Chapter 173: Tuberculosis

Mario C. Raviglione

CONTENT UPDATE

November 27, 2018

Updated to incorporate the new 2018 WHO recommendations for the management of drug-resistant tuberculosis

INTRODUCTION

Tuberculosis (TB), which is caused by bacteria of the *Mycobacterium tuberculosis* complex, is one of the oldest diseases known to affect humans and the top cause of infectious death worldwide. Population genomic studies suggest that *M. tuberculosis* may have emerged ~70,000 years ago in Africa and subsequently disseminated along with anatomically modern humans, expanding globally during the Neolithic Age as human density started to increase. Progenitors of *M. tuberculosis* are likely to have affected prehominids. 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 within 5 years in 50–65% of cases. Transmission usually takes place through the airborne spread of droplet nuclei produced by patients with infectious pulmonary TB.

ETIOLOGIC AGENT

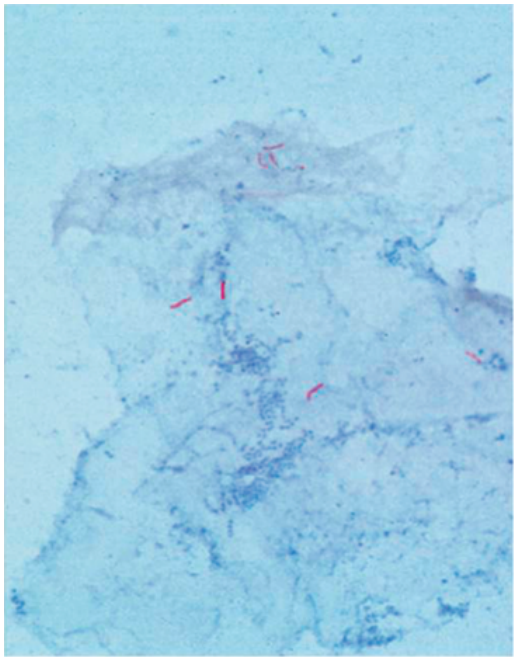
Mycobacteria belong to the family Mycobacteriaceae and the order Actinomycetales. Of the pathogenic species belonging to the *M. tuberculosis* complex, which comprises eight distinct subgroups, the most common and important agent of human disease by far is *M. tuberculosis* (*sensu stricto*). A closely 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 ~150,000 human cases worldwide, 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 environmental reservoir for any of these organisms.

M. tuberculosis is a rod-shaped, non-spore-forming, thin aerobic bacterium measuring 0.5 µm by 3 µm. Mycobacteria, including *M. tuberculosis*, are often neutral on Gram's staining. However, once stained, the bacilli cannot be decolorized by acid alcohol; this characteristic justifies their classification as acid-fast bacilli (AFB; **Fig. 173-1**). 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 fastness 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 arabinogalactan and peptidoglycan. This structure results in very low permeability of the cell wall, thus reducing the effectiveness of most antibiotics. Another molecule in the mycobacterial cell wall, lipoarabinomannan, is involved in the pathogen–host interaction and facilitates the survival of *M. tuberculosis* within macrophages.

FIGURE 173-1

Acid-fast bacillus smear showing *M. tuberculosis* bacilli. *(Courtesy of the Centers for Disease Control and Prevention, Atlanta.)*

The bacilli are thin and rod-shaped. The bacilli are scanty and in singles, overlying the cells. The rods are stained pink against a blue background.



The complete genome sequence of *M. tuberculosis* comprises 4.4 million base pairs, 4043 genes encoding 3993 proteins, and 50 genes encoding RNAs; its high guanine-plus-cytosine content (65.6%) is indicative of an aerobic "lifestyle." A large proportion of genes are devoted to the production of enzymes involved in cell wall metabolism. Substantial genetic variability exists among strains from different parts of the world.

EPIDEMIOLOGY

In 2016, 6.3 million new cases of TB (all forms, both pulmonary and extrapulmonary) were reported to the World Health Organization (WHO) by its member states; 95% of cases were reported from developing countries. However, because of insufficient case detection and incomplete notification, reported cases may represent only about two-thirds of the total estimated cases. As a result, the WHO estimated that 10.4 million (range, 8.8–12.2 million) new (incident) cases of TB occurred worldwide in 2016, 95% of them in developing countries of Asia (6.5 million), Africa (2.6 million), the Middle East (0.77 million), and Latin America (0.26 million). Seven countries accounted for 64% of all new cases: India, Indonesia, China, the Philippines, Pakistan, Nigeria, and South Africa. Two-thirds of cases typically occur in male patients, and 1.04 million children are affected every year. It is further estimated that 1.7 million (range, 1.5–1.8 million) deaths from TB, including 0.37 million among people with HIV infection, occurred in 2016; 96% of these deaths were in developing countries. Estimates of TB incidence rates (per 100,000 population) and numbers of TB-related deaths in 2016 are depicted in Figs. 173-2 and 173-3, respectively. During the late 1980s and early 1990s, numbers of reported cases of TB increased in industrialized countries. These increases were related largely to immigration from countries with a high incidence of TB; the spread of the HIV epidemic; social problems, such as increased urban poverty, homelessness, and drug abuse; and dismantling of TB services. During the past few years, numbers of reported cases have begun to decline again or have stabilized in most industrialized nations. In the United States, with the re-establishment of stronger control programs, the decline resumed in 1993 and had since been maintained until 2015, when numbers increased over the previous year for the first time in more than two decades; in that year, 9557 cases of TB (3.0 cases/100,000 population) were reported to the U.S. Centers for Disease Control and Prevention (CDC). However, in 2016 a slight decline from 2015 was observed in incidence (2.9 cases/100,000 population) and number of cases (9287).

FIGURE 173-2

Estimated tuberculosis (TB) incidence rates (per 100,000 population) in 2016. 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. *(Courtesy of the Global TB Programme, WHO; with permission.)*

The incident rates are indicated per 100,000 population per year. Incidence in various regions are as follows. 0 to 24: North America; Chile, Argentina; Egypt; Western Europe; Saudi Arabia, Iran, Turkey, Japan; Australia, New Zealand. 25 to 99: Latin America; South American countries including Brazil, Columbia, Venezuela, Ecuador, Paraguay, and Uruguay; African countries including Algeria, Libya, Mali, Niger, and Sudan; Yemen, Iraq; Eastern Europe; Russia; Central Asia, China, Malaysia, Singapore. 100 to 199: Peru, Bolivia; African countries along northwestern coast, South Sudan, and Ethiopia; Afghanistan, Mongolia, Thailand, Laos, Vietnam 200 to 299: Greenland; Nigeria, Cameroon, Somalia, Zimbabwe, Tanzania, Madagascar, Pakistan, India, Bangladesh. Greater than 30: Countries in central and southern Africa; Myanmar, Cambodia, Indonesia, Philippines, Micronesia, North Korea.

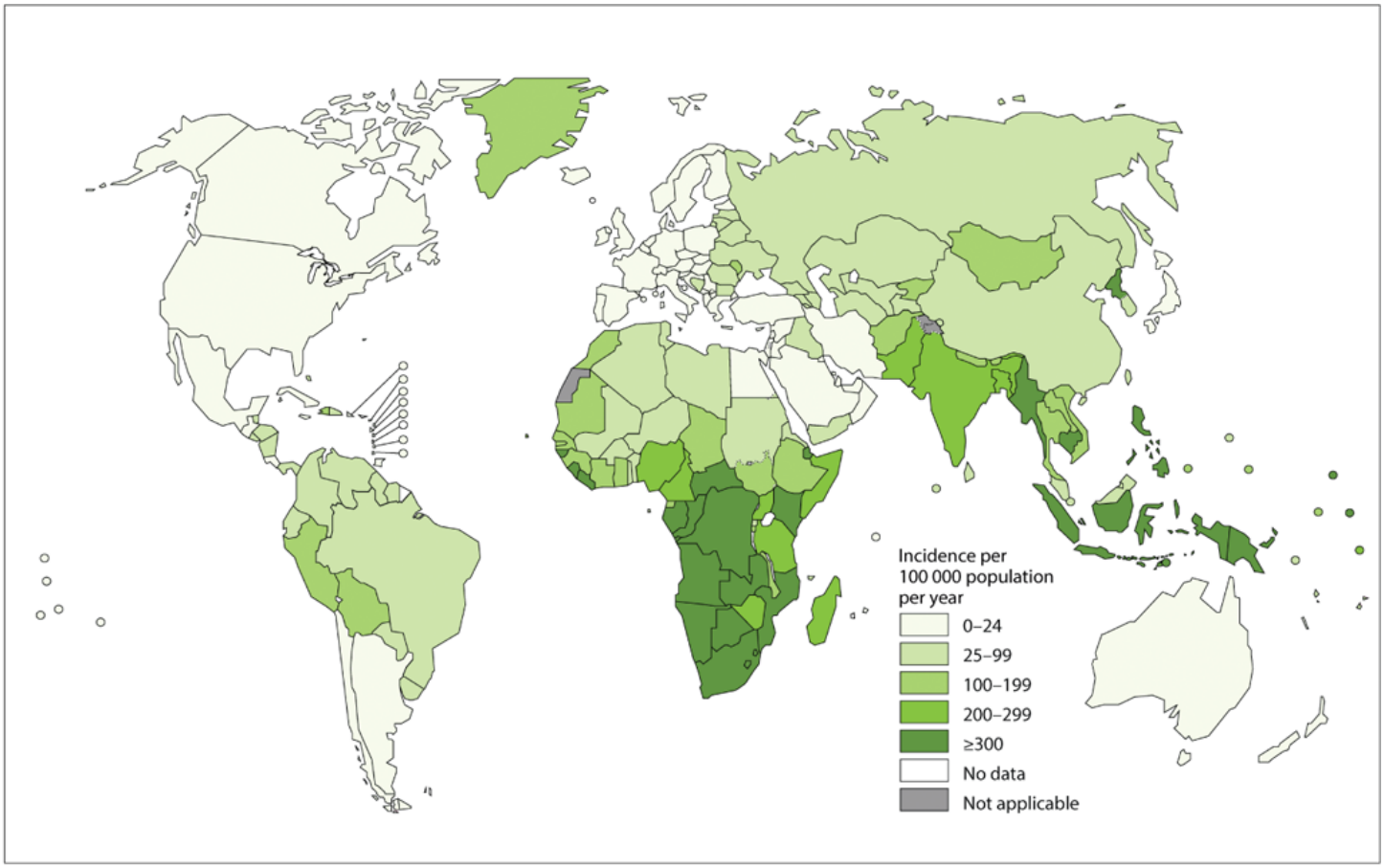
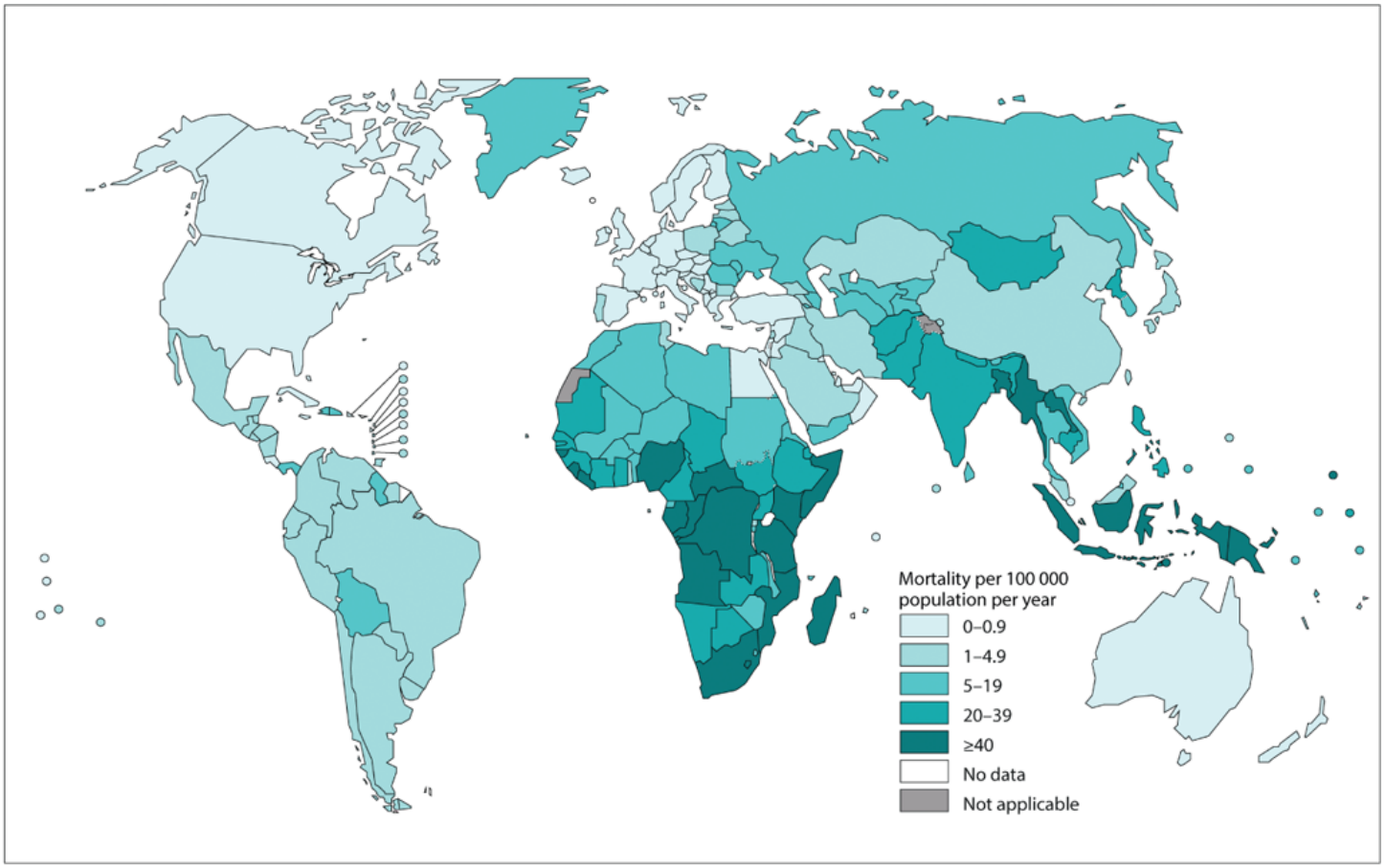


FIGURE 173-3

Estimated tuberculosis mortality rates, excluding tuberculosis-related deaths among HIV-positive people, in 2016. *(See disclaimer in Fig. 173-2. Courtesy of the Global TB Programme, WHO; with permission.)*

The mortality rates are indicated per 100,000 population per year. Incidence in various regions are as follows. 0 to 0.9: United States, Canada; Western Europe; Australia. 1 to 4.9: Mexico, Latin America; most of South America excluding Bolivia and Suriname; Saudi Arabia, Iran, Iraq, Kazakhstan, China, Japan, Malaysia, Singapore. 5 to 19: Bolivia, Suriname; countries in northern Africa; Yemen, Eastern Europe; Russia; Cambodia. 20 to 39: Greenland; African countries along northwestern coast, Chad, Cameroon, South Sudan, Ethiopia, Namibia, Botswana, Zambia, Afghanistan, Pakistan, India, Mongolia, Philippines, North Korea. Greater than 40: Countries in central and southern Africa; Myanmar, Bangladesh, Laos, Indonesia, Micronesia.



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

In the United States, TB is uncommon among young 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 latent *M. tuberculosis* infection (LTBI) is relatively high among elderly whites. In general, adults ≥65 years of age have the highest incidence rate per capita (4.8 cases/100,000 population in 2016) and children <14 years of age the lowest (0.7 case/100,000 population). Among U.S.-born persons, blacks account for the highest proportion of cases (36%; 1062 cases in 2016). TB in the United States is also a disease of adult members of the HIV-infected population, the foreign-born population (68.5% of all cases in 2016), and disadvantaged/marginalized populations. Of the 6307 cases reported among foreign-born persons in the United States in 2016, 31% occurred in persons from the Americas and 47% in persons born in Asia. Overall, the highest rates per capita were among Asian Americans (18 cases/100,000 population). A total of 493 deaths were caused by TB in the United States in 2015. In Canada in 2015, 1639 TB cases were reported (4.6 cases/100,000 population); 71% (1169) of these cases occurred in foreign-born persons, and 17% (470 cases) occurred in members of the Canadian aboriginal peoples, whose per capita rate is disproportionately high (17.1 cases/100,000 population). The highest rate was found in the territory of Nunavut, at 119 cases/100,000 population—a rate similar to that in many highly endemic countries. 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 like London. In 2015, 39.4% of all cases reported from England occurred in London, and the rate per capita (26 cases/100,000 population) was similar to that in some middle-income countries. In most Western European countries, there are more cases annually among foreign-born than native populations.

Recent data on global trends indicate that in 2015 the TB incidence was stable or falling in most regions; this trend began in the early 2000s and appears to have continued, with an average annual decline of 1.5% globally. This global decrease is explained largely by the simultaneous reduction in TB incidence in sub-Saharan Africa, where rates had risen steeply since the 1980s as a result of the HIV epidemic and the lack of capacity of health systems and services to deal with the problem effectively, and in Eastern Europe, where incidence increased rapidly during the 1990s because of a deterioration in socioeconomic conditions and the health care infrastructure (although, after peaking in 2001, incidence in Eastern Europe has since declined slowly).

Of the estimated 10.4 million new cases of TB in 2016, 10% (1.03 million) were associated with HIV infection, and 74% of these HIV-associated cases occurred in Africa. An estimated 0.37 million persons with HIV-associated TB died in 2016. Furthermore, an estimated 500,000 cases of multidrug-resistant TB (MDR-TB)—a form of the disease caused by bacilli resistant at least to isoniazid and rifampin—and an additional 100,000 cases of rifampin-resistant TB (RR-TB), which also requires MDR-TB treatment (range for both forms together, 540,000–660,000), occurred in 2016. Only 25% of these cases were diagnosed because of a lack of culture and drug susceptibility testing (DST) capacity in many settings worldwide. As a consequence, 240,000 people with MDR/RR-TB died in 2016. The countries of the former Soviet Union have reported the highest proportions of MDR disease among new TB cases (up to 35% in some regions of Russia and Belarus). Overall, 47% of all MDR-TB cases occur in India, China, and the Russian Federation. Since 2006, 117 countries, including the United S

ly drug-resistant TB (XDR-TB), in which MDR-TB is compounded by additional resistance to the most powerful

second-line anti-TB drugs (fluoroquinolones and at least one of the injectable drugs amikacin, kanamycin, and capreomycin). About 9.5% of the MDR-TB cases worldwide may be XDR-TB, but the vast majority of XDR-TB cases remain undiagnosed because reliable methods for DST are lacking and laboratory capacity is limited. Lately, a few cases deemed resistant to all anti-TB drugs have been reported; however, this information must be interpreted with caution because susceptibility testing for several second-line drugs is neither accurate nor reproducible.

FROM EXPOSURE TO INFECTION

M. tuberculosis is most commonly transmitted from a person with infectious pulmonary TB by droplet nuclei, 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. There may be as many as 3000 infectious nuclei per cough. 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. The probability of contact with a person who has an infectious 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. Several studies of close-contact situations have clearly demonstrated that TB patients whose sputum contains AFB visible by microscopy (sputum smear–positive cases) are the most likely to transmit the infection. The most infectious patients have cavitary pulmonary disease or, much less commonly, laryngeal TB and produce sputum containing as many as 10^5–10^7 AFB/mL. Patients with sputum smear–negative/culture-positive 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 persons 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.

Because of delays in seeking care and in making a diagnosis, it has been estimated that, in high-prevalence settings, up to 20 contacts (or 3–10 people per year) may be infected by each AFB-positive case before the index case is diagnosed.

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 nonimmunologic 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 associated with high-level transmissibility. When infection is acquired later in life, the chance is greater that the mature immune system will 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 HIV-infected persons. Reinfection of a previously infected individual, which is common in areas with high rates of TB transmission, may also favor the development 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 latent 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 173-1). In absolute terms, the most potent risk factor for TB among infected individuals is clearly HIV co-infection, which suppresses cellular immunity. The risk that LTBI will proceed to active disease is directly related to the patient's degree of immunosuppression. In a study of HIV-infected, tuberculin skin test (TST)–positive persons, this risk varied from 2.6 to 13.3 cases/100 person-years and increased as the CD4+ T cell count decreased.

TABLE 173-1

Risk Factors for Active Tuberculosis in Persons Who Have Been Infected with Tubercle Bacilli

Factor	Relative Risk/Odds[a]
Recent infection (<1 year)	12.9
Fibrotic lesions (spontaneously healed)	2–20
Comorbidities and iatrogenic causes	
HIV infection	21–>30
Silicosis	30
Chronic renal failure/hemodialysis	10–25
Diabetes	2–4
IV drug use	10–30
Excessive alcohol use	3
Immunosuppressive treatment	10
Tumor necrosis factor α inhibitors	4–5
Gastrectomy	2–5
Jejunoileal bypass	30–60
Post-transplantation period (renal, cardiac)	20–70
Tobacco smoking	2–3
Malnutrition and severe underweight	2

[a]Old infection = 1.

NATURAL HISTORY OF DISEASE

Studies conducted in various countries before the advent of chemotherapy showed that untreated TB is often fatal. About one-third of patients died within 1 year after diagnosis, and >50% died within 5 years. The 5-year mortality rate among sputum smear–positive cases was 65%. Of the survivors at 5 years, ~60% had undergone spontaneous remission, while the remainder were still excreting tubercle bacilli. With effective, timely, and proper chemotherapy, 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, 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 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 scytosis. Phagocytosis is enhanced by complement activation leading to opsonization of bacilli with C3 activation

products such as C3b and C3bi. (Bacilli are resistant to complement-mediated lysis.) Binding of certain receptors, such as the mannose receptor, regulates postphagocytic events such as phagosome–lysosome fusion and inflammatory cytokine production. After a phagosome forms, the survival of *M. tuberculosis* within it seems to depend in part on reduced acidification due to lack of assembly of a complete vesicular proton-adenosine 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 maturation (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 replication 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 continue the infection cycle by ingesting dying macrophages and their bacillary content, thus, in turn, becoming infected themselves and expanding the infection.

VIRULENCE OF TUBERCLE BACILLI

M. tuberculosis must be viewed as a complex formed by a multitude of strains that differ in virulence and are capable of producing 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. 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—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. In *M. marinum*, a mutation in the RD1 virulence locus encoding the ESX-1 secretion system impairs the capacity of apoptotic macrophages to recruit uninfected cells for further rounds of infection. The results are less replication and fewer new granulomas. These observations in *M. marinum* are similar in part to events related to the virulence of *M. tuberculosis*; however, ESX-1, although necessary, is probably insufficient to explain virulence, and other mechanisms may be in play. Mutants lacking key enzymes of bacterial biosynthesis 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, respectively. The isocitrate lyase gene (*icl1*) encodes a key step in the glyoxylate 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 associated 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 nonimmune resistance to infection with *M. tuberculosis* and the development of disease. The existence of this resistance, which is polygenic 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 mouse genetics identified a novel host resistance gene, *ipr1*, that is encoded within the *sst1* locus; *ipr1* encodes an IFN-inducible nuclear protein that interacts with other nuclear proteins in macrophages 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.

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 unactivated macrophages; additional naïve macrophages are recruited to the early granuloma. How the bacillus accesses the parenchymal tissue remains 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 zebrafish 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 granuloma 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 pathways 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 during 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. tuberculosis* develop: a macrophage-activating CMI response and a tissue-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 *tissue-damaging response* is the result of a delayed-type hypersensitivity reaction to various bacillary antigens; it destroys unactivated 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 macrophages. 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. LTBI ensues as a result of this dynamic balance between the microorganism and the host. It has been speculated that *latency* may not be an accurate term because bacilli may remain active during this "latent" stage, forming biofilms in necrotic areas within which they temporarily hide. Thus, some have proposed the term *persister* as more accurate to indicate the behavior of the bacilli in this phase. It is important to recognize that latent infection and disease represent not 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 affected 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 dormant 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 progressively damaged. At the center of the lesion, the caseous material liquefies. Bronchial walls and blood vessels are invaded and destroyed, and cavities are formed. The liquefied caseous material, containing large numbers 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. The resulting extrapulmonary lesions may undergo the same evolution as those in the lungs, although most tend to heal. 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), which induce protection through the production of cytokines, especially IFN-γ. After infection with *M. tuberculosis*, alveolar macrophages secrete various cytokines responsible for a number of events (e.g., the formation of granulomas) as well as systemic effects (e.g., fever and weight loss). However, alternatively activated alveolar macrophages may be particularly susceptible 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 reactive oxygen intermediates or nitric oxide) that have a[illegible] 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 mycobacterial proliferation. Activated CD4+ T lymphocytes can differentiate into cytokine-producing T_H1 or T_H2 cells. T_H1 cells produce IFN-γ—an activator of macrophages and monocytes—and IL-2. T_H2 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 nitrogen intermediates and regulate genes involved in bactericidal effects. TNF-α is also important. Although its precise mechanisms are complex and not yet fully clarified, a model has been suggested that foresees an ideal setting for TNF-α between excessive activation—with consequent worsening of immunopathological reactions—and insufficient 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 the 30-kDa (or 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 hypersensitivity to *M. tuberculosis* develops. This reactivity is the basis of the TST, which is used primarily for the detection 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 TST-negative persons), it by no means guarantees protection against reactivation. In fact, cases of active TB are often accompanied by strongly positive skin-test reactions. There is also evidence of reinfection with a new strain of *M. tuberculosis* in patients previously treated for active disease. This evidence underscores the fact that previous latent or active TB may not confer fully protective immunity.

CLINICAL MANIFESTATIONS

TB is classified as pulmonary, extrapulmonary, or both. Depending on several factors linked to different populations 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 pulmonary and extrapulmonary TB or extrapulmonary TB alone.

PULMONARY TB

Pulmonary TB is conventionally 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 with tubercle bacilli. 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. 173-4)**. 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 is also common. The Ghon focus, with or without overlying pleural reaction, thickening, and regional lymphadenopathy, is referred to as the *Ghon complex*.

FIGURE 173-4

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.)*

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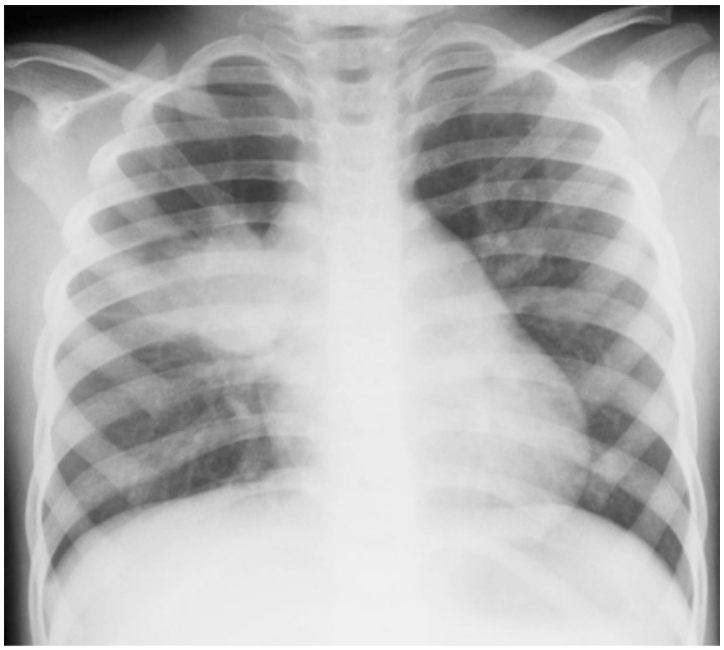

In young children with immature cell-mediated immunity and in persons with impaired immunity (e.g., those with malnutrition or HIV infection), primary pulmonary TB may progress rapidly to clinical illness. The initial lesion increases in size and can evolve in different ways. Pleural effusion, which 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 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. 284) 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. 173-5). 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., patients with HIV infection).

FIGURE 173-5

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.)*

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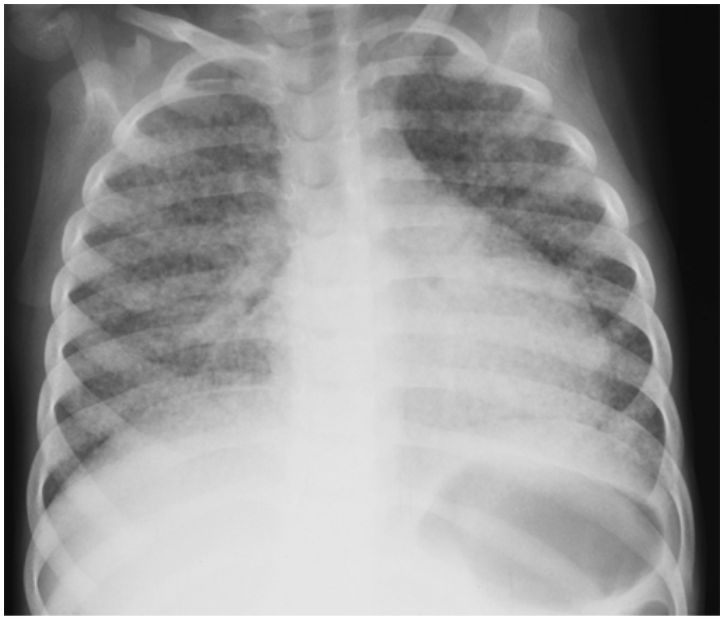

Postprimary (Adult-Type) Disease

Also referred to as *reactivation* or *secondary TB*, postprimary TB is probably most accurately termed *adult-type TB* because it may result from endogenous reactivation of distant LTBI or recent infection (primary infection or reinfection). 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 are also more frequently involved. The extent of lung parenchymal involvement varies greatly, from small infiltrates to extensive cavitary disease. With cavity formation, liquefied 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. 173-6** and **173-7**). Massive involvement of pulmonary segments or lobes, with coalescence of lesions, produces caseating pneumonia. While up to one-third of untreated patients reportedly succumb to severe pulmonary TB 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 (“consumption” 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.

FIGURE 173-6

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, Department of Infectious Diseases, S. Paolo University Hospital, Milan, Italy; with permission.)*

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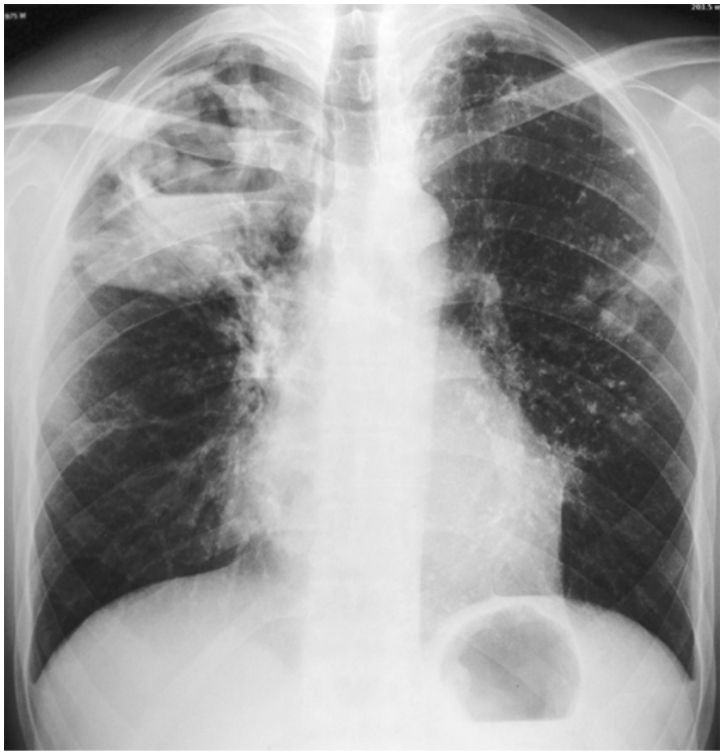

FIGURE 173-7

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.)*

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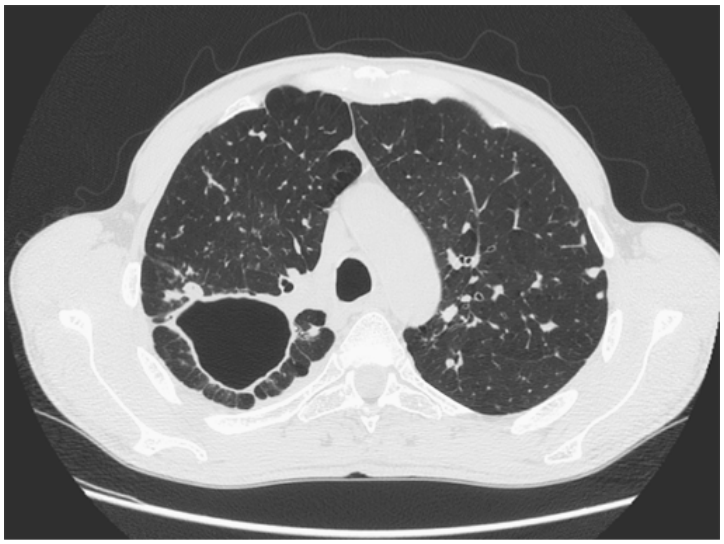


Early in the course of disease, symptoms and signs are often nonspecific and insidious, consisting mainly of diurnal fever and night sweats due to defervescence, weight loss, anorexia, general malaise, and weakness. However, in up to 90% of cases, cough eventually develops—often initially nonproductive 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 parenchymal 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 intermittent) in up to 80% of cases and wasting. Absence of fever, however, does not exclude TB. In some cases, pallor and finger clubbing develop. 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 has also been reported.

EXTRAPULMONARY TB

In descending order of frequency, the extrapulmonary sites most commonly involved in TB are the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, peritoneum, and pericardium. However, virtually any organ system may be affected. As a result of hematogenous dissemination in HIV-infected individuals, 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 HIV-infected patients (35% of cases worldwide and >40% of cases in the United States in recent series), lymph node disease is particularly frequent among HIV-infected patients and among children **(Fig. 173-8)**. 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 disease 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 the vast majority of cases, granulomatous lesions with or without visible AFBs are typically seen, and cultures are positive in 70–80% of cases. Among HIV-infected patients, 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 diagnosis includes a variety of infectious conditions, neoplastic diseases such as lymphomas or metastatic carcinomas, and rare disorders like Kikuchi's disease (necrotizing histiocytic lymphadenitis), Kimura's disease, and Castleman's disease.

FIGURE 173-8

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.)*

The enlargement extends along the neck fold, starting from beneath the neck till the chin. It appears pale red with white margins around a necrotic centre.

Pleural TB

Involvement of the pleura accounts for ~20% of extrapulmonary 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 contiguous parenchymal spread, as in many cases of pleurisy accompanying 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 p[illegible] phocyte predominance is the typical finding later. Mesothelial cells are generally rare or absent. AFBs are rarely seen

on direct smear, and cultures often may be falsely negative for *M. tuberculosis*; positive cultures are more common among postprimary cases. Determination of the pleural concentration of adenosine deaminase may be a useful screening test, and TB may be excluded if the value is very low. Lysozyme is also 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 Amplification 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.

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. Tuberculous 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, dysphonia, and dysphagia in addition to chronic productive cough. Findings 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. Carcinoma of the larynx may have similar features but is usually painless.

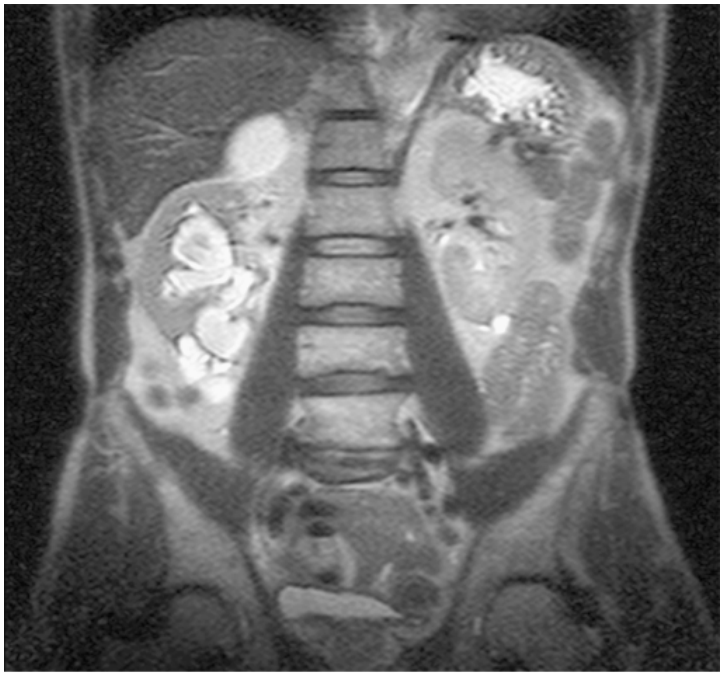
Genitourinary TB

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. Local symptoms predominate, and up to 75% of patients have abnormalities on CXR suggesting previous or concomitant pulmonary disease. Urinary frequency, dysuria, nocturia, hematuria, and flank or abdominal pain are common presentations. However, patients may be asymptomatic and their disease discovered only after severe destructive lesions of the kidneys have developed. Urinalysis gives abnormal results in 90% of cases, revealing pyuria and hematuria. The documentation of culture-negative pyuria in acidic urine should raise the suspicion of TB. IV pyelography, abdominal CT, or MRI **(Fig. 173-9)** 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 and renal damage. Genital TB is diagnosed more commonly in female than in male patients. In female patients, it affects the fallopian 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 prostatitis may also develop. In almost half of cases of genitourinary TB, urinary tract disease is also present. Genitourinary TB responds well to chemotherapy.

FIGURE 173-9

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.)*

The scan image shows several whitish patches in the cortical and medullary regions of the right kidney. These are of varying sizes and extend up to almost half the kidney's image.



Skeletal TB

In the United States, TB of the bones and joints is responsible for ~10% of extrapulmonary cases. In bone and joint disease, 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. 173-10) 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 may also 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 infections. Pyogenic bacterial osteomyelitis, in particular, 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 necessary to establish the diagnosis. Skeletal TB responds to chemotherapy, but severe cases may require surgery.

FIGURE 173-10

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.)*

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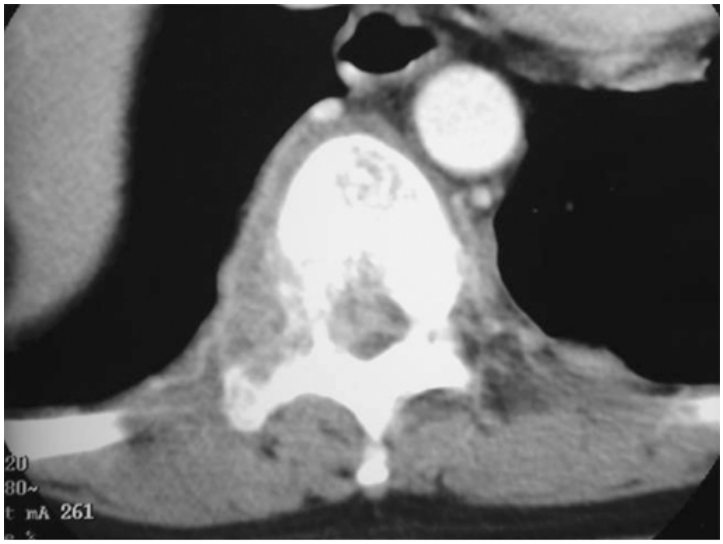


Tuberculous Meningitis and Tuberculoma

TB of the central nervous system accounts for ~5% of extrapulmonary cases in the United States. It is seen most often in young children but also develops in adults, especially those infected with HIV. Tuberculous meningitis 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 irritability. 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 bacterial meningitis. Because meningeal involvement 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, examination of cerebrospinal fluid (CSF) reveals a high leukocyte count (up to 1000/µL), usually with a predominance of lymphocytes but sometimes 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, and repeated lumbar punctures increase the yield. Culture of CSF is diagnostic 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 resolution 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 of age but did not reduce the frequency of neurologic sequelae. The dexamethasone schedule was (1) 0.4 mg/kg per day given IV 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 prednisolone, tapered over 6–8 weeks, should be used in central nervous system TB.

Tuberculoma, an uncommon manifestation of TB of the central nervous system, 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 portion 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 swelling, obstruction, hematochezia, and a palpable mass in the abdomen are common findings at presentation. Fever, weight loss, anorexia, and night sweats are also common. With intestinal-wall involvement, ulcerations and fistulae may simulate Crohn's 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 abdominal pain, fever, and ascites should raise the suspicion of tuberculous peritonitis. The coexistence of cirrhosis (Chap. 335) 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 neutrophils 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 laparoscopy) 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 HIV-infected patients. 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; cardiovascular symptoms and signs of cardiac tamponade may ultimately appear (Chap. 265). 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.

Without treatment, pericardial TB is usually fatal. Even with treatment, complications may develop, including chronic constrictive pericarditis 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 glucocorticoid 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 infected with HIV, and only a fraction were receiving antiretroviral treatment (ART). A supplemental analysis among HIV-negative people showed a small mortality benefit, as did another small study among HIV-infected people. 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.

Caused by direct extension from the pericardium or by retrograde lymphatic extension from affected mediastinal lymph nodes, tuberculous myocarditis is an extremely rare disease. Usually, it is fatal and is diagnosed post-mortem.

Miliary or Disseminated TB

Miliary TB is due to hematogenous spread of tubercle bacilli. Although in children it is often the consequence of primary infection, in adults it may be due to either recent infection or reactivation of old disseminated foci. The lesions are usually yellowish granulomas 1–2 mm in diameter that resemble millet seeds (thus the term *miliary*, coined by nineteenth-century pathologists). 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 symptoms due to pulmonary involvement as well as abdominal symptoms. Physical findings include hepatomegaly, splenomegaly, and lymphadenopathy. 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. 173-5) reveals a miliary reticulonodular pattern (more easily seen on underpenetrated film), although no radiographic abnormality may be evident early in the course and among HIV-infected patients. Other radiologic findings include large infiltrates, interstitial infiltrates (especially in HIV-infected patients), 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. Disseminated intravascular coagulation has been reported. Elevation of alkaline phosphatase levels and other abnormal values in 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 treatment, 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. Pancytopenia 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 chorioretinitis, 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 nodules, plaques, and fissures), miliary lesions, and erythema nodosum. Tuberculous mastitis 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 ingestion of contaminated amniotic fluid. This rare disease affects the liver, spleen, lymph nodes, and various other organs.

Post-TB Complications

TB may cause persisting pulmonary damage in patients whose infection has been considered cured on clinical grounds. Chronic impairment of lung functions, bronchiectasis, aspergillomas, and chronic pulmonary aspergillosis have been associated with TB. Chronic pulmonary aspergillosis may manifest as simple aspergilloma (fungal ball) or chronic cavitary aspergillosis. Early studies revealed that, especially 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 itraconazole 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

TB is one of the most common diseases among HIV-infected persons worldwide **(See also Chap. 197)**. Responsible for an estimated 20–25% of all HIV-related mortality (some 390,000 deaths per year), TB is likely the main cause of death in this population. In certain urban settings in some African countries, the prevalence of HIV infection among TB patients reaches 70–80%. 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 an HIV-infected individual 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 manner (Figs. 173-6 and 173-7), with upper-lobe infiltrates and cavitation and without significant lymphadenopathy or pleural effusion. In late stages of HIV infection, when the CD4+ T cell count is <200/μL, a primary TB–like pattern, with diffuse interstitial and subtle infiltrates, little or no cavitation, pleural effusion, and intrathoracic lymphadenopathy, is more common. However, these forms are becoming less common because of the expanded use of ART. Overall, sputum smears are less frequently positive among TB patients with HIV infection than among those without; thus, the diagnosis of TB with traditional technology may be difficult, especially in view of the variety of HIV-related pulmonary conditions mimicking TB. Extrapulmonary TB is common among HIV-infected patients. In various series, extrapulmonary TB—alone or in association with pulmonary disease—has been documented in 40–60% of all cases in HIV-co-infected individuals. The most common forms are lymphatic, disseminated, pleural, and pericardial. Mycobacteremia and meningitis are also common, particularly in advanced HIV disease. The diagnosis of TB in HIV-infected patients may be complicated not only by the increased frequency of sputum-smear negativity (up to 40% in culture-proven pulmonary cases) but also by atypical radiographic findings, a lack of classic granuloma formation in the late stages, and a negative TST. The Xpert MTB/RIF assay is the preferred initial diagnostic option, and 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. Recent assessment of a test based on the detection of mycobacterial lipoarabinomannan antigen in urine has shown favorable results in assisting with the detection of TB in HIV-positive people (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 (worsening of pulmonary infiltrations, pleural effusion) as well as laboratory or radiographic manifestations of TB. This syndrome has been associated with the administration of ART and occurs in ~10% of HIV-infected TB patients. Usually developing 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 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 mortality risk. The presumed pathogenesis of IRIS consists of an immune response that is elicited by antigens released as bacilli are killed during effective chemotherapy and that is temporally associated with improving immune function. There is no diagnostic test for IRIS, and its confirmation relies heavily 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 development of another infection. Mild paradoxical reactions can be managed with symptom-based treatment and do not worsen outcomes of treatment for TB. However, IRIS can result in serious neurologic complications or death in patients with central nervous system 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 performance 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 HIV-infected individuals are provided below.

DIAGNOSIS

The key to the early diagnosis of TB is a high index of suspicion. Diagnosis 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. 173-6). 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 conditions that cause immunosuppression, the chest radiograph may show typical upper-lobe infiltrates with cavitation (Fig. 173-6). 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 those with HIV infection, may have "atypical" findings on CXR—e.g., lower-zone infiltrates without cavity formation.

The several approaches to the diagnosis of TB require, above all, a well-organized 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, additional technology is necessary, including molecular tests, rapid culture, and DST.

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 preferred 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 specificity 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 first-line diagnostic test in all adults and children with signs or symptoms of active TB. Given the test's high sensitivity, the WHO also recommends its use as the initial diagnostic test for people living with HIV in whom TB is suspected. Likewise, Xpert MTB/RIF should be the initial test applied to CSF from patients in whom TB meningitis is suspected as well as a replacement test (preferable to conventional microscopy, culture, and histopathology) for selected nonrespiratory specimens—those obtained by gastric lavage, fine-needle aspiration, or pleural or other biopsies—from patients in whom extrapulmonary TB is suspected. This test has a sensitivity of 98% among AFB-positive cases and ~70% among AFB-negative specimens. Recently, the new Xpert® MTB/RIF Ultra assay (Ultra), which uses the same GeneXpert® diagnostic platform, has been assessed by the WHO as non-inferior to the Xpert MTB/RIF assay. Overall, its sensitivity is 5% higher, with the greatest increases among smear-negative, culture-positive cases (+17%) and among HIV-infected persons (+12%). However, because of this greater sensitivity, the new Ultra cartridge also detects nonviable bacilli and consequently has 3.2% lower specificity than the original test. In this new assay, "trace calls" (i.e., the "noise" produced by detection of nonviable bacilli or fragments of bacilli) need to be evaluated according to risk/benefit considerations. For instance, trace calls in specimens from HIV-infected patients, children, and persons with extrapulmonary TB should be considered true positives, given the high risk of severe morbidity and premature death, while among other cases they warrant additional tests to confirm the diagnosis of TB and prevent over-treatment. Among patients with a recent history of TB, trace calls may represent false positivity. Accuracy in detection of rifampin resistance by Ultra is similar to that by the Xpert MTB/RIF assay.

Another recently introduced molecular test for detection of *M. tuberculosis* is based on the loop-mediated isothermal amplification (LAMP) temperature-independent technology that amplifies DNA, is relatively simple to use, and is interpreted through a visual display. The new TB-LAMP assay (LoopampTM *M. tuberculosis* complex detection kit; Eiken Chemical Company, Japan) requires minimal laboratory infrastructure and has few biosafety requirements. 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 investigation of smear-negative specimens from adults with suspected pulmonary TB. The TB-LAMP assay should not replace rapid molecular tests that detect both TB and rifampin resistance, and its usefulness in HIV-infected people in whom TB is suspected remains unclear.

AFB MICROSCOPY

In many low- and middle-income settings, a presumptive diagnosis is still commonly based on the finding of AFB on microscopic examination of a diagnostic specimen, 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. The traditional method—light microscopy of specimens stained with Ziehl-Neelsen basic fuchsin dyes—is satisfactory, although time-consuming. 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 dark room. Less expensive light-emitting diode (LED) fluorescence microscopes are now recommended by the WHO as the microscopy tool of choice. They are as sensitive as—or more sensitive than—traditional fluorescence microscopes. 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 pulmonary 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 limited by the low numbers of c

ive results, or the presence of commensal mycobacteria, which can cause false-positive results.

MYCOBACTERIAL CULTURE

Definitive diagnosis depends on the isolation and identification of *M. tuberculosis* from a clinical specimen or the identification of specific DNA sequences in a nucleic acid amplification test. Commercial liquid-culture systems such as the mycobacterial growth indicator tube (MGIT) system (Becton Dickinson, Franklin Lakes, NJ) are recommended by the WHO as the reference standard for culture. The MGIT system uses a fluorescent compound sensitive to the presence of oxygen dissolved in the liquid medium. The appearance of fluorescence, detected by fluorometric 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 incubation 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, including *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 biochemical 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 high-pressure 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 in DST to at least rifampin for all initial isolates of *M. tuberculosis*, as rifampin resistance is an excellent proxy for MDR-TB. Susceptibility testing is particularly important if one or more risk factors for drug resistance are identified or if the patient either fails to respond to initial therapy or has a relapse after the completion of treatment (see "Treatment Failure and Relapse," below). In addition, expanded and rapid susceptibility testing for isoniazid and key second-line anti-TB drugs (especially 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 (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 *rpo*B) and isoniazid (such as those in *kat*G and *inh*A) 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 and Xpert MTB/RIF Ultra assays, which, as mentioned above, detect rifampin resistance, the most widely used tests are molecular line probe assays. 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 reveals the presence of *M. tuberculosis* as well as mutations in target resistance-gene regions. Given the rapidity and accuracy of commercially available line probe assays, the WHO recommends that they (rather than phenotypic culture-based tests) may be 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 culture-based testing 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 and the injectable drugs kanamycin, amikacin, and capreomycin. Therefore, second-line line probe assays (instead of phenotypic culture-based DST) are now recommended by the WHO as the initial test for rapid detection of resistance to the fluoroquinolones or the second-line injectable drugs in isolates from patients with confirmed RR-TB or MDR-TB. As with first-line line probe assays, these recommendations do not eliminate the need for conventional phenotypic, culture-based testing to identify resistance to other drugs and to monitor for the emergence of additional resistance. Finally, a few noncommercial, inexpensive culture and susceptibility testing methods (e.g., microscopically observed drug susceptibility, nitrate reductase, and colorimetric redox indicator assays) have been used in resource-limited settings. Their use is restricted to national reference laboratories with proven proficiency and adequate external quality control as an interim solution while genotypic or automated liquid-culture technology is introduced.

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 undergoing triage for respiratory symptoms. The presence of lesions suggestive of TB should prompt bacteriologic investigations in all cases, without exception. Although the "classic" picture is that of upper-lobe disease with infiltrates and cavities (Fig. 173-6), virtually any radiographic pattern—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 treatment of latent infection. CXR is also helpful as a screening test used preceding rapid molecular assays (Xpert MTB/RIF and line probe 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 running costs are lower, the imaging is of superior quality, and telemedicine assistance is available, including computer-aided detection and interpretation of findings. However, a recent systematic review of studies using computer-aided detection software that analyzes digital imaging for abnormalities compatible with TB concluded that the diagnostic accuracy of this technology is still limited.

CT (Fig. 173-7) may be useful in interpreting questionable findings on plain CXR and in diagnosing some forms of extrapulmonary TB (e.g., Pott's disease; Fig. 173-10). A recent study has shown the potential of positron emission tomography combined with CT for detection of subclinical disease that may be progressing toward full-blown TB in HIV-infected people. MRI is useful in the diagnosis of 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 carcinoma) undergo fiberoptic bronchoscopy with bronchial brushings and endobronchial or transbronchial biopsy of the lesion. Bronchoalveolar lavage of a lung segment containing an abnormality may also 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.

Invasive diagnostic procedures are indicated for patients with suspected 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 a good diagnostic yield in disseminated (miliary) TB, particularly in HIV-infected patients, who also have a high frequency of positive blood cultures. Xpert MTB/RIF should always be the initial diagnostic test in patients where 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 limited 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. 175)**. 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). HIV-infected patients with sputum culture–positive, 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 sensitivity (~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 HIV-infected persons with low CD4+ T cell counts. The lateral-flow urine lipoarabinomannan assay can be performed manually and read by eye. After a systematic review of the evidence, the WHO recommends that this assay be used to assist in the diagnosis of TB in HIV-positive adults who have signs and symptoms of TB and a CD4+ T cell count of ≤100 cells/μL or in HIV-positive patients who are seriously ill regardless of CD4+ T cell count or with an unknown CD4+ count. The WHO also recommends that this test not be used, pending information on recent promising technological test advances, for TB diagnosis or as a screening test for TB in any other patient categories.

SEROLOGIC AND OTHER DIAGNOSTIC TESTS FOR ACTIVE TB

A number of serologic tests based on detection of antibodies to a variety of mycobacterial antigens have been carefully assessed by the WHO and found not to be useful as diagnostic aids because of their low sensitivity and specificity and their poor reproducibility. In 2011, after a rigorous evaluation of these tests, the WHO issued a "negative" recommendation in order to prevent their abuse in the private sector of many resource-limited countries. Various methods aimed at detection of mycobacterial antigens in diagnostic specimens are being investigated but are limited at present by low sensitivity. Determinations of adenosine deaminase and IFN-γ levels in pleural fluid may be useful adjunctive tests in the diagnosis of pleural TB; their utility in the diagnosis of other forms of extrapulmonary TB (e.g., pericardial, peritoneal, and meningeal) is less clear.

DIAGNOSIS OF LATENT *M. TUBERCULOSIS* INFECTION

Two tests currently exist for identification of individuals with LTBI: the TST and IGRAs. Both of these tests have limitations, especially in settings or populations with high TB and/or HIV prevalence.

Tuberculin 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 interpretation, 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 LTBI. 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 LTBI and active disease. False-negative reactions are common in immunosuppressed patients and in those with overwhelming TB. False-positive reactions may be caused by infections with nontuberculous mycobacteria (Chap. 175) 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 considerations. For instance, true conversions are likely after BCG vaccination in a previously TST-negative person or in a close contact of an infectious patient.

IFN-γ Release Assays

Two in vitro assays that measure T cell release of IFN-γ in response to stimulation with the highly TB-specific RD1-encoded antigens ESAT-6 and CFP-10 were introduced in the early 2000s and are commercially available. The T-SPOT®. TB test (Oxford Immunotec, Oxford, United Kingdom) is an enzyme-linked immunospot assay, and the QuantiFERON®-TB Gold test (Qiagen GmbH, Hilden, Germany) is a whole-blood enzyme-linked immunosorbent assay for measurement of IFN-γ. The QuantiFERON®-TB Gold In-Tube assay, which facilitates blood collection and initial incubation, also contains another specific antigen, TB7.7. These tests likely measure the response of recirculating memory T cells—normally part of a reservoir in the spleen, bone marrow, and lymph nodes—to persisting bacilli producing antigenic signals.

In settings or population groups with low TB and HIV burdens, IGRAs have previously been reported to be more specific than the TST as a result of less cross-reactivity with BCG vaccination and sensitization by nontuberculous mycobacteria; i.e., RD1 antigens are not encoded in the genome of either BCG strains or most nontuberculous mycobacteria. Recent studies suggest that IGRAs may not perform well in serial testing (e.g., among health care workers) and that interpretation of results depends on cutoff values used to define positivity. Potential advantages of IGRAs include logistical convenience, the need for fewer patient visits 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 laboratory in a timely fashion. IGRAs also require that testing be performed by specially trained technicians in a laboratory setting. These requirements 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 LTBI diagnosis in low-incidence, high-income settings. However, in high-incidence TB and HIV settings and population groups, evidence about the performance and usefulness of IGRAs is still limited, and cost considerations may currently limit wider use.

A number of national guidelines on the use of IGRAs for LTBI 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 LTBI. However, for individuals at high risk of progression to active TB (e.g., HIV-infected persons), either test—or, to optimize sensitivity, both tests—may be used. Because of the paucity of data on the use of IGRAs in children, the TST is preferred for LTBI testing of children aged <5. In Canada and some European countries, a two-step approach for those with positive TSTs—i.e., an initial TST followed by an IGRA—is recommended. However, a TST may boost an IGRA response if the interval between the two tests exceeds 3 days.

In conclusion, both the TST and IGRAs, although useful as diagnostic aids, are imperfect tests for LTBI: while they can identify latently infected persons, they have low predictive value in identifying individuals with the highest risk of progression toward disease, cannot differentiate between active TB and LTBI, cannot distinguish new infections from reinfections, and display reduced sensitivity in immunocompromised patients.

TREATMENT

TREATMENT

TUBERCULOSIS

The two main aims of TB treatment are (1) to prevent morbidity and death by curing TB while preventing the emergence of drug resistance and (2) to interrupt transmission by rendering patients noninfectious to others. Chemotherapy for TB became possible with the discovery of streptomycin in 1943. Randomized clinical trials clearly indicated that the administration of streptomycin to patients with chronic TB reduced mortality rates and led to cure in the majority of cases. However, monotherapy with streptomycin was soon associated with the development of resistance to this drug and the resulting failure of treatment. With the introduction into clinical practice of para-aminosalicylic acid (PAS) and isoniazid, it became axiomatic in the early 1950s that cure of TB required the concomitant administration of at least two agents to which the organism was susceptible. Furthermore, early clinical trials demonstrated that a long period of treatment—i.e., 12–24 months—was required to prevent recurrence. The introduction of rifampin (rifampicin) in the early 1970s heralded the era of effective short-course chemotherapy, with a treatment duration of <12 months. The discovery that pyrazinamide, which was first used in the 1950s, augmented the potency of isoniazid/rifampin regimens led to the use of a 6-month course of this triple-drug regimen as standard therapy. Streptomycin was added as the fourth drug mainly to prevent the emergence of drug resistance. These four drugs (with streptomycin eventually replaced by ethambutol) still form the basis of the optimal treatment regimen for rifampin-susceptible TB. The emergence of drug-resistant TB in the 1990s prompted attempts to standardize the approach to treatment of this condition mainly on the basis of expert opinion. This event has also stimulated research on and development of new anti-TB agents in the past 15 years. In 2013 and 2014, respectively, bedaquiline and delamanid—the first two drugs specifically developed for TB during nearly half a century—received conditional approval by the U.S. Food and Drug Administration (FDA) and other drug-regulatory authorities; approval was based on the results of phase 2b clinical trials in which the drugs were added to the 18- to 24-month WHO-recommended regimen for MDR-TB. Bedaquiline and delamanid are being used increasingly for treatment of MDR-TB under specific conditions.

DRUGS

Four major drugs are considered first-line agents for the treatment of TB: isoniazid, rifampin, pyrazinamide, and ethambutol. Table 173-2 presents currently recommended dosages in adults and children. Some studies have suggested increased effectiveness when isoniazid, rifampin, and pyrazinamide are given at higher dosage; thus, if these findings are confirmed, dosages may be revised in the future. These drugs are well absorbed after oral administration, with peak serum levels at 2–4 h and nearly complete elimination within 24 h. Isoniazid and rifampin, two key anti-TB drugs, are recommended on the basis of their bactericidal activity (i.e., their ability to rapidly reduce the number of viable organisms and render patients noninfectious). All four agents are recommended in light of their sterilizing activity (i.e., their ability to sterilize the affected tissues, measured in terms of the ability to prevent relapses) and the lowered risk that drug-resistant mutant bacilli will be selected when the drugs are used in combination. Two additional rifamycins, rifapentine and rifabutin, are also available; however, their level of cross-resistance with rifampin is high. For a detailed discussion of the drugs used for the treatment of TB, see **Chap. 176**.

Because of a lower degree of effectiveness and tolerability, several classes of second-line drugs are generally used only for the treatment of patients with drug-resistant TB. These agents have previously 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. Group A drugs include three classes of oral agents: the fluoroquinolones levofloxacin and moxifloxacin; the oxazolidinone linezolid; and the recently introduced diarylquinoline bedaquiline, which was granted accelerated approval by the FDA in late 2012. 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 resistance levels worldwide are high and it is more toxic than the other drugs in the same class); ethionamide or prothionamide; and PAS. In addition, the first-line anti-TB drugs ethambutol and pyrazinamide (both included in Group C) as well as high-dose isoniazid (only for the shorter regimen; see below) are used for MDR-TB treatment. Information about drugs used in the treatment of drug-resistant TB (including dosages) can be found in the following WHO Handbook: http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf. Recent information from the phase 3 clinical trial of delamanid (a drug granted accelerated approval by the European Medicines Agency [EMA] in late 2013) added to an optimized longer WHO background regimen shows that treatment success is not different from that obtained with the addition of placebo. The future role of delamanid as a replacement drug in MDR-TB treatment remains to be assessed. The new classification scheme excludes the second-line injectable aminoglycoside kanamycin and the polypeptide capreomycin. Amithiozone, which has been associated with severe and at times fatal skin reactions—including Stevens-Johnson syndrome—among HIV-infected patients, is no longer recommended. Finally, amoxicillin–clavulanic acid is recommended only as an adjunct to carbapenems.

REGIMENS

Standard regimens are divided into an intensive (bactericidal) phase and a continuation (sterilizing) phase. During the intensive phase, the majority of tubercle bacilli are killed, symptoms resolve, and usually the patient becomes noninfectious. The continuation phase is required to eliminate persisting mycobacteria and prevent relapse.

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 isoniazid and rifampin **(Table 173-3)**. 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. Systematic reviews have demonstrated that the use of an intermittent thrice-weekly regimen in the intensive phase is associated with increased risk of treatment failure, relapse, and acquisition of drug resistance. Furthermore, a thrice-weekly regimen in the continuation phase only has also been associated with increased rates of failure and relapse, while a twice-weekly regimen in the continuation phase increased the risk of acquisition of drug resistance as well as rates of failure and relapse. Therefore, the WHO now recommends that TB treatment in all cases be administered daily. The 2016 guidelines by the ATS, the CDC, and the IDSA, while recommending daily administration of drugs, include a provision for use of intermittent thrice-weekly supervised regimens among patients who are not infected with HIV and are at low risk of relapse (i.e., have pulmonary TB caused by drug-susceptible organisms that, at the start of treatment, is noncavitary and/or sputum smear–negative). The same guidelines suggest that a 4-month regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol may be adequate for treatment of HIV-negative adults with sputum smear–negative and culture-negative pulmonary TB (i.e., paucibacillary TB).

A continuation phase of once-weekly rifapentine and isoniazid is effective in HIV-seronegative patients without cavitation on CXR. In general, however, this regimen should be used with great caution. Patients with cavitary pulmonary TB and delayed sputum-culture conversion (i.e., those who remain culture-positive at 2 months) should be re-tested immediately for drug-resistant TB, and a change of regimen should be considered. A full course of therapy should not include interruptions of >4 weeks. In some developing countries where the ability to ensure adherence to treatment is limited, a continuation-phase regimen of daily isoniazid and ethambutol for 6 months has been used in the past. This regimen is clearly associated with a higher rate of relapse, treatment failure, and death, especially among HIV-infected patients, and is no longer recommended by the WHO. Several studies attempting to reduce treatment duration to 4 months by using fluoroquinolones (with moxifloxacin replacing ethambutol or isoniazid, or gatifloxacin replacing ethambutol) were conducted over the last decade. The main finding was that shorter (4-month) fluoroquinolone-containing regimens are associated with significantly higher rates of relapse at 18 months than the standard 6-month rifampin-containing regimen. In addition, the studies showed no reduction in adverse events with the fluoroquinolone-containing regimen and no difference in all-cause and TB-related mortality rates. Therefore, shortening of the treatment duration to 4 months through the use of fluoroquinolones is not recommended. Alternative regimens for patients who exhibit drug intolerance or adverse reactions are listed in Table 173-3. 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 B_6

deficiency (e.g., alcoholics; 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).

PATIENT CARE AND SUPPORT

Poor adherence to treatment is one of the most important impediments 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 support; fear of the stigma and discrimination associated with TB; and poverty, with attendant joblessness and homelessness. Provider-related 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 people 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 people 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 allowances, 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.

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 communication 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 people 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 treatment administration that minimizes the chance of non-adherence. Such options traditionally include unsupervised, self-administered therapy; in-person directly observed therapy (DOT); and non-daily 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 treatment 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 with in-person DOT has shown similar outcomes. Video-observed therapy 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 pill box 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, provision of fixed-dose combination products that reduce the number of tablets the patient needs to swallow is recommended over separate drug formulations. Various fixed-dose combination products are available (e.g., isoniazid/rifampin, isoniazid/rifampin/pyrazinamide, and isoniazid/rifampin/pyrazinamide/ethambutol). Fixed-dose combinations increase patient satisfaction 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 management 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 organisms, AFB smear conversion may lag behind culture conversion as a r[illegible]opic 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 re-testing 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. 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, monitoring by AFB smear examination should be undertaken at 2, 5, and 6 months. Bacteriologic monitoring of patients with extrapulmonary 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 recommended because radiographic changes may lag behind bacteriologic response and are not highly sensitive. After the completion of treatment, 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 also be monitored for drug toxicity. The most common adverse reaction of significance among people 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 3-fold increase in serum levels of AST and/or ALT, and for patients without symptoms of hepatic injury who have marked (at least 5-fold) elevations in serum levels of AST and/or ALT. Drugs should be reintroduced one at a time after liver function has 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 regimens available, it usually is not necessary—although it is possible—to desensitize patients. Hyperuricemia and arthralgia caused by pyrazinamide can usually be managed by the administration of acetylsalicylic 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 generally 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 is also higher when second-line regimens are used.

TREATMENT FAILURE AND RELAPSE

As stated above, 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 re-tested (or tested for the first time if, for some reason, rapid molecular susceptibility testing was not performed at the start of treatment) for susceptibility to first-line agents and, if resistance to rifampin is detected, to second-line agents as well. The treatment approach should start with molecular testing for—at the least—resistance to rifampin and isoniazid. Since 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.

Patients who experience a recurrence after apparently successful 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 regimen. 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 empirical MDR-TB regimen that includes second-line agents (Table 173-3). Once drug susceptibility results are available, the regimen can be adjusted accordingly.

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 a[illegible]apy; or of the bioavailability of poor-quality 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 drug-resistant 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 resistance 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. As described above, MDR-TB is an increasingly serious problem in some regions, especially in the countries of the former Soviet Union and some countries of Asia (**Fig. 173-11**). Even more serious is the occurrence of MDR strains that are also resistant to additional second-line agents used in treatment. These include XDR-TB strains, which by definition are resistant to any of the fluoroquinolones and any second-line injectable agents. 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 complete 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 people with active TB followed by immediate initiation of treatment with an effective regimen.

Isoniazid-Resistant TB For the treatment of patients with isoniazid-resistant 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 diagnostic test to avoid inadvertent treatment of MDR-TB with an inadequate regimen. Ideally, a laboratory test for susceptibility should also be done 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 pyrazinamide. 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 in the presence of additional resistance (e.g., to pyrazinamide or ethambutol) or of drug intolerance.

RR-, MDR-, and XDR-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 the most potent first-line agents available and because associated resistance to other first-line drugs as well (e.g., ethambutol) is not uncommon. Treatment for RR-TB and MDR-TB has traditionally been a topic of much debate, given its complexity, long duration, toxicity, and limited efficacy; the cost of most second-line drugs; and the lack of randomized controlled clinical trials to support combinations. Until recently, recommendations were therefore based largely on low-quality evidence from observational studies and on best-practice consensus among experts. Recent developments, including the accrual of individual datasets for patients treated worldwide and the release of findings from two randomized controlled 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), resulted in a mid-2018 update of WHO guidance for the treatment of MDR-TB and all other RR-TB cases in which isoniazid resistance is absent or unknown. The recommendations were informed primarily by a meta-analysis of pooled data from the most recent studies. Based on this recent review and the subsequent revisiting of previous recommendations, two approaches are now recommended by the WHO: (1) a longer regimen of 18–20 months' duration consisting of an optimal combination of oral drugs chosen according to a rational approach derived from the latest information; and (2) in eligible patients, a shorter standardized regimen of 9–12 months' duration. While any recommendations are likely to change with new data that may become available in the near future, the longer regimen is currently the preferred choice as it is fully oral and has a lower likelihood of treatment failure or relapse, if completed as recommended, than the shorter regimen. However, patients need to be well informed and closely monitored, as drug intolerance and side effects remain major concerns and this regimen is twice as long as the shorter regimen, with a consequently greater risk of treatment interruption.

Longer MDR-TB Regimen In MDR/RR-TB patients, especially in those whose infecting strains have or are presumed to have additional resistance (e.g., resistance to the fluoroquinolones, the injectable drugs, or both [XDR-TB]) or who for some other reason do not qualify for a shorter regimen (see below), a longer regimen is recommended. **Table 173-4** shows the grouping of drugs now recommended by the WHO and the approach to the design of a longer regimen for both adults and children. The new regimen, composed as much as possible by all group A and group B agents, has important differences from previously recommended ones. The use of bedaquiline and linezolid is promoted, together with a fluoroquinolone (levofloxacin or moxifloxacin), whenever possible, in all patients. Clofazimine and cycloserine (group B) are the two preferred 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 (e.g., amikacin, streptomycin, and the carbapenems) are assigned a lower priority; the implication is that a fully oral regimen is the first-choice and most desirable option for most patients. Kanamycin and capreomycin have been removed from the list of potential drugs, both having been associated with higher risks of failure and relapse in the longer regimens in which they were used. A treatment course of at least 18–20 months is recommended, but duration may depend on the patient's response. Important considerations when treating MDR-TB patients include the safety and effectiveness of bedaquiline use beyond 6 months, which are currently unknown. This drug, when given in addition to an optimized MDR-TB regimen for the first 24 weeks, accelerated sputum conversion in phase 2B clinical trials. Likewise, the ideal duration of use of linezolid, which is known to be highly effective when administered for at least 6 months but also very frequently produces toxicity (e.g., peripheral and optic neuropathy, and bone marrow suppression), is unclear. Additional considerations concern the use of pyrazinamide and of the aminoglycosides amikacin and streptomycin, which is now restricted to cases with proven susceptibility to those agents. The role of delamanid in the treatment of MDR-TB remains to be assessed, although, as stated earlier, data from the phase 3 clinical trial of this agent as an addition to the longer regimen previously recommended by the WHO did not demonstrate a higher rate of treatment success than was obtained with the background regimen plus placebo. Furthermore, evidence on the safety and effectiveness of delamanid given for >6 months is presently incomplete. Information about the simultaneous use of

delamanid and bedaquiline remains insufficient for a recommendation; it is therefore prudent to limit the use of this combination to clinical trials or to situations in which no other option is available.

Shorter MDR-TB Regimen Results from the STREAM Stage 1 trial showed that, in eligible patients, the efficacy of the standardized 9- to 12-month regimen is similar to that of the previous WHO-recommended 18- to 24-month regimen. These findings are consistent with data from observational studies, although the risk of failure or relapse may be higher than that for longer regimens that include more potent drugs like bedaquiline and linezolid. Therefore, in the context of a program that is already using the standardized shorter MDR-TB regimen with good results and has all drugs available, and where there is capacity to monitor drug toxicity, a shorter standardized seven-drug MDR-TB regimen given for 9–12 months may still be offered to patients with MDR- or RR-TB. The criteria used to define eligible patients are listed in **Table 173-5**. Adults and children eligible for the shorter regimen may still be offered the option of a new longer regimen if their completion of the full duration is adequately supported; with the longer regimen, the likelihood of relapse-free cure could be increased, and its administration is fully oral. The recommended shorter regimen consists of 4–6 months of amikacin (replacing kanamycin), moxifloxacin, clofazimine, prothionamide (or ethionamide), pyrazinamide, high-dose isoniazid (10–15 mg/kg per day), and ethambutol followed by 5 months of moxifloxacin, clofazimine, pyrazinamide, and ethambutol. As with any anti-TB regimen, the risk of creating additional resistance is high if the regimen is used incorrectly. Furthermore, given the lack of evidence, variations made to the standardized shorter regimen by replacing any of the seven drugs (for instance, the injectable drug amikacin with bedaquiline or other oral agents) should not be undertaken except as part of a study.

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 fluoroquinolones) 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.

Patients with complex patterns of MDR-TB and those with XDR-TB (N.B., a definition that might change in the future, given the new WHO recommendations that have reduced the injectables to a secondary role in treatment) have fewer treatment options and a poorer prognosis. However, the new longer regimen offers more options for a reasonably effective and tolerable regimen. The design of regimens for complex patterns of MDR-TB follows the same principles outlined in Table 173-4 through the selection of agents likely to be effective and tolerated. Observational studies have shown that aggressive management of XDR-TB patients, with early drug susceptibility testing, use of a rational combination of at least five 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 disease and sufficient pulmonary reserve, lobectomy or wedge resection may be considered as part of treatment. A novel regimen composed of bedaquiline, the nitroimidazole compound pretomanid, and linezolid (BPaL) is being tested by the Global Alliance for TB Drug Development in South Africa in patients with XDR-TB as well as in patients with MDR-TB who are intolerant of therapy or in whom treatment has failed; the cure rate has been in the 85–90% range after a 6-month course of treatment. If the final results for the full patient cohort (available in mid-2019) confirm the current rate of treatment success, this promising regimen may become an important therapeutic option in the future. Another regimen being tested by the Global Alliance is composed of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (BPaMZ). In a phase 2B trial, MDR-TB patients became culture-negative within 8 weeks of treatment three times faster than drug-sensitive TB patients treated with the standard regimen. The BPaMZ regimen is now being tested for both MDR-TB and drug-susceptible TB, with the aim of reducing treatment duration to 6 months and 4 months, respectively. Results are expected in 2021.

Because the management of MDR- and other complex forms 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 community support. When patients are in stable condition, treatment and care on an ambulatory basis at a decentralized health care facility 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 are associated with significant reductions in mortality risk and AIDS-related events. Evidence from randomized controlled trials shows that early initiation of ART during anti-TB 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 immediately 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 within the first 8 weeks of anti-TB therapy; ART should be started within the first 2 weeks of TB treatment for profoundly immunosuppressed patients with CD4+ T cell counts of <50/μL. In general, the standard 6-month daily regimen is equally efficacious in HIV-negative and HIV-positive patients with drug-susceptible TB. However, in the uncommon situation where an HIV-infected patient cannot receive ART, prolongation of the continuation phase of TB treatment by 3 months can be considered. As in any other TB patient, intermittent regimens should not be used in HIV-infected people. As for any other adult living with HIV **(Chap. 197)**, first-line ART for TB patients consists of two nucleoside reverse transcriptase inhibitors plus a nonnucleoside reverse transcriptase inhibitor or an integrase inhibitor. Although TB treatment modalities are similar to those in HIV-negative patients, adverse drug reactions may be more pronounced in HIV-infected patients. In this regard, three important considerations are relevant: an increased f

ractions between ART components and rifamycins, and development 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 protease inhibitors and some nonnucleoside reverse transcriptase inhibitors—essential drugs used in ART. In such cases, rifabutin, which has much less enzyme-inducing activity, has been used in place of rifampin. However, dosage adjustments for rifabutin and protease inhibitors are still being assessed. Several clinical trials have found that patients with HIV-associated TB whose degree of immunosuppression 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 recommendations are frequently updated, consultation of the following websites is advised: *www.who.int/hiv*, *www.who.int/tb*, *www.cdc.gov/hiv*, and *www.cdc.gov/tb*.

SPECIAL CLINICAL SITUATIONS

Although comparative clinical trials of treatment for extrapulmonary TB are limited, the available evidence indicates that most forms of disease can be treated with the 6-month regimen recommended 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 American Academy of Pediatrics recommend that children with bone and joint TB, tuberculous meningitis, or miliary TB receive up to 12 months of treatment. Treatment for TB may be complicated by underlying medical problems that require special consideration. As a rule, patients with chronic renal failure should not 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 dosages of isoniazid and pyrazinamide should be reduced for all patients with severe renal failure except those undergoing hemodialysis. 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 by 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 173-3) is 9 months of treatment with isoniazid and rifampin supplemented by ethambutol for the first 2 months. Although the WHO has recommended 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 should also be avoided in the treatment of pregnant women with MDR-TB. Treatment for TB is not a contraindication to breast-feeding; 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 U.S. CDC Regional Training and Medical Consultation Centers (*www.cdc.gov/tb/education/rtmc/*).

TABLE 173-2

Recommended Dosage[a] for Initial Treatment of Tuberculosis in Adults and Children

Drug	Daily Dose	
	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[b]	15 mg/kg	20 (15–25) mg/kg

[a]The duration of treatment with individual drugs varies by regimen, as detailed in Table 173-3. [b]In certain settings, streptomycin (15 mg/kg daily, with a maximal dose of 1 g; or 25–30 mg/kg thrice weekly, with a maximal dose of 1.5 g) can replace ethambutol in the initial phase of treatment. However, streptomycin generally is no longer considered a first-line drug.

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.

TABLE 173-3

Recommended Antituberculosis Treatment Regimens

INDICATION	INITIAL PHASE		CONTINUATION PHASE	
	DURATION, MONTHS	DRUGS	DURATION, MONTHS	DRUGS
New smear- or culture-positive cases	2	HRZE[a,b]	4	HR[a,c]
New culture-negative cases	2	HRZE[a]	4	HR[a,d]
Pregnancy	2	HRE[e]	7	HR
Relapses and treatment default[f]	← Tailored according to rapid drug susceptibility testing →			
Failures[f]	← Tailored according to rapid drug susceptibility testing →			
Resistance (or intolerance) to H	Throughout (6)	RZEQ		
Resistance (or intolerance) to R	← Same as for MDR-TB; see below →			
MDR-TB (resistance to at least H + R)	← See Tables 173-4 and 173-5 →			
XDR-TB	← See Table 173-4 →			
Intolerance to Z	2	HRE	7	HR

[a]All drugs should be given daily. [b]Streptomycin was used in the past in place of ethambutol but is no longer considered a first-line drug. [c]A clinical trial showed that HIV-negative patients with noncavitary pulmonary tuberculosis who have negative sputum AFB smears after the initial phase of treatment can be given once-weekly rifapentine/isoniazid in the continuation phase. However, this regimen is rarely used. [d]The 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. [e]The 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. [f]The availability of rapid molecular methods to identify drug resistance allows initiation of a proper regimen at the start of treatment.

Abbreviations: E, ethambutol; H, isoniazid; MDR-TB, multidrug-resistant tuberculosis; Q, a quinolone antibiotic; R, rifampin; WHO, World Health Organization; XDR-TB, extensively drug-resistant tuberculosis; Z, pyrazinamide.

TABLE 173-4

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: Drugs to be prioritized and included in all regimens, unless they cannot be used	Levofloxacin *or* moxifloxacin Bedaquiline Linezolid
Group B: Drugs to be added in all regimens, unless they cannot be used	Clofazimine Cycloserine *or* terizidone
Group C: Drugs to be used to complete the regimen and when drugs from groups A and B cannot be used	Ethambutol Delamanid Pyrazinamide Imipenem-cilastatin *or* meropenem Amikacin (*or* streptomycin) Ethionamide *or* prothionamide *p*-Aminosalicylic acid

Source: Adapted from the World Health Organization, 2018.

Table 173-5

Criteria for Offering the Standardized Shorter Regimen to Patients with Confirmed Multidrug- or Rifampin-Resistant (MDR/RR) Tuberculosis

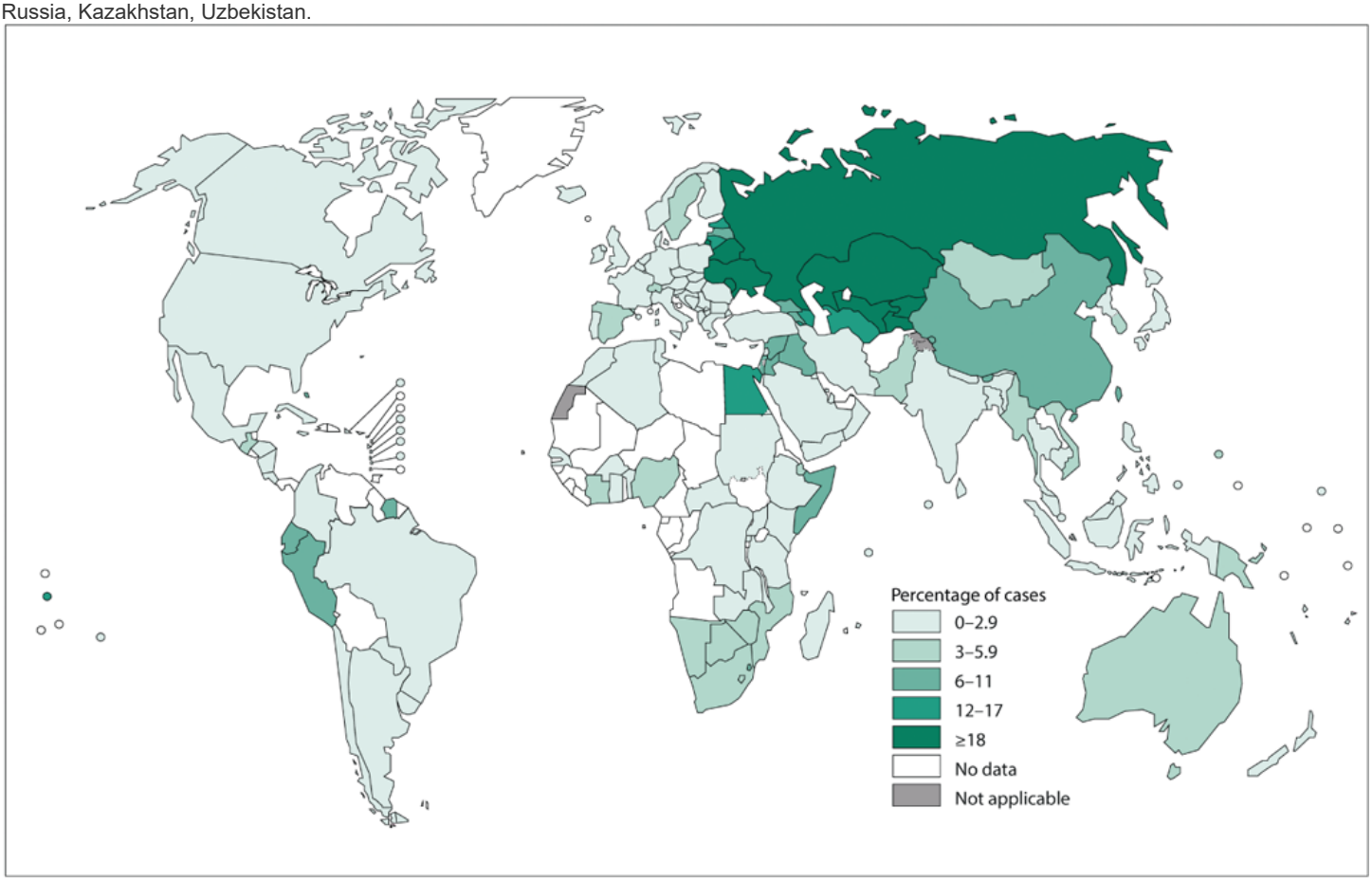
- Confirmed absence of resistance to or lack of suspicion of the ineffectiveness of a drug in the shorter MDR-TB regimen (except for isoniazid resistance)
- No history of exposure to one or more second-line drugs used in the shorter MDR-TB regimen for >1 month (unless susceptibility to these second-line drugs is confirmed)
- No intolerance to drugs in the shorter MDR-TB regimen or risk of toxicity (e.g., drug–drug interactions)
- No pregnancy
- No disseminated, meningeal, or central nervous system TB
- No evidence of extrapulmonary disease in a person with HIV infection
- Availability of all drugs in the shorter MDR-TB regimen

Source: Adapted from the World Health Organization, 2018.

FIGURE 173-11

Percentage of new cases of multidrug-resistant/rifampin-resistant TB in all countries surveyed by the World Health Organization (WHO) Global Drug Resistance Surveillance Project during 1994–2016. 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. 173-2. Courtesy of the Global TB Programme, WHO; with permission.)*

The percentage of new cases in various regions are as follows. 0 to 2.9: North and Latin Americas; most of South America excluding Peru, Ecuador, and Guyana; African countries including Morocco, Algeria, Ethiopia, Sudan, Kenya, Uganda, Tanzania, Democratic Republic of Congo, Central African Republic, and Madagascar; Western Europe; Saudi Arabia, Yemen, Oman, Mongolia, Japan, India, Bangladesh, Thailand, Cambodia, Malaysia, Singapore, Indonesia, Philippines, Micronesia. 3 to 5.9: Australia; countries in southern Africa; Pakistan, Myanmar, Vietnam. 6 to 11: Peru, Ecuador, Guyana; Somalia; Iraq, Syria, Lebanon, Israel, China. 12 to 17: Egypt; Turkmenistan. Greater than 18: Eastern Europe; Russia, Kazakhstan, Uzbekistan.



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 treatment of persons with LTBI who are at high risk of developing active disease.

BCG VACCINATION

BCG was derived from an attenuated strain of *M. bovis* and was first administered to humans in 1921. Many BCG vaccines are available worldwide; 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. 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 immunodeficiency 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 general 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.

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. The MVA-85A vaccine (a modified poxvirus-vectored vaccine that expresses the immune-dominant *M. tuberculosis* antigen 85A), developed at the University of Oxford, was the first new TB vaccine to be tested in a phase 2B proof-of-concept trial in infants in South Africa. The aim was to evaluate the efficacy of a new preventive TB vaccine candidate against clinical TB or *M. tuberculosis* infection. Results were published in early 2013: MVA-85A was well tolerated and modestly immunogenic but did not confer significant protection against clinical TB or *M. tuberculosis* infection.

As of late 2017, 12 candidate vaccines were in various stages of clinical trials. They included whole-cell or mycobacterial whole-cell or lysates, viral vector vaccines, and adjuvant recombinant protein vaccines. Several challenges must be faced in the development of a TB vaccine. For instance, the lack of predictive animal models and protection correlates renders trials long and expensive. Furthermore, the decision about whether a candidate vaccine should be developed for prevention of infection (pre-exposure) or prevention of reactivation (post-exposure) without an exact understanding of its precise mechanism of action is complex. Therefore, introduction of a new vaccine on a large scale is not likely in the near future. This step will require an intensified and much larger investment in research and development.

TREATMENT

TREATMENT

LATENT TUBERCULOSIS INFECTION

It is estimated that 1.7 billion people—more than one-quarter of the human population—have been infected with *M. tuberculosis.* Although only a small fraction of these infections will progress toward active disease in a lifetime, new active cases will continue to emerge from this pool of "latently" infected individuals. 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 individuals with LTBI will develop active TB. Therefore, latently infected individuals among persons in defined high-risk groups can only be presumably identified by TST or IGRA. 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). Multipuncture 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 reactions as TST converters. The cutoff for a positive TST (and thus for treatment) 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 173-6 suggests possible conventional cutoff by risk group. Thus, positive reactions for persons with HIV infection, recent close contacts of infectious cases, organ transplant recipients, previously untreated persons whose chest radiograph shows fibrotic lesions consistent with old 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.) A positive IGRA is based on the manufacturer's recommendations; however, good clinical practice requires that epidemiologic and clinical factors also guide the decision to implement treatment for LTBI and that active TB be definitively excluded before the initiation of chemoprophylaxis. The WHO recommends systematic testing for and treatment of LTBI for the following high-risk groups: people living with HIV, adult and child contacts of patients with infectious pulmonary TB, patients preparing for organ or hematologic transplantation, patients with silicosis, patients starting

anti-TNF treatment, and patients on dialysis. Systematic testing for and treatment of LTBI should also be considered for prisoners, health care workers, immigrants from countries with a high TB burden, homeless persons, and illicit drug users.

Some TST- and IGRA-negative individuals are also candidates for treatment. Once an appropriate clinical evaluation has excluded active TB, infants and children who have come into contact with infectious cases should be treated for presumed LTBI. HIV-infected persons who have been exposed to an infectious TB patient should receive treatment regardless of the TST result. Any HIV-infected candidate for LTBI treatment must be screened carefully to exclude active TB, which would necessitate full treatment. The use of a clinical algorithm based on four signs/symptoms (current cough, fever, weight loss, and night sweats) helps to define which HIV-infected person is a candidate for LTBI treatment. The absence of all four symptoms tends to exclude active TB. The presence of one of these four manifestations, on the other hand, warrants further investigation for active TB before treatment of LTBI is started. Although a TST is prudent, this test is not an absolute requirement—given the logistical challenges—among people living with HIV in high-TB-incidence and low-resource settings.

Among people living with HIV and receiving ART, conversion of the TST from negative to positive can occur during the first few months of treatment. 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.

Treatment of selected persons with LTBI aims at preventing active disease. Potential candidates for treatment of LTBI are listed in Table 173-6. This intervention (*preventive chemotherapy* or *chemoprophylaxis*) is based on the results of a large number of randomized, placebo-controlled clinical trials demonstrating that a 6- to 9-month course of isoniazid reduces the risk of active TB in infected people 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 persons with HIV infection. Studies in HIV-infected patients have also demonstrated the effectiveness of shorter courses of rifampin-based treatment. Several regimens (**Table 173-7**) can be used to treat LTBI. The most widely used is 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 is currently recommended by the WHO. Isoniazid can be administered intermittently (twice weekly) at a dose of 15 mg/kg (up to 900 mg) but only as DOT. An alternative regimen for adults is 3–4 months of daily rifampin. A 3- to 4-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. A previously recommended 2-month regimen of rifampin and pyrazinamide has been associated with serious or even fatal hepatotoxicity and is not recommended. The rifampin-containing regimens should be considered for persons who are likely to have been infected with an isoniazid-resistant strain. A clinical trial showed that a regimen of isoniazid (900 mg) and rifapentine (900 mg), given once weekly for 12 weeks, is as effective 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 higher (4.9 vs 3.7%).

Currently, the isoniazid–rifapentine regimen is not recommended for children <2 years of age or pregnant women. Rifampin and rifapentine are contraindicated in HIV-infected individuals receiving protease inhibitors and most nonnucleoside reverse transcriptase inhibitors. However, efavirenz can be used for simultaneous administration with a rifamycin. Clinical trials to assess the efficacy of long-term isoniazid administration (i.e., for at least 3 years) among people living with HIV 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. Isoniazid should not be given to persons with active liver disease. All isoniazid recipients at increased risk of hepatotoxicity (e.g., those abusing alcohol 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. Moreover, 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.

Treatment of LTBI among persons likely to have been infected by a multidrug-resistant strain is a challenge because no regimens have yet been tested in clinical trials. 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 immunosuppressive therapy), preventive therapy may be considered on the basis of individualized risk assessment and clinical criteria. In the absence of evidence of efficacy 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. Drug selection should be based on the drug susceptibility profile of the index case. Confirmation of infection with LTBI testing is required.

It may be more difficult to ensure compliance when treating persons with LTBI than when treating those with active TB. If family members of active cases are being treated, compliance and monitoring may be easier. When feasible, supervised therapy may increase the likelihood of completion. As in active cases, the provision of incentives may also be helpful. Currently, no evidence shows that LTBI treatment leads to significant development of drug resistance. However, before treatment of LTBI begins, it is mandatory to carefully exclude active TB in order to prevent the development of resistance.

TABLE 173-6

Tuberculin Reaction Size and Treatment of Latent *Mycobacterium tuberculosis* Infection

Risk Group	Tuberculin Reaction Size, mm
HIV-infected persons	≥5
Recent contacts of a patient with TB	≥5[a]
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 conditions[b]	≥5
Recent immigrants (≤5 years) from high-prevalence countries	≥10
Injection drug users	≥10
Mycobacteriology laboratory personnel; residents and employees of high-risk congregate settings[c]	≥10
Children <5 years of age; children and adolescents exposed to adults in high-risk categories	≥10
Low-risk persons[d]	≥15

[a]Tuberculin-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. [b]These conditions include silicosis and end-stage renal disease managed by hemodialysis. [c]These settings include correctional facilities, nursing homes, homeless shelters, and hospitals and other health care facilities. [d]Except 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: TB elimination—treatment options for latent tuberculosis infection (2011). Available at *http://www.cdc.gov/tb/publications/factsheets/testing/skintestresults.pdf.*

TABLE 173-7

Recommended Regimens and Drug Dosages for Treatment of Latent *Mycobacterium tuberculosis* Infection[a]

Regimen	Dose	Adverse Events
Isoniazid alone for 6 or 9 months	Adults: 5 mg/kg (max, 300 mg) per day Children: 10 mg/kg per day	Drug-induced liver injury, nausea, vomiting, abdominal pain, skin rash, peripheral neuropathy, dizziness, drowsiness, seizure
Rifampin alone for 3–4 months	Adults: 10 mg/kg per day Children: 10 mg/kg (max: <45 kg, 450 mg; >45 kg, 600 mg) per day	Flu-like syndrome, skin rash, drug-induced liver injury, anorexia, nausea, abdominal pain, neutropenia, thrombocytopenia, renal reactions (e.g., acute tubular necrosis and interstitial nephritis)
Isoniazid plus rifampin for 3–4 months	As above	As above
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, drug-induced liver injury Anorexia, nausea, abdominal pain Hypotensive reactions

[a]See text for full description of evidence on and limitations of these regimens.

Source: World Health Organization.

PRINCIPLES OF TB CONTROL

The highest priority in any TB control program is the prompt detection of cases and the provision of chemotherapy to all TB patients under proper case-management conditions, including DOT and social support. In addition, screening of high-risk groups, including immigrants from high-prevalence countries, migrant workers, prisoners, homeless individuals, substance abusers, and HIV-seropositive persons, is recommended. TST- or IGRA-positive high-risk persons should be treated for LTBI as described above. Contact investigation is an important component of efficient TB control. In the United States and other countries worldwide, a great deal of attention has been given to the transmission of TB (particularly in association with HIV infection) 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 (at least by sputum AFB smear negativity), proper ventilation in rooms of patients with infectious TB, use of ultraviolet irradiation in areas of increased risk of TB transmission, and periodic screening of personnel who may come into contact with known or unsuspected cases of TB. In the past, radiographic surveys, especially those conducted with portable equipment and miniature films, were advocated for case finding. Today, however, the prevalence of TB in industrialized countries is sufficiently low that “mass miniature radiography” is not cost-effective.

In high-prevalence countries, most TB control programs have made remarkable progress in reducing morbidity and mortality since the mid-1990s by adopting and implementing the standards and strategies internationally promoted by the WHO. Between 2000 and 2016, an estimated 52.5 million lives were saved. The essential elements of good TB care and control were established in the mid-1990s and consist of well-defined interventions that were the basis of the “DOTS strategy”: early detection of cases and bacteriologic confirmation of the diagnosis; administration of standardized short-course chemotherapy, with direct supervision to ensure adherence to treatment and the provision of 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—e.g., cure, completion of treatment without bacteriologic proof of cure, death, treatment failure, and default—in all cases registered and notified as well as measurement of the impact of control methods on classical TB indicators such as mortality, incidence, prevalence, and drug resistance. In 2006, the WHO indicated that, besides pursuing these essential elements that remain the fundamental components of any control strategy, additional steps had to be undertaken in order to reach international TB control targets. These steps included addressing HIV-associated TB and MDR-TB with additional measures; operating in harmony with general health services; engaging all care providers beyond the public providers; empowering people with TB and their communities; and enabling and promoting research. Evidence-based International Standards for Tuberculosis Care—focused on diagnosis, treatment, and public health responsibilities—were introduced for wide adoption by medical and professional societies, academic institutions, and all practitioners worldwide.

Care and control of HIV-associated TB are particularly challenging in poor countries because existing interventions require collaboration between HIV/AIDS and TB programs as well as standard services. TB programs must test every patient for HIV in order to provide access to trimethoprim-sulfamethoxazole [illegible] and ART. HIV/AIDS programs must regularly screen persons living with HIV/AIDS for active TB, provide treatment for LTBI, and ensure infection control in settings where people living with HIV congregate.

Early and active case detection is considered an important intervention not only among persons living with HIV/AIDS but also among other vulnerable populations, as it reduces transmission in a community and provides early effective care. Additional measures are indicated for the management of MDR-TB, RR-TB, and other forms of drug-resistant TB; they include upgrades of laboratory capacity to perform rapid DST and ensure surveillance of drug resistance; availability of drug regimens that are recommended for RR/MDR-TB, with assured quality of drugs; and infection control measures in all settings where patients with drug-resistant forms of TB may congregate. In the new era of the United Nations Sustainable Development Goals (2016–2030), the approach to TB control and care needs to evolve further and become multisectoral and more holistic. Engagement beyond dedicated programs and even the health sector is now essential. Therefore, the new "End TB" strategy promoted by WHO since 2016 builds on three pillars and relies on increased investments and efforts by all governments, their national programs, and a multitude 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. The first pillar incorporates all technological innovations, such as early diagnostic approaches (including universal DST and systematic screening of identified, setting-specific, high-risk groups); well-designed treatment regimens for all forms of TB; proper management of HIV-associated TB and other comorbidities; and preventive treatment of persons at high risk. The second pillar is fundamental and is normally beyond the scope of dedicated programs, relying on policies forged by the highest-level health and governmental authorities: availability of adequate human and financial resources; engagement of civil organizations and all relevant public and private providers to pursue proper care for all patients and prevention for all people at risk; a policy of universal health coverage (which, together with social protection, implies avoidance of catastrophic expenditures caused by TB among the poorest); regulatory frameworks for case notifications, vital registration, quality and rational use of medicines, and infection control; social protection mechanisms as part of poverty alleviation strategies; and promotion of interventions against the broader determinants of TB. Finally, the third pillar of the new strategy emphasizes intensification of research and development on new tools and interventions as well as optimal implementation and rapid adoption of new tools in endemic countries. Besides specific clinical care and control interventions 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, malnutrition, indoor air pollution) with clearly implemented policies within the health sector and other sectors linked to human development and welfare.

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