picture is that of upper-lobe disease with infiltrates and cavities (Fig. 183-6), virtually any radiographic pat tern—from a normal film or a solitary pulmonary nodule to diffuse alveolar infiltrates in a patient with adult respiratory distress syndrome— may be seen. In the era of HIV/AIDS, no radiographic pattern can be considered pathognomonic, but CXR can assist in diagnosing TB or ruling it out before initiation of any preventive treatment. CXR is also helpful as a screening test preceding rapid molecular assays to improve their predictive value. Digital CXR technology, which allows display of images in a digital format on a computer screen instead of on x-ray film, offers several advantages: the procedure time is reduced, the run ning costs are lower, the imaging is of superior quality, and telemedi cine assistance is available, including computer-aided detection (CAD) and interpretation of findings using software programs that analyze digital imaging for abnormalities compatible with TB. However, lim ited evidence suggests that while sensitivity may be high, specificity is variable. A recent systematic review of CAD studies concluded that the diagnostic accuracy of this technology is still limited and that general izability to low-prevalence settings is still uncertain. CT (Fig. 183-7) may be useful in interpreting questionable findings on plain CXR and in diagnosing some forms of extrapulmonary TB (e.g., intrabdominal disease, Pott’s disease; Fig. 183-10). MRI is useful in the diagnosis of bone lesions and intracranial TB. ■ ■ADDITIONAL DIAGNOSTIC PROCEDURES Other diagnostic tests may be used when pulmonary TB is suspected.

Sputum induction by ultrasonic nebulization of hypertonic saline may be useful for patients who cannot produce a sputum specimen spontaneously. Frequently, patients with radiographic abnormalities that are consistent with other diagnoses (e.g., bronchogenic carci noma) undergo fiberoptic bronchoscopy with bronchial brushings and endobronchial or transbronchial biopsy of the lesion. Bronchoalveo lar lavage of a lung segment containing an abnormality also may be performed. In all cases, it is essential that specimens be submitted for molecular testing with the Xpert MTB/RIF assay, mycobacterial culture, and AFB smear. For the diagnosis of primary pulmonary TB in children, who often do not expectorate sputum, induced sputum specimens and specimens from early-morning gastric lavage may yield positive results in the Xpert MTB/RIF assay or on culture. Recently, a promising artificial intelligence (AI)-powered monitoring of cough counts has been tested for prediction of TB disease and treatment monitoring, and AI-powered classification of cough sounds for TB screening. Once fully developed, these non-invasive tools may be use ful complements to the diagnostic armamentarium. Invasive diagnostic procedures are indicated for patients with sus pected extrapulmonary TB. In addition to testing of specimens from involved sites (e.g., CSF for tuberculous meningitis, pleural fluid and biopsy samples for pleural disease), biopsy and culture of bone marrow and liver tissue have good diagnostic yields in disseminated (miliary) TB, particularly in PLWH, who also have a high frequency of positive blood cultures. Xpert MTB/RIF should always be the initial diagnostic test in patients in whom TB meningitis is suspected; any positive results should prompt immediate treatment initiation, while negative results should be followed up by additional testing. In some cases, the results of culture or Xpert MTB/RIF are negative but a clinical diagnosis of TB is supported by consistent epidemiologic evidence (e.g., a history of close contact with an infectious patient) and a compatible clinical and

radiographic response to treatment. In the United States and other industrialized countries with low rates of TB, some patients with lim ited abnormalities on CXR and sputum positive for AFB are infected with nontuberculous mycobacteria, most commonly organisms of the M. avium complex or M. kansasii (Chap. 185). Factors favoring the diagnosis of nontuberculous mycobacterial disease over TB include an absence of risk factors for TB and the presence of underlying chronic pulmonary disease.

Patients with HIV-associated TB pose several diagnostic problems (see “HIV-Associated TB,” above). PLWH with sputum culture–posi tive, AFB-positive TB may present with a normal chest radiograph. The Xpert MTB/RIF assay is the preferred rapid diagnostic test in this population of patients because of its simplicity and increased sensitiv ity (~60–70% among AFB-negative, culture-positive cases and 97–98% among AFB-positive cases). With the advent of ART, the occurrence of disseminated M. avium complex disease that can be confused with TB has become much less common. A test based on the detection of mycobacterial lipoarabinomannan antigen in urine has emerged as a potentially useful point-of-care test for TB in PLWH with low CD4+ T-cell counts. The lateral-flow urine lipoarabinomannan (LF-LAM) assay can be performed manually and read by eye. The WHO recom mends that this assay be used to assist in the diagnosis of TB only (1) in HIV-positive adults and children in inpatient settings who have signs and symptoms of TB, or who have advanced HIV disease or are seriously ill, or, irrespective of signs and symptoms of TB, who have a CD4+ T-cell count of ≤200 cells/μL or (2) in outpatient settings in HIV-positive adults and children who have signs and symptoms of TB, or irrespective of signs and symptoms, who have a CD4+ T cell count of <100 cells/μL. CHAPTER 183 ■ ■BIOMARKERS In view of the limitations of current diagnostics, research on TB biomarkers and multiple marker biosignatures

that could be used as a point-of-care test for disease or triage is a high priority and has been crystallized in well-defined target product profiles by the WHO. Recent systematic reviews revealed that promising host biomarkers under study, such as antibodies, cytokines, chemokines, and RNA signatures, by far exceed pathogen biomarkers that can be obtained from urine or blood. However, currently, candidate biomarkers require additional studies to fully assess their performance. Tuberculosis ■ ■DIAGNOSIS OF M. TUBERCULOSIS INFECTION Two modalities currently exist for identification of individuals with TB infection: the skin tests and IGRA, both of which measure host immu nologic response to TB antigens. These tests have limitations, especially in settings or populations with high TB and/or HIV prevalence. Skin Testing In 1891, Robert Koch discovered that components of M. tuberculosis in a concentrated liquid-culture medium, subsequently named “old tuberculin,” were capable of eliciting a skin reaction when injected subcutaneously into patients with TB. In 1932, Seibert and Munday purified this product by ammonium sulfate precipitation to produce an active protein fraction known as tuberculin purified protein derivative (PPD). In 1941, PPD-S, developed by Seibert and Glenn, was chosen as the international standard. Later, the WHO and UNICEF sponsored large-scale production of a master batch of PPD (RT23) and made it available for general use. The greatest limitation of PPD is its lack of mycobacterial species specificity, a property due to the large number of proteins in this product that are highly conserved in the various species. In addition, subjectivity of the skin-reaction interpre tation that is dependent on the operator, deterioration of the product, and batch-to-batch variations limit the usefulness of PPD. The skin test with tuberculin PPD (TST) is most widely used in screening for TB infection. It probably measures the response to antigenic stimulation by T cells that reside in the skin rather than the response of recirculating memory T cells. The test is of limited value in the diagnosis of active TB because of its relatively low sensitivity and specificity and its inability to discriminate between TB infection and active disease. False-negative reactions are common in immunosup pressed patients and in those with overwhelming TB. False-positive

reactions may be caused by infections with nontuberculous myco bacteria (Chap. 185) and by BCG vaccination. A repeated TST can produce larger reaction sizes due to either boosting or true conversion. The “boosting phenomenon” is a spurious TST conversion resulting from boosting of reactivity on a subsequent TST 1–5 weeks after the initial test. Distinguishing boosting from true conversion is difficult yet important and can be based on clinical and epidemiologic consider ations. For instance, true conversions are likely after BCG vaccination in a previously TST-negative person or in a close contact of an infec tious patient.

Recently, new Mycobacterium tuberculosis antigen-based skin tests (TBSTs) using ESAT-6 and CFP-10 antigens have been introduced. Combining the simplicity of the TST approach with the specificity of IGRAs, three different TBSTs were assessed by the WHO and consid ered to have an accuracy similar to that of IGRAs and greater than that of TST, therefore being useful also for PLWH, children, and BCGvaccinated persons. IFN-γ Release Assays In-vitro assays that measure T cell release of IFN-γ in response to stimulation with the highly TB-specific RD1encoded antigens ESAT-6 and CFP-10 were introduced in the early 2000s and are commercially available. The T-SPOT.TB test (Oxford Immunotec; Oxford, UK) is an enzyme-linked immunospot assay, and the QuantiFERON-TB Gold test (Qiagen GmbH; Hilden, Ger many) is a whole-blood enzyme-linked immunosorbent assay for measurement of IFN-γ. The QuantiFERON-TB Gold In-Tube (QFTGIT) assay, which facilitates blood collection and initial incubation, also contains another specific antigen, TB7.7. These tests mainly measure the response of recirculating memory CD4+ T

cells—normally part of a reservoir in the spleen, bone marrow, and lymph nodes—to persisting bacilli-producing antigenic signals. However, CD8+ cells can also release IFN-γ in vitro in response to stimulation with TB antigens, and they seem to do so especially in the early phase of infection and in the phase of reactivation. Therefore, a new version of the QFT-GIT assay, called QuantiFERON-TB Gold Plus (QFT-Plus), has been developed and operates through two antigen tubes: TB1, containing long peptides from ESAT-6 and CFP-10 and inducing a CD4+ T cell response, and TB2, which also contains shorter peptides stimulating CD8+ cells. PART 5 Infectious Diseases Potential advantages of IGRAs include logistical convenience, the need for only one patient visit to complete testing, and the avoidance of somewhat subjective measurements (e.g., skin induration). However, IGRAs require that blood be drawn and then delivered to the labora tory in a timely fashion. IGRAs also require that testing be performed by specially trained technicians in a laboratory setting. These require ments pose challenges similar to those faced with the TST, including cold-chain requirements and batch-to-batch variations. Because of higher specificity and greater availability of resources, IGRAs have usually replaced the TST for TB infection diagnosis in low-incidence, high-income settings. However, in high-incidence TB and HIV set tings and population groups, evidence regarding the performance and usefulness of IGRAs is still limited, and cost considerations may limit wider use. A number of national guidelines on the use of IGRAs for TB infec tion testing have been issued. In the United States, an IGRA is preferred to the TST for most persons over the age of 5 years who are being screened for TB infection. However, for individuals at high risk of progression to active TB (e.g., PLWH), either test—or, to optimize sen sitivity, both tests—may be used. Because of the paucity of data on the use of IGRAs in children, the TST is preferred for TB infection testing of children aged <5 years. In Canada and some European countries, a two-step approach for those with positive TSTs—i.e., an initial TST fol lowed by an IGRA—is often recommended. However, a TST may boost an IGRA response if the interval between the two tests exceeds 3 days. Because the IGRA uses elaboration of IFN-γ for its readout, patients with anti-IFN-γ autoantibodies may have an indeterminate test result. In conclusion, both the TST and IGRA, although useful as diagnos tic aids, are imperfect tests for TB infection: while they can identify TB infected persons, they have low predictive value in identifying

TABLE 183-2 Recommended Dosagea for Initial Treatment of Tuberculosis in Adults and Children DAILY DOSE DRUG ADULT PEDIATRIC Isoniazid 5 mg/kg, max 300 mg 10 (7–15) mg/kg, max 300 mg Rifampin 10 mg/kg, max 600 mg 15 (10–20) mg/kg, max 600 mg Pyrazinamide 25 mg/kg, max 2 g 35 (30–40) mg/kg Ethambutol 15 mg/kg 20 (15–25) mg/kg aThe duration of treatment with individual drugs varies by regimen, as detailed in Table 183-3. Source: Based on recommendations of the American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention and the World Health Organization. individuals with the highest risk of progression toward disease, cannot differentiate between active TB and TB infection, cannot distinguish new infections from reinfections, and display reduced sensitivity in immunocompromised patients. TREATMENT Tuberculosis The two main aims of TB treatment are (1) to prevent morbidity and death by curing TB while preventing recurrences and emer gence of drug resistance, and (2) to interrupt transmission by rendering patients noninfectious. Four major drugs are considered first-line agents for the treatment of TB: isoniazid, rifampin, pyra zinamide, and ethambutol. Table 183-2 presents currently recom mended dosages in adults and children. An additional rifamycin, rifapentine, also is available and is recommended in some treatment and prevention regimens. For a detailed discussion of the drugs used for the treatment of TB, see Chap. 186. Because of a lower degree of effectiveness and tolerability, several classes of second-line

drugs are generally used mainly for the treat ment of patients with drug-resistant TB. These agents have previ ously been classified in various manners to facilitate a standardized approach to their use. In the latest WHO guidance on the treatment of MDR-TB, they are now grouped in three ranked categories for the purpose of designing more individualized regimens of 18–20 months' duration (Table 183-3). Group A drugs include three TABLE 183-3 Groups of Drugs Recommended for Use in Longer MDR-TB Regimens and Approach to the Design of a Longer Regimen for Adults and Children GROUP DRUG Group A: All three drugs should be included to ensure that at least four likely effective agents (including one from group B below) are started and at least three are included for the rest of treatment if bedaquiline is stopped Levofloxacin or moxifloxacin Bedaquiline Linezolid Group B: At least one of these drugs should always be included Clofazimine Cycloserine or terizidone Group C: Drugs to be used to complete the regimen and when drugs from groups A and B cannot be useda Ethambutol Delamanid Pyrazinamide Imipenem-cilastatin or meropenem Amikacin (or streptomycin if amikacin is not available) Ethionamide or prothionamideb p-Aminosalicylic acidb aKanamycin and capreomycin are not to be included in the longer regimen. bTo be included only if bedaquiline, linezolid, clofazimine, or delamanid are not used, or if better options are not possible. Source: Adapted from the World Health Organization, 2022.

classes of oral agents: the fluoroquinolones levofloxacin and moxi floxacin; the oxazolidinone linezolid; and the diarylquinoline beda quiline. Group B drugs include two other oral agents: clofazimine and cycloserine (or its analogue terizidone). Group C drugs include the nitroimidazole delamanid; imipenem-cilastatin or meropenem; the injectable aminoglycosides amikacin and streptomycin (the latter formerly a first-line agent, now rarely used for drug-resistant TB because of their toxicity and high resistance levels worldwide); ethionamide or prothionamide; and P-aminosalicylic acid (PAS). In addition, the first-line anti-TB drugs ethambutol and pyr azinamide as well as high-dose isoniazid are used for MDRTB treatment. Information about drugs used in the treatment of drug-resistant TB (including dosages) can be found in the following WHO Handbook: https://iris.who.int/bitstream/han dle/10665/365308/9789240063129-eng.pdf?sequence=1. This classi fication scheme excludes the second-line injectable aminoglycoside kanamycin and the polypeptide capreomycin. Amithiozone, which has been associated with severe and at times fatal skin reac tions—including Stevens-Johnson syndrome—among PLWH, is no longer recommended. REGIMENS Standard regimens are traditionally divided into an intensive (bac tericidal) phase and a continuation (sterilizing) phase. During the intensive phase, the majority of tubercle bacilli are killed, symp toms resolve, and usually the patient becomes noninfectious. The continuation phase is required to eliminate persisting mycobacteria and prevent relapse. TABLE 183-4 Recommended Antituberculosis Treatment Regimens INDICATION DURATION, MONTHS DRUGS DURATION, MONTHS DRUGS New drug-susceptible pulmonary or extrapulmonarya TB cases

HRZEb

HRb,c New drug-susceptible pulmonary TB (12 years or older)

HPMZb,d

HPMb,d New non-severee TB in children and adolescents aged 3 months to

16 years

HRZ(E)b

HRb Pregnancy

HREf

HR Intolerance to Z

HRE

HR Relapses, treatment default, failures Tailored according to rapid drug susceptibility testing Resistance (or intolerance) to H Throughout (6) RZELfx MDR/RR-TB (see text for further details) Throughout (6) BPaLMg for patients aged ≥14 years without previous exposure to B, L, and Pa. Throughout (6) BDLLfxCfz for patients with no previous exposure to B, D, and L, including children, adolescents, and pregnant and breastfeeding women. Either Lfx and Cfz may be omitted depending on fluoroquinolone drug susceptibility testing. This regimen may be used in place of 9-month or longer regimens described below. Throughout (9) BLMZ or BLLfxCfzZ or BDLLfxZ for patients with no previous exposure to B, D, and L, and in whom resistance to fluoroquinolones has been excluded. These regimens may be used in place of currently recommended longer (18-month) regimens described below. Alternatively: all-oral, B-containing, 9-month regimen: 4 months of B (used for up to 6 months), Lfx or M, Eto or Pto, E, Hh, Z, Cfz followed by 5 months of Lfx or M, E, Z, Cfz for adults and children with no previous exposure to second-line treatment including B, in whom resistance to fluoroquinolones has been excluded, and in the absence of extensive pulmonary TB or severe forms of extrapulmonary TB. In more complex forms of MDR/RR-TB (e.g., XDR-TB) longer (≥18 months) individualized regimens need to be formulated as per Table 183-3. aExcept for TB of central nervous system, bone, or joint, for which longer therapy should be used. bAll drugs should be given daily. cThe American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America suggest that a 2-month continuation phase could be used in HIV-seronegative patients with sputum smear–negative and culture-negative TB. dRifapentine is given at the daily dose of 1200 mg. eIt is considered non-severe: TB of peripheral lymph nodes, intrathoracic lymph node without air obstruction, uncomplicated pleural effusion, or paucibacillary, non-cavitary disease confined to one lobe of the lungs and without a miliary pattern. fThe 6-month regimen with pyrazinamide can probably be used safely during pregnancy and is recommended by the WHO and the International Union Against Tuberculosis and Lung Disease. If pyrazinamide is not included in the initial treatment regimen, the minimal duration of therapy is 9 months. gLinezolid is given at the dosage of 600 mg daily. This regimen may be used without moxifloxacin in case of documented resistance to fluoroquinolones. Abbreviations: B, bedaquiline; Cfz, clofazimine; D, delamanid; E, ethambutol; Eto, ethionamide; H, isoniazid; Hh, high-dose isoniazid (900 mg); L, linezolid; Lfx, levofloxacin; M, moxifloxacin; MDR/RR-TB, multidrug-resistant and rifampin-resistant tuberculosis; Pa, pretomanid; Pto, prothionamide; R, rifampin; WHO, World Health Organization; XDR-TB, extensively drug-resistant tuberculosis; Z, pyrazinamide.

Six-month regimen The treatment regimen of choice for virtually all forms of drug-susceptible TB in adults consists of a 2-month initial (intensive) phase of isoniazid, rifampin, pyrazinamide, and ethambutol followed by a 4-month continuation phase of isonia zid and rifampin (2HRZE/4HR)

(Table 183-4). This regimen can cure TB in >90% of patients. In children, most forms of TB in the absence of HIV infection or suspected isoniazid resistance can be safely treated without ethambutol in the intensive phase. Treatment should be given daily throughout the course, as systematic reviews have demonstrated that the use of intermittent (twice-weekly or thrice-weekly) regimens are associated with increased risk of treatment failure, relapse, and acquisition of drug resistance. The latest guidelines by the ATS, the CDC, and the IDSA, while recom mending daily administration of drugs, include a provision for use of intermittent thrice-weekly supervised regimens mainly among patients who are not infected with HIV, do not have cavitary dis ease, and are at low risk of relapse.

Patients with cavitary pulmonary TB and delayed sputum-culture conversion (i.e., those who remain culture-positive at 2 months) should be retested immediately for drug-resistant TB, and a change of regimen should be considered. A full course of 6 months with four-drug therapy should be performed not including interruptions of >4 weeks. Four-month regimens In children and adolescents between 3 months and 16 years of age with nonsevere TB, the WHO also recommends the use of a 4-month regimen consisting of a 2-month initial (intensive) phase of isoniazid, rifampin, pyrazinamide, and CHAPTER 183 INITIAL PHASE CONTINUATION PHASE Tuberculosis

ethambutol followed by a 2-month continuation phase of isoniazid and rifampin.

The recent Tuberculosis Trials Consortium Study 31/AIDS Clin ical Trials Group A5349 (Study 31/A5349) showed that a 4-month daily regimen that included isoniazid, pyrazinamide (for the first 2 months only), rifapentine at a daily dose of 1200 mg, and moxi floxacin at a daily dose of 400 mg was noninferior to the standard 6-month regimen and had a similar adverse-event profile. This option (2HPMZ/2HPM) is now recommended by the WHO and CDC as an alternative for patients aged 12 years or older, including PLWH, provided that rigorous antibacterial stewardship is ensured especially to prevent fluoroquinolone resistance. This regimen has not been evaluated, and therefore should not be used, in patients with body weight <40 kg; children aged <12 years; patients with severe extrapulmonary or disseminated forms of TB; PLWH with a CD4+ count of <100/μL, pregnant, breastfeeding or postpar tum women; or those with history of prolonged QT syndrome or receiving medications with known clinically relevant drug–drug interactions or infected with an isolate known or suspected to be resistant to the regimen drugs. Alternative regimens for patients who exhibit drug intolerance or adverse reactions are listed in Table 183-4. However, severe side effects prompting discontinuation of any of the first-line drugs and use of these alternative regimens are uncommon. To prevent isoniazid-related neuropathy, pyridoxine (10–25 mg/d) should be added to the regimen given to persons at high risk of vitamin B6 deficiency (e.g., those with alcohol use dis order; malnourished persons; pregnant and lactating women; and patients with conditions such as chronic renal failure, diabetes, and HIV infection, which are also associated with neuropathy). Finally, to facilitate absorption of rifampin, the drug should be taken on an empty stomach and without meals. PART 5 Infectious Diseases PATIENT CARE AND SUPPORT Poor adherence to treatment is one of the most important impedi ments to cure. Moreover, the tubercle bacilli harbored by patients who do not fully adhere to the prescribed regimen are likely to become resistant to the drugs to which they are irregularly exposed. Both patient- and provider-related factors may affect adherence. Patient-related factors include a lack of belief that the illness is worth the cost of adherence; the existence of concomitant medical conditions (notably alcohol or substance abuse); lack of social sup port; fear of the stigma and discrimination associated with TB;

and poverty, with attendant joblessness and homelessness. Providerrelated factors that may prevent adherence include lack of support, education, and encouragement of patients and inconvenient clinical services. A variety of interventions to increase the chances of completion of the months-long treatment course are available. First, a package of social support interventions that are complementary and not mutually exclusive, consisting of educational, psychological, and material goods and services, may enable patients with TB to address hurdles to treatment adherence. Health education and counseling on the disease's seriousness and solutions and on the importance of treatment adherence until cure should be provided to all patients at the start of and throughout the course of TB therapy. Psychological support (i.e., counseling sessions or peer-group support) can be particularly relevant in the context of the stigma and discrimination often affecting persons with TB and their families. Material support (e.g., food or financial support in forms such as meals, food baskets, food supplements, food vouchers, transport subsidies, living allow ances, housing incentives, or financial bonuses) reduces indirect costs incurred by patients or their attendants in accessing health services and mitigates the consequences of income loss related to the disease. The recent RATIONS clinical trial in India showed that nutritional support provided to a cohort of undernourished TB patients resulted in rapid weight gain and a substantially decreased mortality. In the same trial, nutritional support of household con tacts was associated with a 39–48% reduction in TB incidence in the household during 2 years of follow-up.

Second, it is paramount that health services be arranged to meet the needs and reasonable expectations of patients. Components of optimal health services include a suitable geographic location, a schedule responsive to patients' needs, functional channels of com munication between patients and their health care providers (e.g., a telephone short-messaging system, audio/video call capability, home or workplace visits), and a staff willing and competent to care for patients with TB, to address their concerns, and to base the care they provide on sound ethical standards. Third, it is crucial to offer the patient a suitable option for treat ment administration that minimizes the chance of nonadherence. Such options traditionally include unsupervised, self-administered therapy; in-person directly observed therapy (DOT); and nondaily DOT (e.g., supervision not for every dose but weekly or a few times per week) at a location mutually agreed on by patient and health care provider, with supervisory responsibility delegated to a qualified person. Direct supervision of adherence is crucial in view of the lack of tools to accurately predict adherence to self-administered treatment and of the public health importance of TB. The WHO, along with the ATS, the CDC, and the IDSA, states that ideally all patients should have their therapy directly supervised, especially during the initial phase, with proper social support based on a patient-centered approach as described above. In several countries, personnel to supervise therapy are usually available through TB control programs of local public health departments, often involving members of the community who are accepted by the patient and who have been properly trained and educated by health workers to undertake the supervisory role. Direct supervision with social support has been shown to significantly increase the proportion of patients completing treat ment in all settings and to lessen the chances of treatment failure, relapse, and default. In general, community- or home-based DOT is recommended over health facility–based DOT or unsupervised treatment; DOT administered by trained lay providers or health care workers is recommended over DOT administered by family members. Recently, comparison of video-observed therapy (VOT) with in-person DOT has shown similar outcomes. In a multicenter, analyst-blinded, randomized, controlled superiority trial of VOT through daily remote observation using a smartphone app versus DOT done 3−5 times weekly at home, community, or clinic set tings, VOT was superior to DOT in

ensuring scheduled obser vation of drug intake. Therefore, VOT can replace DOT when Internet access is good and video communication technology (e.g., smartphones, tablets, computers) is available. The system can be appropriately organized and operated by health care providers and patients. Other digital health tools can facilitate the monitoring of adherence, including digital medication monitors; these monitors can register when the pillbox is opened, with options to emit audio signals or a short message to remind patients to take medicines. These tools are customized to the needs and preferences of the individual patient and the provider. In addition to the above measures promoting adherence, provi sion of fixed-dose combination products that reduce the number of tablets the patient needs to swallow is recommended by the WHO over separate drug formulations. Various fixed-dose combi nation products are available (e.g., isoniazid/rifampin, isoniazid/

rifampin/pyrazinamide, and isoniazid/rifampin/pyrazinamide/ ethambutol). Fixed-dose combinations increase patient satisfac tion and minimize the likelihood of prescription error or of development of drug resistance resulting from monotherapy if a drug is out of stock or the patient prefers one drug over others. In addition, these combinations facilitate programmatic manage ment of procurement and supply. In the past, the bioavailability of rifampin was found to be substandard in some formulations of fixed-dose combinations. Medical regulatory authorities should ensure that combination products are of good quality; however, top standards for drug quality assurance are not always operative, especially in limited-resource countries. Prescribers should be aware of this potential problem.

MONITORING TREATMENT RESPONSE

AND DRUG TOXICITY Bacteriologic evaluation through commercial liquid-culture systems (or—when liquid-culture capacity is not yet available—through smear microscopy) is essential in monitoring the response to TB treatment. In addition, the patient’s weight should be monitored regularly and the drug dosage adjusted with any significant weight change. Patients with pulmonary disease should have their sputum examined monthly until cultures become negative to allow early detection of treatment failure. With the recommended 6-month standard first-line regimen, >80% of drug-susceptible TB patients will have negative sputum cultures at the end of the second month of treatment. By the end of the third month, the sputum of virtually all patients should be culture negative. In some patients, especially those with extensive cavitary disease and large numbers of organ isms, AFB smear conversion may lag behind culture conversion as a result of the expectoration and microscopic visualization of dead bacilli. Therefore, as capacity is built, smear microscopy should be progressively abandoned as a monitoring tool in favor of liquid culture. As noted above, patients with cavitary disease in whom sputum culture conversion does not occur by 2 months require immediate testing or retesting for drug resistance. When a patient’s sputum cultures or smears remain positive at ≥3 months despite good adherence, treatment failure caused by drug resistance is likely. Nontuberculous mycobacteria may confound and confuse AFB microscopy. The pattern of drug resistance should guide the choice of the best treatment option (see below). A sputum specimen should be collected at the end of treatment to document cure. In settings where mycobacterial cultures are not yet available, moni toring by AFB smear examination should be undertaken at 2, 5, and 6 months. Bacteriologic monitoring of patients with extrapul monary TB is more difficult and often is not feasible. In these cases, the response to treatment must be assessed clinically with the help of medical imaging. Monitoring of the response to

chemotherapy by nucleic acid amplification technology, such as the Xpert MTB/RIF assay, is not suitable because these tests can produce positive results due to nonviable bacilli. Likewise, serial chest radiographs are not recom mended because radiographic changes may lag behind bacteriologic response and are not highly sensitive. After the completion of treat ment, neither sputum examination nor CXR is recommended for routine follow-up purposes. However, a chest radiograph obtained at the end of treatment may be useful for comparative purposes should the patient develop symptoms of recurrent TB months or years later. Patients should be instructed to report promptly for medical assessment if they develop any such symptoms. During treatment, patients should be monitored for drug tox icity. The most common adverse reaction of significance among those treated for drug-susceptible TB is hepatitis. Patients should be carefully educated about the signs and symptoms of drug-induced hepatitis (e.g., dark urine, loss of appetite, nausea) and should be instructed to discontinue treatment promptly and see their health care provider if these manifestations occur. Although biochemical monitoring is not routinely recommended, all adult patients should undergo baseline assessment of liver function (e.g., measurement of serum levels of hepatic aminotransferases and bilirubin). Older patients, those with concomitant diseases, those with a history of hepatic disease (especially hepatitis C), and those using alcohol daily should be monitored especially closely (i.e., monthly), with repeated measurements of aminotransferases, during the initial phase of treatment. Up to 20% of patients have small increases (up to three times the upper limit of normal) in serum levels of aspartate aminotransferase that are not accompanied by symptoms and are of no consequence. Suspension of treatment should be considered for patients with symptomatic hepatitis, especially when accompanied by at least a three-fold increase in serum levels of AST and/or ALT, and for patients without symptoms of hepatic injury who have marked (at least fivefold) elevations in serum levels of AST and/or ALT. Drugs should be reintroduced one at a time after

liver functions have returned to normal. Hypersensitivity reactions usually require the discontinuation of all drugs and rechallenge to determine which agent is the culprit. Because of the variety of regi mens available, it usually is not necessary—although it is possible—to desensitize patients. Hyperuricemia and arthralgia caused by pyra zinamide can usually be managed by the administration of acetyl salicylic acid; however, pyrazinamide treatment should be stopped if the patient develops gouty arthritis. Individuals who develop autoimmune thrombocytopenia secondary to rifampin therapy should not receive the drug thereafter. Similarly, the occurrence of optic neuritis with ethambutol is an indication for permanent discontinuation of this drug. Other common manifestations of drug intolerance, such as pruritus and gastrointestinal upset, can gener ally be managed without the interruption of therapy. Treatment with second-line agents for drug-resistant TB is associated with a variety of adverse drug reactions that are more frequent and severe than in patients receiving first-line TB regimens (see below). The likelihood of drug–drug interactions also is higher when secondline regimens are used.

TREATMENT FAILURE AND RELAPSE Treatment failure should be suspected when a patient’s cultures (or sputum smears, when cultures are not available) remain positive after 3 months of treatment. In the management of such patients, it is imperative that the current isolate be urgently retested (or tested for the first time if, for some reason, rapid molecular susceptibility testing was not performed at the start of treatment) for susceptibil ity to first-line agents. If resistance to rifampin is detected, test ing should be done to second-line agents as well. The treatment approach should start with molecular testing for—at the least— resistance to rifampin and

isoniazid. Because results are expected to become available within a few days, changes in the regimen can be postponed until that time. However, if the patient's clinical condition is deteriorating rapidly, an earlier change in regimen may be indicated. A cardinal rule in the latter situation is always to add more than one drug, preferably two or three, at a time to a failing regimen; in practice, starting an empirical regimen for MDR-TB (see "Drug-Resistant TB," below) is warranted. The patient may continue to take isoniazid and rifampin along with these new agents pending the results of susceptibility tests. CHAPTER 183 Tuberculosis Patients who experience a recurrence after apparently success ful treatment (i.e., a relapse) are less likely to harbor drug-resistant strains than are patients in whom treatment has failed. Acquired resistance is uncommon among strains from patients in whom relapse follows the proper completion of a standard 6-month regi men. The treatment decision depends on a general assessment of the risk of drug resistance, the severity of the case, and the results of rapid susceptibility testing. Patients whose treatment has been interrupted and who have a high likelihood of MDR-TB should receive an MDR-TB regimen that includes second-line agents as soon as possible and according to DST results (Table 183-4). DRUG-RESISTANT TB Strains of M. tuberculosis resistant to individual drugs arise by spontaneous point mutations in the mycobacterial genome that occur at low but predictable rates (10−7–10−10 for the key drugs). Resistance to rifampin is associated with mutations in the rpoB gene in 95% of cases, that to isoniazid with mutations mainly in the katG gene (50–95% of cases) and the inhA gene promoter region (up to 45%), that to pyrazinamide in the pncA gene (up to 98%), that to ethambutol in the embB gene (50–65%), that to the fluoroquinolones in the gyrA–gyrB genes (75–95%), and that to the aminoglycosides mainly in the rrs gene (up to 80%); the C-12T mutation is the most common mutation in the eis promoter region associated with aminoglycoside resistance, especially in Eastern European countries. Because there is no cross-resistance among the commonly used classes of drugs, the probability that a strain will be resistant to two drug classes is the product of the probabilities of resistance to each drug class and thus is low. The development of

drug-resistant TB almost invariably follows monotherapy—i.e., the failure of the health care provider to prescribe at least two drugs to which tubercle bacilli are susceptible; of the patient to absorb or take properly prescribed therapy; or of the bioavailability of poorquality drugs or preparations (e.g., due to crushing of tablets). Drug-resistant TB may be either primary or acquired. In primary drug resistance, the patient is infected from the start by a drugresistant strain. Acquired resistance develops in the infecting strain during treatment. In North America, Western Europe, most of Latin America, and the Persian Gulf states, rates of primary resis tance are generally low and isoniazid resistance is most common. In the United States, although rates of primary isoniazid resistance have been stable at ~7–8%, the rate of primary MDR-TB has declined from 2.5% in 1993 to <1% since 2000. MDR-TB is a serious problem in some regions, especially in the countries of the former Soviet Union and some countries of Asia (Fig. 183-12). Even more serious is the occurrence of MDR strains that are also resistant to additional second-line agents used in treatment, such as the fluoro quinolones. Creation of drug-resistant TB can be prevented by adherence to the principles of sound treatment: inclusion of at least two quality-assured, bactericidal drugs to which the organism is susceptible; use of effective combination regimens; supervision of treatment with patient support; and verification that patients com plete the prescribed course. The use of fixed-dose combination products may prevent selective drug intake and therefore possibly protect against the creation of drug resistance. Transmission of drug-resistant strains can be prevented by the implementation of respiratory infection-control measures (see below) and by early detection of

persons with active TB followed by immediate initia tion of treatment with an effective regimen.

PART 5 Infectious Diseases Isoniazid-Resistant TB For the treatment of patients with isoni azid-resistant but rifampin-susceptible disease, a combination of rifampin, ethambutol, pyrazinamide, and levofloxacin for 6 months is recommended. This fluoroquinolone-containing regimen should not be used until rifampin resistance has been excluded by a reliable FIGURE 183-12 Percentage of new cases of multidrug-resistant/rifampin-resistant tuberculosis (TB) in all countries surveyed by the World Health Organization (WHO) Global Drug Resistance Surveillance Project during 1994–2022. Figures are based on the most recent year for which data have been reported, which varies among countries. Data reported before the year 2002 are not shown. (See disclaimer in Fig. 183-2. Reproduced with permission from Global Tuberculosis Report 2023. Geneva, World Health Organization; 2023.)

diagnostic test to avoid inadvertent treatment of MDR-TB with an inadequate regimen. Susceptibility should also be tested for the fluoroquinolones and pyrazinamide. If the fluoroquinolone is contraindicated because of intolerance or resistance, the patient can be given a 6-month regimen of rifampin, ethambutol, and pyra zinamide. Isoniazid probably does not contribute to a successful outcome in these regimens but may be retained (also to facilitate treatment with the four-drug fixed-dose formulation). Other drugs, such as the injectable aminoglycosides, are unlikely to play a role in the treatment of most isoniazid-resistant TB cases. However, they may be considered only in the presence of additional resistance or of drug intolerance. RR-, MDR-TB MDR-TB, in which bacilli are resistant to (at least) isoniazid and rifampin, is more difficult to manage than is disease caused by drug-susceptible organisms because these two bactericidal drugs are potent first-line agents and because associated resistance to other first-line drugs as well (e.g., eth ambutol) is not uncommon. Treatment for RR-TB and MDR-TB has traditionally been a topic of much debate, given its complex ity, long duration, toxicity, and limited efficacy; the cost of most second-line drugs; and the lack of randomized controlled clinical trials to support combinations. Recent developments include the accrual of individual datasets for patients treated worldwide; the release of findings from randomized, controlled, phase 3 clinical trials (the STREAM stage 1 trial comparing a 9-month, shorter MDR-TB regimen with the previous optimized WHO background regimen, and Otsuka’s phase 3 trial 213 comparing the addition of the new drug delamanid to the previous optimized WHO background regimen with the addition of placebo); results of the Nix-TB and ZeNix trials enrolling highly drug-resistant cases on a regimen composed of three oral drugs (bedaquiline, pretomanid, and linezolid [BPaL]) at different dosages; the TB-PRACTECAL trial testing BPaL-based regimens against multiple comparators; the NExT trial testing several drug combinations for 6–9 months; the assessment of programmatic data from South Africa on Percentage of cases 0–2.9 3–5.9 6–11 12–17 18–24 ≥25 No data Not applicable

 the large-scale use of shorter all-oral bedaquiline-containing regimens; the BEAT-Tuberculosis trial testing a new 6-month fully oral regimen consisting of BDLLfxCfz; and the endTB trial testing five different 9-month regimens consisting of different combinations of BLfx (or M) LCfzD. The assessment of this information resulted in a recent 2024 update of WHO guidance for the treatment of MDR-TB and all other RR-TB cases in which isoniazid resistance is absent or unknown (https://iris.who.int/ bitstream/handle/10665/378472/B09123-eng.pdf?sequence=1). As a

result, the WHO is now recommending four approaches to treat MDR/RR-TB (see Table 183-4): (1) a 6-month, fully oral regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin; (2) a 6-month oral regimen consisting of beda quiline, delamanid, and linezolid (600 mg), plus levofloxacine and clofazimine; (3) different 9-months oral bedaquiline-containing regimens; and (4) an individualized longer regimen of at least 18 months' duration consisting of an optimal combination of oral drugs chosen according to a rational approach and using the WHO priority grouping of medicines (Table 183-4). All-oral regimens are now the preferred options, and the use of either a shorter or a longer regimen depends on the assessment of the severity of dis ease, knowledge of drug resistance pattern, and history of previous treatment. Six-month, All-Oral, Bedaquiline, Pretomanid, Linezolid, and Moxi floxacin (BPaLM) Regimen New evidence generated through three recent clinical trials (Nix-TB, Ze-Nix, and TB-PRACTECAL) prompted WHO in 2022 to recommend that a regimen composed of the four drugs bedaquiline, the new nitroimidazole compound pretomanid, linezolid 600 mg daily, and moxifloxacin (BPaLM) should be preferred to previously recommended regimens for MDR/RR-TB. This regimen has shown treatment success rates of nearly 90% and, with a linezolid dosage of 600 mg daily, fewer adverse events than in the previous Nix-TB trial when the drug was administered at the dosage of 1200 mg daily. DST for fluoro quinolones should be obtained at the start of treatment and guide the decision to retain moxifloxacin in the regimen or administer only the other three drugs. This regimen is recommended for (1) patients with MDR/RR-TB or pre-XDR-TB aged 14 years or older regardless of HIV status, (2) all forms of disease except for dis seminated, central nervous system, and osteoarticular TB, and (3) patients with no previous or <1 month exposure to bedaquiline, pretomanid and linezolid (with the possibility of usage also among those previously treated as long as susceptibility is confirmed). Pregnant and breast-feeding women should not be administered this regimen given the incomplete evidence on pretomanid safety in those conditions. Six-Month Regimen, All-Oral (BDLLfxCfz) A 6-month regimen consisting of bedaquiline, delamanid, and linezolid (600 mg), plus levofloxacin and clofazimine has been recently shown to be noninferior to the 9-month or longer regimens. Either levofloxacin or clofazimine can be omitted depending on fluoroquinolone drug susceptibility testing: in case of proven resistance to fluoroquino lone, clofazimine can be administered while in case of fluoroqui nolone susceptibility, clofazimine can be avoided. This regimen can be used in all patients who have not been exposed (or who have been exposed for less than 1 month) to bedaquiline, delamanid, and linezolid. It can also be used in children, adolescent, and pregnant or breastfeeding women. 9-Month, All-Oral MDR-TB Regimens Although the 6-month regimens described above should be the first and second choice, in MDR/RR-TB patients without resistance to fluoroquinolones and who have not been exposed (or who have been exposed for less than 1 month) to bedaquiline, delamanid and linezolid, the use of 9-month, all-oral, bedaquiline-containing regimens has been proven to be non-inferior to longer, 18-month regimens. These regimens consist of, in order of preference: (i) bedaquiline, line zolid, moxifloxacin and pyrazinamide (BLMZ); (ii) bedaquiline, linezolid, levofloxacin, clofazimine, and pyrazinamide (BLLfxCfzZ); and (iii) bedaquiline, delamanid, linezolid, levofloxacin, and pyra zinamide (BDLLfxZ). In addition, in patients with no extensive pulmonary disease or severe extrapulmonary disease, with no or <1 month exposure to second-line drugs such as bedaquiline, fluoroquinolones, ethionamide, linezolid, and clofazimine (with the possibility of usage also among those previously treated as long as susceptibility is confirmed), an all-oral, bedaquiline-containing regimen may be used rather than the longer (18-month) regimens. Observational programmatic data from South Africa showed that a fully oral regimen starting with 6 months of bedaquiline accompa nied by 4−6 months of levofloxacin or moxifloxacin, ethionamide, ethambutol, pyrazinamide, high-dose

isoniazid (10–15 mg/kg per day), and clofazimine, and followed by 5 months of levofloxacin (or moxifloxacin), clofazimine, pyrazinamide, and ethambutol, was associated with low toxicity and better outcomes than the older, standardized, injectable-containing regimen. This regimen may also be used in children as well as in pregnant women for whom ethionamide is replaced with linezolid 600 mg daily. As in all TB cases, DST is essential to detect resistance, especially to rifampin and fluoroquinolones, before starting the 9-month regimen. Longer MDR-TB Regimens In some MDR/RR-TB patients a lon ger regimen could be administered. Table 183-3 shows the priority grouping of drugs recommended by the WHO and the approach to the design of a longer regimen for both adults and children. As much as possible, the regimen is composed of all three group A agents and at least one group B agent to ensure that at least four active drugs likely to be effective are administered and at least three of them can be continued throughout the treatment if bedaquiline is discontinued. A second group B agent should be added if one or two group A agents cannot be used. Group C agents can be added to complete a regimen when group A or B agents alone cannot be used as described. Levofloxacin or moxifloxacin, bedaquiline, and linezolid should always be included in longer regimens. Clofazi mine and cycloserine (or terizidone) are the two group B options to be added to group A drugs. Group C drugs can replace group A and B agents that cannot be used, and the choice should be based on drug susceptibility testing, drug resistance levels in the population, the patient's history of previous use of these drugs, and potential intolerance or toxicity. The injectable agents kanamycin and capreo mycin should not be included in any regimen, since they have been associated with higher risks of failure and relapse when compared with longer regimens in which other agents were used instead. Ami kacin (or streptomycin if the other aminoglycoside is not available) may be used among those aged ≥18 years as long as susceptibility is demonstrated and adverse reactions are strictly monitored. The use of ethionamide (or prothionamide) and PAS is restricted to situa tions in which bedaquiline, linezolid, clofazimine, and delamanid are not used, while clavulanic acid should not be included. A treat ment course of at least 18–20 months is recommended, but dura tion may depend on patient response. In principle, a duration of 15–17 months after culture conversion is suggested. Most patients should receive an intensive course of 6–7 months. Important considerations when treating MDR-TB patients include the safety and effectiveness of several agents especially when used for long periods of time. As in past recommendations, informed consent should be sought from patients treated with all MDR-TB regimens, and active TB drug safety monitoring is recommended. Patients taking QT interval– prolonging drugs (bedaquiline, delamanid, clofazimine, and fluoro quinolones) should be closely monitored, with electrocardiography performed at the start of treatment and repeated during treatment; patients with a QTc interval >500 ms or a history of ventricular arrhythmias should not be given these drugs. Patients taking amikacin should undergo serial audiometry to detect any hearing loss early on. Incentives and other forms of support can encourage patients not to interrupt treatment. The design of regimens for complex patterns of MDR-TB, includ ing XDR-TB, follows the same principles outlined in Table 183-3

through the selection of agents likely to be effective and tolerated. Observational studies have shown that aggressive management in such patients, with early drug susceptibility testing, use of a rational combination of effective drugs, strict adherence to directly observed therapy, monthly bacteriologic monitoring, and intensive patient support, may—besides interrupting transmission—increase the chances of cure and avert death. For patients with localized dis ease and sufficient pulmonary reserve, lobectomy or wedge resec tion may be considered as part of treatment.

Because the management of MDR-TB is complicated by both social and medical factors, care of seriously ill patients is ideally provided in specialized centers or, in their absence, in the context of programs with adequate resources and capacity, including com munity support. When patients are in stable condition, treatment and care on an ambulatory basis at a decentralized health care facil ity should be prioritized, as this approach may increase treatment success and reduce loss to follow-up. This approach should not, however, preclude hospitalization when it is necessary. Respiratory infection-control measures should be observed throughout. As part of a patient-centered approach, palliative and end-of-life care should be provided as a priority when all recommended treatment options have been exhausted. HIV-ASSOCIATED TB Several observational studies and randomized controlled trials have shown that treatment of HIV-associated TB with anti-TB drugs and simultaneous use of ART is associated with significant reductions in mortality risk and AIDS-related events. Evidence from randomized controlled trials shows that early initiation of ART during antiTB treatment is associated with a 34–68% reduction in mortality rates, with especially good results in patients with CD4+ T cell counts of <50/μL. Therefore, the main aim in the management of HIV-associated TB is to initiate anti-TB treatment and to immedi ately consider initiating or continuing ART. All HIV-infected TB patients, regardless of CD4+ T cell count, are candidates for ART, which optimally is initiated as soon as possible after the diagnosis of TB and with the strong recommendation to start within the first 2 weeks of anti-TB therapy, especially for profoundly immuno suppressed patients with CD4+ T cell counts of <50/μL. Notably, patients affected by TB involving the CNS require special consid eration. In these instances, it is recommended to delay the initia tion of ART for the initial 8 weeks, irrespective of the CD4+ T cell count. In general, the standard 6-month daily regimen is equally effective in HIV-negative and HIV-positive patients with drugsusceptible TB. However, in the uncommon situation in which a PLWH cannot receive ART, prolongation of the continuation phase of TB treatment by 3 months can be considered. The new 4-month daily regimen including isoniazid, pyrazinamide, rifapentine at a daily dose of 1200 mg, and moxifloxacin at a daily dose of 400 mg (2HPMZ/2HPM) can also be used among PLWH and a CD4+ T cell counts of >100/μL. As in any other TB patient, intermittent regimens should not be used in PLWH. As for any other adult PLWH (Chap. 208), first-line ART for TB patients consists of two nucleoside reverse transcriptase inhibitors plus a nonnucleoside reverse transcriptase inhibitor or an integrase or protease inhibi tor. Recent guidelines have also considered a two-drug treatment consisting of one nucleoside reverse transcriptase inhibitor plus an integrase inhibitor. Although TB treatment modalities are similar to those in HIV-negative patients, adverse drug reactions may be more pronounced in PLWH. In this regard, three important consider ations are relevant: an increased frequency of paradoxical reactions, interactions between ART components and rifamycins, and devel opment of rifampin monoresistance with intermittent treatment. IRIS—i.e., the exacerbation of symptoms and signs of TB—has been described above. Rifampin, a potent inducer of enzymes of the cytochrome P450 system, lowers serum levels of many HIV prote ase inhibitors, some nonnucleoside reverse transcriptase inhibi tors, and some integrase inhibitors—essential drugs used in ART. Typically, the ART regimens used alongside a rifampicin-based TB PART 5 Infectious Diseases

regimen include the integrase inhibitors dolutegravir or raltegravir (but not bictegravir, cabotegravir, or elvitegravir) at double the standard dose, combined with two nucleoside analogues. Other wise, the nonnucleoside reverse transcriptase inhibitor efavirenz is a valid alternative to the integrase inhibitor. Alternatively, rifabutin, which has much less enzyme-inducing activity, has been used in place of rifampin. However, dosage adjustments for rifabutin and

protease or integrase inhibitors are still being assessed. Several clinical trials have found that PLWH whose degree of immuno suppression is advanced (e.g., CD4+ T cell counts of <100/μL) are prone to treatment failure and relapse with rifampin-resistant organisms when treated with “highly intermittent” (i.e., once- or twice-weekly) rifamycin-containing regimens. Consequently, it is now recommended that all TB patients who are infected with HIV, like all other TB patients with rifampin-susceptible disease, receive a rifampin-containing regimen on a daily basis. Because recom mendations are frequently updated, consultation of the following websites is advised: www.who.int/health-topics/hiv-aids, www.who

.int/health-topics/tuberculosis, www.cdc.gov/hiv, and www.cdc.gov/tb. SPECIAL CLINICAL SITUATIONS Although comparative clinical trials of treatment for extrapulmo nary TB are limited, the available evidence indicates that most forms of disease should be treated with a 6-month regimen recom mended for patients with pulmonary disease. For TB meningitis, the ATS, the CDC, and the IDSA recommend extension of the continuation phase for 7–10 months. The WHO and the Ameri can Academy of Pediatrics recommend that children with bone and joint TB, tuberculous meningitis, or miliary TB receive up to 12 months of treatment (2-month induction treatment followed by 10-month consolidation treatment). Treatment for TB may be complicated by underlying medical problems that require special consideration. As a rule, patients with chronic renal failure should never receive aminoglycosides and should receive ethambutol only if serum drug levels can be monitored. Isoniazid, rifampin, and pyrazinamide may be given in the usual doses in cases of mild to moderate renal failure, but the dosage of pyrazinamide should be modified for patients with renal failure. Patients with hepatic disease pose a special problem because of the hepatotoxicity of isoniazid, rifampin, and pyrazinamide. Patients with severe hepatic disease may be treated with ethambutol, streptomycin, and possibly another drug (e.g., a fluoroquinolone); if required, isoniazid and rifampin may be administered under close supervision. The use of pyrazinamide in patients with liver failure should be avoided. Silicotuberculosis necessitates the extension of therapy by at least 2 months. The regimen of choice for pregnant women (Table 183-4) is 9 months of treatment with isoniazid and rifampin supplemented by ethambutol for the first 2 months. Although the WHO has rec ommended routine use of pyrazinamide for pregnant women in combination with isoniazid and rifampin, this drug has not been recommended for pregnant women in the United States because of insufficient data documenting its safety in pregnancy. Streptomycin is contraindicated because it is known to cause eighth-cranial-nerve damage in the fetus. The thioamides, bedaquiline, and delamanid also should be avoided in the treatment of pregnant women with MDR-TB. Treatment for TB is not a contraindication to breastfeeding; most of the drugs administered will be present in small quantities in breast milk, albeit at concentrations far too low to provide any therapeutic or prophylactic benefit to the child. Medical consultation on difficult-to-manage cases is provided by the US CDC Regional Training and Medical Consultation Centers (https://www.cdc.gov/tb-programs/php/about/tb-coe.html). PREVENTION The primary way to prevent TB is to diagnose and isolate infectious cases rapidly and to administer appropriate treatment until patients are rendered noninfectious (usually 2–4 weeks after the start of proper

treatment) and the disease is cured. Additional strategies include BCG vaccination and preventive treatment of persons with TB infection who are at high risk of developing active disease. ■ ■BCG VACCINATION One of the most used vaccines in the history of medicine, BCG was derived from an attenuated strain of M. bovis and was first admin istered to humans in 1921. Many BCG vaccines

are available world wide; all are derived from the original strain, but the vaccines vary in efficacy, ranging from 80% to nil in randomized, placebo-controlled trials. A similar range of efficacy was found in observational studies (case-control, historic cohort, and cross-sectional) in areas where infants are vaccinated at birth. These studies and a meta-analysis also found higher rates of efficacy in the protection of infants and young children from serious disseminated forms of childhood TB, such as tuberculous meningitis and miliary TB. BCG vaccine is safe and rarely causes serious complications except in those with underly ing immunodeficiencies. The local tissue response begins 2–3 weeks after vaccination, with scar formation and healing within 3 months. Side effects—most commonly, ulceration at the vaccination site and regional lymphadenitis—occur in 1–10% of vaccinated persons. Some vaccine strains have caused osteomyelitis in ~1 case per million doses administered. Disseminated BCG infection ("BCGitis") and death have occurred in 1–10 cases per 10 million doses administered, although this problem is restricted almost exclusively to persons with impaired immunity, such as children with severe combined immuno deficiency syndrome or adults with HIV infection. BCG vaccination induces TST reactivity, which tends to wane with time. The presence or size of TST reactions after vaccination does not predict the degree of protection afforded. BCG vaccine is recommended for routine use at birth in countries or among populations with high TB prevalence. However, because of the low risk of transmission of TB in the United States and other high-income countries, the variability in protection afforded by BCG, and its impact on the TST, the vaccine is not recommended for gen eral use. HIV-infected adults and children should not receive BCG vaccine. Moreover, infants whose HIV status is unknown but who have signs and symptoms consistent with HIV infection or who are born to HIV-infected mothers should not receive BCG, nor should siblings of those with immunodeficiencies unless they are known to be unaffected. Over the past decade, renewed research and development efforts have been made toward a new TB vaccine, and several candidates have been developed and tested. A promising candidate vaccine, M72/AS01E, a subunit vaccine pairing two M. tuberculosis antigens (Mtb32A and Mtb39A) with the adjuvant system AS01E, was tested in a randomized phase 2b trial showing an estimated efficacy of about 50% at 36 months. Adverse events were not different in the vaccine and placebo groups. This vaccine is now under development. The investigators aim to enroll up to 20,000 participants, including people living with HIV, at 60 trial sites in South Africa and six other countries including Zambia, Malawi, Mozambique, Kenya, Indonesia, and Vietnam. Participants in the double-blind trial will receive either M72/AS01E or a placebo. Completion of this trial is expected to take at least 5 years. As of the end of 2024, 15 candidate vaccines were in the 4 stages of clinical trials. They included mycobacterial live attenuated or inac tivated vaccines, viral vector vaccines, adjuvant recombinant protein vaccines and RNA vaccines. Several challenges must be faced in the development of a TB vaccine. For instance, the lack of predictive ani mal models and protection correlates renders trials long and expensive. Furthermore, the decision about whether a candidate vaccine should be developed for prevention of infection (preexposure) or prevention of reactivation (postexposure) without an exact understanding of its precise mechanism of action is complex. ■ ■TB PREVENTIVE TREATMENT (TPT) It is estimated that nearly 2 billion individuals—a quarter of the human population—have been infected with M. tuberculosis in their lifetime.

Although only a small fraction of these infections will progress toward active disease, new active cases will continue to emerge from this pool of infected individuals. Therefore, TPT (also called chemoprophylaxis or preventive chemotherapy, and previously referred to as treatment of latent TB infection) is a fundamental intervention in TB control and elimination strategies.

Infection can be tested using TST, the new Mycobacterium tubercu losis antigen-based skin tests (TBSTs), or IGRA, although these tests just measure host immune response to TB antigens. Unfortunately, at present, there is no gold-standard diagnostic test that can confirm true infection (as opposed to immunologic memory of previous exposure) or predict which infected individuals will develop active TB. As a result, decisions to treat infection should include consideration of the risk of progression in an individual. For skin testing, five tuberculin units of polysorbate-stabilized PPD should be injected intradermally into the volar surface of the forearm (i.e., the Mantoux method). Mul tipuncture tests are not recommended. Reactions are read at 48–72 h as the transverse diameter (in millimeters) of induration; the diameter of erythema is not considered. In some persons, TST reactivity wanes with time but can be recalled by a second skin test administered ≥1 week after the first (i.e., two-step testing). For persons periodically undergoing the TST, such as health care workers and individuals admitted to long-term-care institutions, initial two-step testing may preclude subsequent misclassification of those who have boosted reac tions as TST converters. The cutoff for a positive TST (and thus for TPT) is related both to the probability that the reaction represents true infection and to the likelihood that the individual, if truly infected, will develop TB. Table 183-5 suggests possible conventional cutoff by risk group. Thus, positive reactions for PLWH, recent close contacts of infectious cases, organ transplant recipients, previously untreated per sons whose chest radiograph shows fibrotic lesions consistent with old CHAPTER 183 Tuberculosis TABLE 183-5 Tuberculin Reaction Size and Cutoff for Tuberculosis (TB) Preventive Treatment TUBERCULIN REACTION SIZE, mm RISK GROUP HIV-infected persons ≥5 Recent contacts of a patient with TB ≥5a Organ transplant recipients ≥5 Persons with fibrotic lesions consistent with old TB on chest radiography ≥5 Persons who are immunosuppressed—e.g., due to the use of glucocorticoids or tumor necrosis factor α inhibitors ≥5 Persons with high-risk medical conditionsb ≥5 Recent immigrants (≤5 years) from high-prevalence countries ≥10 Injection drug users ≥10 Mycobacteriology laboratory personnel; residents and employees of high-risk congregate settingsc ≥10 Children <5 years of age; children and adolescents exposed to adults in high-risk categories ≥10 Low-risk personsd ≥15 aTuberculin-negative contacts, especially children, should receive prophylaxis for 2–3 months after contact ends and should then undergo repeat tuberculin skin testing (TST). Those whose results remain negative should discontinue prophylaxis. HIV-infected contacts should receive a full course of treatment regardless of TST results. bThese conditions include silicosis and end-stage renal disease managed by hemodialysis. cThese settings include correctional facilities, nursing homes, homeless shelters, and hospitals and other health care facilities. dExcept for employment purposes where longitudinal TST screening is anticipated, TST is not indicated for these low-risk persons. A decision to treat should be based on individual risk/benefit considerations. Source: Adapted from Centers for Disease Control and Prevention: https://www.cdc.
gov/tb/publications/factsheets/testing/Tuberculin_Skin_Testing_Information_for_
Health_Care_Providers.pdf.

TB, and persons receiving drugs that suppress the immune system are defined as an area of induration ≥5 mm in diameter. A 10-mm cutoff is used to define positive reactions in most other at-risk persons. For persons with a very low risk of developing TB if infected, a cutoff of 15 mm is used. (Except for employment purposes where longitudinal screening is anticipated, the TST is not indicated for these low-risk persons.) Criteria for positive TBSTs are based on manufacturer rec ommendations, and some require induration with a diameter cutoff of 5 mm. A positive IGRA also is based on manufacturer recom mendations. Good clinical practice requires that, in addition to test

results, epidemiologic and clinical factors also guide the decision to implement TPT and that active TB be definitively excluded before the initiation of a prophylactic regimen. The WHO recommends system atic testing for infection and TPT for the following groups at high risk of progression from infection to disease or of exposure and infection: adults, adolescents and children older than 12 months living with HIV; infants with HIV aged <12 months who are contacts of persons with TB; all household contacts of patients with infectious pulmonary TB including children <5 years of age; patients with silicosis, patients starting anti-TNF treatment, patients on dialysis, and patients pre paring for organ or hematologic transplantation. In addition, testing and TPT may be considered for persons living or working in at-risk institutional or crowded settings, such as prisoners, health care work ers, recent immigrants from high-TB-burden countries, and homeless persons who use drugs.

Some skin test- and IGRA-negative individuals are also candidates for TPT. Once an appropriate clinical evaluation has excluded active TB, infants and children <5 years of age who were in contact with infectious cases should be offered TPT even in the absence of a positive test for TB infection. PLWH >1 year of age who have been exposed to an infectious TB patient should receive TPT regardless of the results of a TB infection test. Any HIV-infected candidate for TPT must be screened carefully to exclude active TB, which would necessitate full disease treatment. The use of a clinical algorithm based on four signs/ symptoms (current cough, fever, weight loss, and night sweats) helps to decide which PLWH can start TPT. The absence of all four symptoms tends to exclude active TB in PLWH. The presence of one of these four manifestations, on the other hand, warrants further investigation for active TB before TPT is started. Although a test for TB infection is pru dent before starting TPT, this test is not an absolute requirement—given the logistical challenges—among contacts aged <5 years and PLWH in high-TB-incidence and low-resource settings. PART 5 Infectious Diseases Among PLWH receiving ART, conversion of the TST from negative to positive can occur during the first few months of TPT. Conversions (from negative to positive) and reversions (from positive to negative) are more common with IGRAs than with TSTs among serially tested health care workers in the United States. TPT in selected persons at risk aims to prevent active disease and, in the absence of an immunizing vaccine, is a critical component of TB elimination strategies. This intervention is based on the results of a large number of randomized, placebo-controlled clinical trials dem onstrating that a 6- to 9-month course of isoniazid reduces the risk of active TB in infected patients by up to 90%. Analysis of available data indicated that the optimal duration of treatment with this drug was ~9 months. In the absence of reinfection, the protective effect is believed to be lifelong. Clinical trials have shown that isoniazid reduces rates of TB among TST-positive PLWH. Studies in HIVinfected patients have also demonstrated the effectiveness of shorter TPT regimens containing a rifamycin. Several TPT regimens (Table 183-6) can be used. The most widely used has been that based on isoniazid alone at a daily dose of 5 mg/kg (up to 300 mg/d) for 9 months. On the basis of cost–benefit analyses and concerns about feasibility, a 6-month period of treatment at the same dose is considered adequate by the WHO. A clinical trial showed that a regimen of isoniazid (900 mg) and rifapentine (900 mg), given once weekly for 12 weeks, is as effec tive as the standard 9-month isoniazid regimen. This regimen was associated with higher rates of treatment completion (82% vs 69%) and less hepatotoxicity (0.4% vs 2.7%) than isoniazid alone, although the rate of permanent discontinuation due to an adverse event was

TABLE 183-6 Recommended Regimens and Drug Dosages for Tuberculosis Preventive Treatmenta
REGIMEN DOSE ADVERSE EVENTS Isoniazid alone for

6 or 9 months Adults: 5 mg/kg (max, 300 mg) per day Children <10 years of age: 10 mg/kg per day (range, 7–15 mg) Drug-induced liver injury, nausea, vomiting, abdominal pain, skin rash, peripheral neuropathy, dizziness, drowsiness, seizure Rifapentine plus isoniazid for

3 months Adults and children: Isoniazid: 15 mg/kg (900 mg) weekly Rifapentine: 15–30 mg/kg (900 mg) weekly Hypersensitivity reactions, petechial skin rash, druginduced liver injury Anorexia, nausea, abdominal pain Hypotensive reactions Isoniazid plus rifampin for

3 months As below As above Rifampin alone for

4 months Adults: 10 mg/kg per day Children <10 years of age: 15 mg/kg (range, 10–20 mg) per day Flulike syndrome, skin rash, drug-induced liver injury, anorexia, nausea, abdominal pain, neutropenia, thrombocytopenia, renal reactions (e.g., acute tubular necrosis and interstitial nephritis) Rifapentine plus isoniazid for

1 month Age >13 years only: isoniazid 300 mg and rifapentine 600 mg daily (28 doses) Essentially similar to those of rifapentine plus isoniazid for

3 months with neutropenia more common and elevation in liver enzyme levels and neuropathy less common Levofloxacin for

6 months Daily: adults 10–15 mg/kg;

children 15–20 mg/kg (maximum 750 mg) No grade 3, 4 or serious adverse events reported aSee text for full description of evidence on and limitations of these regimens. Source: Reproduced with permission from World Health Organization. higher (4.9% vs 3.7%). Currently, the isoniazid–rifapentine regimen is not recommended for children <2 years of age or pregnant women. A 3-month regimen of daily isoniazid and rifampin is used in some countries (e.g., the United Kingdom) for both adults and children who are known not to have HIV infection. An alternative regimen for adults is 4 months of daily rifampin, which should also be effective against isoniazid-resistant strains. Recently, an open-label, randomized, phase 3 noninferiority trial has shown that among PLWH, a 1-month regimen of daily rifapen tine plus isoniazid was noninferior to the 9-month daily isoniazid regimen and ensured a higher treatment completion. As a result, the WHO has included a 1-month regimen composed of daily isoniazid (300 mg) and rifapentine (600 mg) among the available options for patients aged 13 years or more. Rifampin and rifapentine are contra indicated in PLWH receiving protease inhibitors or most nonnucleo side reverse transcriptase inhibitors (e.g., nevirapine), as well as in those with chronic hepatitis B receiving tenofovir alafenamide. Efavi renz and tenofovir disoproxil can be used for simultaneous adminis tration with a rifamycin without dose adjustment. However, the dose of the integrase inhibitor dolutegravir needs to be increased to 50 mg twice daily when given together with rifampin, a dose that is usually well tolerated and gives equivalent efficacy in viral suppression and recovery of CD4+ cell count compared with efavirenz. Administra tion of rifapentine with raltegravir was found to be safe and well tolerated. A recent phase 1/2 trial of a 3-month regimen of isoniazid plus rifapentine and dolutegravir in adults with HIV reported good tolerance and viral load suppression, reported no adverse events of grade >3, and did not indicate that rifapentine reduced dolutegravir levels sufficiently to require dose adjustment. Clinical trials to assess the efficacy of long-term

isoniazid administration (i.e., for at least

3 years) among PLWH in high-TB-transmission settings have shown that this regimen can be more effective than 9 months of isoniazid

and is therefore recommended under those circumstances. Studies looking at whether briefer treatment with rifapentine-based regimens could achieve similar efficacies have been undertaken. Isoniazid should not be given to persons with active liver disease. All isoniazid recipients at increased risk of hepatotoxicity (e.g., those abusing alco hol daily and those with a history of liver disease) should undergo baseline and then monthly assessment of liver function; they should be carefully educated about hepatitis and instructed to discontinue use of the drug immediately should any symptoms develop. More over, these patients should be seen and questioned monthly during therapy about adverse reactions and should be given no more than a 1-month supply of drug at each visit. Persons receiving high-dose isoniazid and who are at risk of vitamin B6 (pyridoxine) deficiency should receive pyridoxine to prevent peripheral neuropathy. TPT among persons likely to have been infected by a multidrugresistant strain is a challenge because no clinical trial results are avail able to guide treatment. Close observation for early signs of disease is one option. However, in selected high-risk household contacts of patients with MDR-TB (e.g., children, recipients of immunosuppres sive therapy), TPT may be considered on the basis of individualized risk assessment and clinical criteria. In the absence of evidence of effi cacy of any regimen, important factors in the decision to treat include intensity of exposure, certainty about a source case, information on the drug resistance pattern of the index case, and potential adverse events. Confirmation of infection with available testing is generally required. Drug selection should be based on the drug susceptibility profile of the index case. WHO recommends daily levofloxacin for 6 months in people exposed to MDR-TB. Some studies are currently investigating the role of delamanid and bedaquiline as TPT. It may be more difficult to ensure adherence to TPT than when treating those with active TB. If family members of patients with active TB are being treated, adherence and monitoring may be easier. When feasible, supervised therapy may increase the likelihood of completion. As in active cases, the provision of incentives also may be helpful. Cur rently, no evidence shows that large-scale use of TPT leads to signifi cant development of drug resistance. However, before TPT begins, it is mandatory to carefully exclude active TB in order to prevent under treatment and development of drug resistance. ■ ■PRINCIPLES OF TB CONTROL The highest priority in any TB control program is the early detection of all infectious cases and the provision of treatment under optimal case-management conditions with social support until cure. In addi tion, regular screening of high-risk groups, including immigrants from high-prevalence countries, migrant workers, prisoners, home less individuals, substance abusers, and HIV-seropositive persons, is recommended to detect either infection or disease and treat promptly. Contact investigation is an important component of efficient TB control. A great deal of attention should been given to interrupt and prevent transmission of TB in institutional settings such as hospitals, homeless shelters, and prisons. Measures to limit such transmission include respiratory isolation of persons with suspected TB until they are proven to be noninfectious, proper ventilation in rooms of patients with infectious TB, use of ultraviolet irradiation in areas of increased risk of TB transmission, correct use of personal protective equipment, and periodic screening of personnel who may come into contact with known or unsuspected cases of TB. In high-prevalence countries, the essential elements of good TB care and control consist of well-defined interventions including early detection of cases and bacteriologic confirmation of the diagnosis and drug resistance

pattern; administration of the proper regimen ensur ing adherence to treatment and social support to patients; availability of drugs of proven quality, with an effective supply and management system; and a monitoring and evaluation system, including assessment of treatment outcomes and measurement of the impact of control measures on indicators such as mortality, incidence, and prevalence of drug resistance. In the era of the United Nations (UN) Sustainable Development Goals (2016–2030) and of high political visibility of TB

with international targets established by the UN General Assembly, the TB response is multisectoral and holistic. Engagement beyond dedicated programs and even the health sector is essential, as is multi sectoral accountability. The “End TB” strategy promoted by the WHO since 2016 builds on three pillars and relies on increased investments and efforts by all governments, their national programs, and a multi tude of partners within and beyond the health sector: (1) integrated, patient-centered care and prevention; (2) bold policies and supportive systems; and (3) intensified research and innovation. A “fourth” multisectoral pillar is however necessary to pursue TB elimination in the distant future. In fact, besides specific clinical care and control inter ventions as described in this chapter, elimination of TB in a society ultimately will require control and mitigation of the multitude of direct risk factors (e.g., HIV infection, smoking, alcohol abuse, diabetes) and socioeconomic determinants (e.g., extreme poverty, inadequate living conditions and poor housing, undernutrition, indoor air pollution) with clearly implemented policies within the health sector and other sectors linked to human development and welfare.

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