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249 *Mycobacterium tuberculosis*

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SHORT VIEW SUMMARY

Microbiology

- Humans are the only reservoir for *Mycobacterium tuberculosis.*
- The organism is an acid-fast, aerobic bacillus with a high cell wall content of high-molecular-weight lipids.
- Incomplete necrosis produces cheesy, acellular material (i.e., caseous necrosis).
- Pulmonary cavities contain huge numbers of organisms.

Epidemiology

- *M. tuberculosis* infects one-quarter of the world's population, with 10.4 million new cases reported each year.
- Almost all infections are due to inhalation of droplet nuclei.
- Key determinants of infection are closeness of contact and infectiousness of the source.
- The strongest risk factor for progression to active tuberculosis (TB) is acquired immunodeficiency syndrome (AIDS).
- The highest case rates are in countries heavily affected by human immunodeficiency virus (HIV)/AIDS.
- Drug resistance can be primary or secondary.
- Multidrug-resistant tuberculosis (MDR-TB) indicates resistance to both isoniazid (INH) and rifampin (RIF).
- Extensively drug-resistant tuberculosis (XDR-TB), which indicates resistance to INH, RIF, a fluoroquinolone, and a second-line injectable drug, is of immense concern.

Immunology and Pathogenesis

- Infection requires a cellular immune response.
- Airborne droplet nuclei reach the terminal air spaces, where they are ingested by alveolar macrophages and then carried by lymphatics to regional lymph nodes.
- Occult preallergic lymphohematogenous dissemination occurs to the lung apices and elsewhere.
- Granulomas form when antigen load is small and tissue hypersensitivity is high.
- Age influences likelihood and pattern of disease.
- TB in advanced AIDS is characterized by middle or lower lung field location, absence of cavitation, increased extrapulmonary disease, and a negative test for *M. tuberculosis* infection (e.g., tuberculin skin test or interferon-γ release assay).

Tuberculin Skin Testing and Interferon-γ Release Assays

- To detect *M. tuberculosis* infection, a positive tuberculin test is defined by induration. Interpretation depends on the diameter of induration.
- Interferon-γ release assays may be used instead of skin testing. They are more specific for *M. tuberculosis* than tuberculin skin testing. Results are positive, negative, or indeterminate. T-Spot results can also be borderline.
- Testing for *M. tuberculosis* latent infection is recommended for persons at high risk for developing TB if untreated.
- Test results (particularly the skin test) are negative in at least 20% of active TB cases.

Diagnosis

- Culture is the gold standard.
- Visible growth takes 3 to 8 weeks on solid media, and a mean of 10 days for smear-positive and 20 days for smear-negative specimens on liquid media.
- An estimated 10,000 organisms per milliliter are required for sputum smear positivity. Nucleic acid amplification testing (NAAT; e.g., Xpert MTB/RIF and Xpert MTB/RIF Ultra) have sensitivities and specificities that approach those of culture and can be completed in 1 day.
- The use of three sputum specimens increases sensitivity.
- A radiograph showing a patchy or nodular infiltrate in the lung apices is highly suggestive, especially if the infiltrate is cavitary.
- Pulmonary TB can occur in persons with normal chest radiographs, particularly in HIV-positive persons with advanced immunosuppression.

Therapy (see Tables 249.7 and 249.8)

- Multidrug regimens, typically starting with at least four active drugs, are recommended for initial treatment.
- At least 6 months of therapy is usually required.
- INH is the cornerstone of therapy; RIF, the second major antituberculous agent, causes many drug-drug interactions; 2 months of pyrazinamide is essential for 6-month regimens.
- Adjustment of doses of antiretroviral agents during treatment of TB with RIF and rifabutin is shown in Chapter 39, Tables 39.3 and 39.5. The time to initiate antiretroviral therapy during TB treatment is shown in Chapter 39, Table 39.2.
- Directly observed therapy is crucial.
- Susceptibility testing is important to guide therapy. NAAT and DNA sequencing are offering more rapid approaches to susceptibility testing.
- With appropriate chemotherapy, patients usually become noninfectious within 2 weeks.
- Treatment of XDR-TB is usually associated with poor outcomes.
- Bedaquiline is an approved drug for MDR-TB.

Therapy for Latent Infection

- Short-course regimens are replacing 9 months of INH for latent infection, particularly in low–TB incidence settings.
- Twelve weeks of directly observed, once-weekly INH plus rifapentine, and 4 months of daily rifampin, are as effective as 9 months of INH.

Prevention

- Case finding and treatment comprise the most effective method of control of TB.
- Hospitalized HIV-positive patients with respiratory symptoms should be admitted to negative-pressure isolation rooms. N95 masks are used for health care workers.
- Childhood bacillus Calmette-Guérin vaccination in high-burden countries decreases incident TB. Other vaccines are in clinical trial.

The term *tuberculosis* describes a broad range of clinical illnesses caused by *Mycobacterium tuberculosis* (or, less commonly, *Mycobacterium bovis*). Tuberculosis (TB) is the leading cause of death due to a single infectious agent worldwide, and ranks ninth among all causes of death. In 2014 the World Health Assembly embraced a resolution to reduce deaths from TB by 95% by the year 2035. In 2016 there were an estimated 10.4 million new cases of TB and 1.7 million deaths from TB worldwide.[1] TB can affect virtually every organ, most importantly the lungs, and is typically associated with granuloma formation.

HISTORY

There is evidence of spinal TB in Neolithic, pre-Columbian, and early Egyptian remains. However, TB did not become a major problem until the Industrial Revolution, when crowded living conditions favored its spread. In the 17th and 18th centuries, TB caused one-fourth of all adult deaths in Europe. Before antimicrobial agents became available, the cornerstone of treatment was rest in the open air in specialized sanatoria. Sanatorium regimens probably benefited some patients who were diagnosed before cavitation but had little impact on cavitary disease. When it became clear that cavitation was the pivotal event in progressive pulmonary TB, most special therapies focused on cavity closure.

The modern era of TB began in 1946 with demonstration of the efficacy of streptomycin (STM). In 1952, the availability of isoniazid (INH) made TB curable in most patients, and the addition of rifampin (RIF) in 1970 allowed for even more effective combination therapy. With drug coverage, it became possible to successfully resect tuberculous tissue, but with drug treatment, resection was rarely necessary. Bed rest and collapse therapy added nothing to chemotherapy; treated patients rapidly became noninfectious; and specialized sanatoria ultimately disappeared. The duration of chemotherapy progressively decreased from approximately 2 years before the availability of RIF, to 9 months with INH plus RIF, and to 6 months with multidrug therapy including INH, RIF, and pyrazinamide (PZA). With INH it also became practical to treat asymptomatic people believed to harbor tubercle bacilli based on positive tuberculin test results.

In the United States, reported cases of TB had declined nearly every year since accurate statistics became available. However, in 1985, case rates began increasing, driven largely by human immunodeficiency virus (HIV) infection. TB-control programs in some large cities were not equipped to manage this emerging problem. The often-interrelated factors of illicit drug use, homelessness, and HIV infection predispose to reactivation of remote TB, to the acquisition and spread of new disease, and, because of irregular adherence to drug therapy, to the development and spread of drug-resistant strains. Epidemics involving strains that were resistant to at least INH and RIF (i.e., multidrug-resistant [MDR] strains) emerged in these populations and spread to HIV-negative persons, including health care workers. Many outbreaks were caused by the Beijing strain, with "strain W" dominating in New York City. Estimates based on data from 2006 through 2008 suggest that 80% of cases in the United States are due to reactivation.[2]

Treatment programs failed because of drug resistance, medication nonadherence, and nosocomial transmission of *M. tuberculosis*. Since 1992, however, TB incidence rates in the United States have progressively declined and in 2016 reached the lowest in history.[3] This attests to the success that can be achieved with intensified diagnostic, treatment, and prevention efforts, and with control of HIV-induced immunocompromise by means of antiretroviral therapy (ART).

The global situation has, unfortunately, not been as successful. The HIV pandemic fueled increased TB case rates in resource-limited countries worldwide, especially in sub-Saharan Africa. Scant resources and fragile infrastructure, together with a high prevalence of HIV infection and acquired immunodeficiency syndrome (AIDS), have driven the global burden of TB. As in the United States, multidrug-resistant tuberculosis (MDR-TB) emerged and spread. In response, the World Health Organization (WHO) has worked diligently to expand TB treatment services, including directly observed therapy, short-course (DOTS) programs. In parallel, second-line medications, including fluoroquinolones, were made increasingly available worldwide. Since 2011, WHO has recommended that MDR-TB be treated using mainly ambulatory care, which appears to be more effective than hospitalization.[4]

With widespread use of second-line agents, selection for *M. tuberculosis* resistant to both first- and second-line drugs was inevitable. Extensively drug-resistant tuberculosis (XDR-TB), defined as resistance to at least INH, RIF, a fluoroquinolone, and a second-line injectable drug (kanamycin, capreomycin, amikacin), first occurred as early as 2001 in KwaZulu-Natal, South Africa,[5,6] and by 2016 it had been reported in at least 121 countries worldwide.[1] Although application of established TB public health principles, supported by ample funding, may ultimately control this dire situation,[7] the immensity of this challenge is daunting. There are added challenges in reaching vulnerable populations, including those who experience inequality, prejudice, marginalization, and limits on their social, economic, cultural, and other rights.[8]

MICROBIOLOGY

The *M. tuberculosis* complex comprises at least nine species in the genus *Mycobacterium,* family Mycobacteriaceae, and order Actinomycetales that are causes of human TB and zoonotic disease. The *M. tuberculosis* complex species share 99.9% sequence identity and likely evolved from a single clonal ancestor.[9] The species *M. tuberculosis* sensu stricto causes the vast majority of human TB worldwide. *Mycobacterium africanum* causes human TB in West Africa, where it accounts for up to 50% of cases.[10] *Mycobacterium canettii* is an extremely rare cause of human TB in the Horn of Eastern Africa. *M. bovis* causes disease in cattle and spreads to humans through animal contact and consumption of unpasteurized milk. An investigation of six TB cases in the United Kingdom demonstrated that *M. bovis* can be transmitted by aerosol from patients with pulmonary lesions.[11] *Mycobacterium caprae,* another cattle pathogen, *Mycobacterium microti,* a pathogen for rodents, and *Mycobacterium pinnipedii,* a pathogen for seals, have been reported to cause zoonotic TB in humans. *Mycobacterium orygis* (antelope) and *Mycobacterium mungi* (mongoose) have been described in animals but have not been reported in humans.

Advances in genetic analysis, including whole-genome sequencing (WGS), have shed new light on the phylogenetics of the *M. tuberculosis* complex.[12,13] These studies show that *M. tuberculosis* sensu stricto and *M. africanum,* the predominant causes of human disease, can be further divided into seven phylogenetic lineages, L1 to L7. This is a rapidly changing field of study, with multiple nomenclatures in use. For example, the L2 lineage is also called the East Asian lineage or the Beijing strain. There is some evidence that different lineages vary in virulence, host adaptation, transmissibility, or ability to acquire drug resistance, but further research is needed to clarify the clinical importance of such differences.

Humans are the only reservoir for the species *M. tuberculosis,* although many animals are susceptible to infection.[14] Some have postulated that an ancient ancestor of *M. tuberculosis* infected hominids in East Africa 3 million years ago and has since coevolved with its human host.[15] *M. tuberculosis* is an aerobic, non–spore-forming, nonmotile bacillus with a high cell wall content of high-molecular-weight lipids. Growth is slow, the generation time being 15 to 20 hours, compared with much less than 1 hour for most common bacterial pathogens, and visible growth takes from 3 to 8 weeks on solid media. The organism tends to grow in parallel groups, producing the colony characteristic of serpentine cording. In radical contrast to other bacteria, a very large portion of *M. tuberculosis* genes encode enzymes involved in lipogenesis and lipolysis.

A wide spectrum of laboratory techniques has been developed to diagnose active TB. No single test is perfect, and, unfortunately, some diagnostics on which clinicians still rely were developed over 100 years ago. Advantages and limitations of various methods are presented in Table 249.1.

Acid-Fast Staining

The term *acid-fast bacilli* (AFB) is practically synonymous with mycobacteria, although *Nocardia* and some other organisms are variably acid fast. In the Ziehl-Neelsen stain, a fixed smear covered with carbol-fuchsin is heated, rinsed, decolorized with acid-alcohol, and counterstained with methylene blue. The Kinyoun stain is modified to make heating unnecessary. The organisms appear as slightly bent, beaded rods 2 to 4 μm long and 0.2 to 5 μm wide. In sputum they often lie parallel, or

TABLE 249.1 Comparison of Assays Used in the Diagnosis of Active Tuberculosis

CLINICAL LABORATORY QUESTION	DIAGNOSTIC ASSAY	ADVANTAGES	LIMITATIONS
Are mycobacteria present in a clinical specimen?	Culture on solid media (Löwenstein-Jensen egg-based or Middlebrook agar-based media)	Gold standard for isolating *Mycobacterium tuberculosis*; detects 10–100 organisms/mL; shows colony morphology, detects mixed infection, allows quantification of growth; provides organisms for speciation, strain identification, susceptibility testing	Visible growth takes 3–8 wk
	Culture in liquid broth	Sensitivity and specificity similar to solid media; automated systems decrease workload; provides organisms for speciation, strain identification, and susceptibility testing; turn positive in a mean of 10 days for smear-positive and 20 days for smear-negative specimens	Does not show colony morphology, detect mixed cultures, or quantify growth
	Acid-fast stain (Ziehl-Neelsen, Kinyoun, auramine rhodamine)	Same-day results; simple technology; inexpensive light microscope; fluorescence microscope required for auramine-rhodamine stain	Less sensitive than culture, requiring 10,000 organisms/mL; cannot distinguish *M. tuberculosis* from other mycobacteria
	Nucleic acid amplification (e.g., PCR)	Same-day results; sensitivity intermediate between acid-fast stain and culture; identifies organisms as members of *M. tuberculosis* complex	Requires advanced laboratory techniques; cannot distinguish dead from viable organisms; culture still needed for speciation, strain identification, and susceptibility testing
	Nucleic acid amplification with GeneXpert MTB/RIF and Xpert MTB/RIF Ultra	Sensitivity of Xpert MTB/RIF roughly 100 CFUs/mL, requires 100 min, detects rifampin resistance mutations with sensitivity of 95% and specificity of 98% Xpert MTB/RIF Ultra is more sensitive than Xpert MTB/RIF but with slightly less specificity	Expensive equipment; detects dead bacilli; culture needed for other susceptibility testing
	Urinary antigen detection (e.g., ELISA for LAM)	Point-of-care testing; relatively high sensitivity in advanced untreated AIDS (<50 CD4 T cells/mm^3)	Sensitivity very low in situations other than advanced AIDS
Is a mycobacterium isolated from a clinical specimen a member of *M. tuberculosis* complex? (*M. tuberculosis, Mycobacterium bovis, M. bovis*–BCG, *Mycobacterium africanum, Mycobacterium microti,* or *Mycobacterium canettii*)	Nucleic acid amplification	(See above)	(See above)
	Nucleic acid probes	Results available in 2 h; sensitivity and specificity approach 100%; does not require amplification	Requires at least 10^5 organisms; most useful for pure culture, not directly on clinical specimen; cannot distinguish among members of *M. tuberculosis* complex
	BACTEC *p*-nitroacetyl-aminohydroxypropiophenone assay (NAP)	Provides preliminary identification of *M. tuberculosis* complex (NAP susceptible)	Need for paired cultures increases cost (growth with and without NAP)
	High-performance liquid chromatography (HPLC)	Same-day results; sensitivity and specificity approach 100%; can distinguish *M. bovis* BCG from other members of *M. tuberculosis* complex	Requires HPLC technology; only useful with pure culture
To which species of *M. tuberculosis* complex does a clinical isolate belong?	Colony morphology and biochemical assays (e.g., niacin test, heat-sensitive catalase, nitrate reduction, pyrazinamide monodrug resistance)	Classic approach for speciation of *M. tuberculosis*	Time-consuming and labor-intensive
	PCR genomic analysis	May rapidly distinguish among *M. tuberculosis* complex species	Not yet commercially available for this purpose
Do different *M. tuberculosis* isolates represent the same strain?	Genotyping by restriction fragment length polymorphism analysis, spoligotyping, mycobacterial interspersed repetitive unit analysis, and whole-genome sequencing	The CDC offers free strain typing through the National Tuberculosis Genotyping and Surveillance Network	Sophisticated assay available only at specialized centers
Is an *M. tuberculosis* isolate drug resistant?	Agar proportion method	Quantifies the proportion of organisms resistant to a drug	Requires as long as 8 wk
	Liquid BACTEC method	Results within 5–14 days	Does not quantify proportion of resistance
	Molecular line probe assays and whole-genome sequencing for chromosomal mutations associated with drug resistance (see above for GeneXpert MTB/RIF)	Allow same-day determination of drug resistance; line probe assay can be performed directly on smear positive sputum samples or culture isolates; can detect resistance to isoniazid, rifampin, quinolones, and second line injectibles	Need to be validated in multiple clinical settings and not yet FDA approved

AIDS, Acquired immunodeficiency syndrome; BCG, bacillus Calmette-Guérin; *CDC,* Centers for Disease Control and Prevention; CFU, colony-forming unit; *ELISA,* enzyme-linked immunosorbent assay; *FDA,* US Food and Drug Administration; *LAM,* lipopolysaccharide lipoarabinomannan; *PCR,* polymerase chain reaction.

two organisms adhere at one end to form a V. An estimated 10,000 organisms per milliliter of sputum are required for smear positivity, and detection of at least 10 organisms on a slide is optimal; a single organism on a slide is highly suggestive. The sensitivity of sputum acid-fast bacillus smear when compared with culture is approximately 60%.[16] Sensitivity is significantly lower with noncavitary disease and HIV infection. Sensitivity increases by approximately 10% with the collection of a second sputum sample, and 2% with a third.[17] Sputum processing with bleach and concentration before acid-fast staining also increases sensitivity.[18] Most laboratories in the United States now use a fluorochrome stain with phenolic auramine or auramine-rhodamine, a slightly modified acid-alcohol decolorization step, and potassium permanganate counterstaining. Because the mycobacteria are easily seen with a 20× or 40× low-magnification objective, fluorescence microscopy requires less technician time and may increase the sensitivity over conventional acid-fast bacillus smears.[19] Advances in ultrabright light-emitting diode (LED) microscopes make the technology more robust for use in resource-poor settings.[20] WHO recommends that LED microscopy replace conventional fluorescence microscopy and that it be phased in as an alternative for conventional Ziehl-Neelsen microscopy.[21] As with all laboratory procedures, strict quality control is needed for acid fast staining, or rates of false positives and negatives quickly rise.[22]

Any biologic fluid or material can be examined directly (e.g., pleural fluid, cerebrospinal fluid [CSF], urine, gastric lavage fluid), although thin fluids are best examined after sedimentation by centrifugation. Positive smears from concentrated gastric aspiration material are usually due to *M. tuberculosis* and are especially important in young children from whom sputum collection may not be possible.

Culture Methods for *Mycobacterium tuberculosis*

Culture is the gold standard for detecting mycobacteria in clinical specimens. Samples of sputum or tissue require initial decontamination to remove fast-growing nonmycobacterial organisms and liquefaction to allow access of decontaminants to nonmycobacterial organisms and media nutrients to surviving mycobacteria. Decontamination-liquefaction is most commonly done using *N*-acetyl-L-cysteine as a mucolytic in 1% sodium hydroxide solution. Mycobacteria are relatively protected during this procedure by a fatty acid–rich cell wall. However, normally sterile tissues or fluids such as CSF or pleural fluid should not be decontaminated, because some loss of mycobacterial viability does occur. The sample is then neutralized and centrifuged, and the sediment is inoculated onto media.

Three types of media may be used for culture of mycobacteria: solid egg-based media (e.g., Löwenstein-Jensen), solid agar-based media (e.g., Middlebrook 7H11), and liquid broth (e.g., Middlebrook 7H12). Media are made selective for mycobacteria by adding antibiotics. Nonselective media, on which growth is more rapid, are available. Growth is more rapid in 5% to 10% carbon dioxide. Liquid broth cultures require a mean of 10 days of incubation for smear-positive and 20 days for smear-negative specimens for detection of organisms, as compared with solid media, which require 3 to 8 weeks. However, solid media allow examination of colony morphology, detection of mixed cultures, and quantification of growth. Furthermore, occasional strains of mycobacteria may grow only on solid media. For these reasons, experts suggest using liquid and solid media in conjunction, with inoculation of at least one solid medium culture.[23]

Commercial automated liquid broth systems greatly facilitate mycobacterial culture. They monitor mycobacterial growth through detection of CO_2 production or O_2 consumption with radiometric, fluorometric, or colorimetric indicators. The BACTEC mycobacterial growth indicator tube (MGIT) system (Becton Dickinson Microbiology Systems, Sparks, MD), which detects growth in 1 to 3 weeks by means of a fluorometric method, is widely used.[24,25]

A noncommercial liquid broth assay was developed in which mycobacteria are cultured in liquid media on a multiwell plate and then examined microscopically for characteristic serpentine cording. The addition of antimicrobial agents to the media allows drug susceptibility testing to be performed simultaneously. This microscopic-observation drug-susceptibility (MODS) assay yields results in 7 to 10 days, with sensitivity and specificity similar to those of commercially available liquid broth systems.[26] Sensitivity is diminished (65.4%) when the source of diagnostic material is not sputum (lymph node sampling).[27] An automated MODS (Auto-MODS) has been compared with conventional culture in Thailand. With 95.5% sensitivity and 97.1% specificity and a time to culture positivity of 10 days (interquartile range, 8–13 days), this test appears to be effective and attractive in resource-limited settings.[28] In addition, a commercial kit (the Hardy TB MODS Kit; Hardy Diagnostics, Santa Maria, CA) now provides results comparable to those of the conventional MODS, with the ability to detect INH and RIF resistance in a Biosafety Level 2 setting and 97.9% concordance with indirect proportion susceptibility testing.[29]

Nucleic Acid Amplification

Nucleic acid amplification testing (NAAT) offers another technique for the direct detection of *M. tuberculosis* in clinical specimens. The Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA) is a US Food and Drug Administration (FDA)–approved automated molecular test for detection of *M. tuberculosis* with sensitivity and specificity that approach those of culture.[30] The test is simple to perform and gives results in 100 minutes. It uses real-time polymerase chain reaction (PCR) amplification of an *M. tuberculosis* gene for detection. GeneXpert MTB/RIF assay had an overall sensitivity of 89% and specificity of 99% for detection of *M. tuberculosis* in sputum samples compared with gold standard culture testing. Sensitivity was 98% for smear- and culture-positive cases and 67% for smear-negative culture-positive cases.[31] Analysis of three sputum samples further increases sensitivity.[32] These initial reports continue to be modified under the influence of factors such as prevalence of disease, prevalence of HIV coinfection, and variable performance on smear-positive and smear-negative samples.[33,34] The GeneXpert MTB/RIF simultaneously detects RIF resistance (see "Drug Susceptibility Testing" later).

The Xpert MTB/RIF assay has also been used on nonrespiratory samples (e.g., pleural fluid, CSF, peritoneal fluid, urine, fine-needle aspirates), but the performance in nonrespiratory specimens varies by population, TB prevalence, and type of fluid sampled. Detection in pleural fluid in a report from India revealed a sensitivity of only 54.8%.[35]

The assay has been endorsed by WHO and is rapidly being deployed to countries with high rates of endemic TB. A pooled testing strategy, which might ameliorate some of the cost burden, has been reported with encouraging results.[36] With increased use, the examination of the clinical utility now extends to the test's impact on mortality, and in South Africa no reduction associated with the use of the Xpert MTB/RIF was found compared with microscopy.[37] FDA approval has been extended to an indication for use of the test in removing patients from airborne isolation after one or two negative test results.[38] A single-institution analysis of 207 airborne-isolation cases found that the efficiency (time to result and sensitivity) was greatest with a two-test strategy, and a one-test strategy missed one case.[39] A multisite (Burkino Faso, Cambodia, Cameroon, and Vietnam) assessment comparing Xpert MTB/RIF testing of nasopharyngeal aspirates and stool versus culture in HIV-infected children younger than 13 years yielded a sensitivity on all samples of 79.3% and 75.8%, respectively, on the alternative sources.[40]

The confounding issue of detection of residual DNA not representative of replication-competent bacteria has been addressed in South Africa, where patients with re-treatment cases were significantly more likely to have false-positive results (14%) than those with newly diagnosed cases.[41]

A new version, the Xpert MTB/RIF Ultra assay (Cepheid, Sunnyvale, CA) has been developed. Initial studies suggest that it improves sensitivity by approximately 15% in smear negative-culture positive pulmonary TB; however, there is a small decrease in specificity from 99% to 98%.[42,43] The newer Xpert MTB/RIF Ultra assay may also improve sensitivity in nonrespiratory samples. In a study in Uganda of 129 HIV-infected patients with suspected meningitis, the Xpert MTB/RIF Ultra had a sensitivity of 70% versus a clinical case definition of tuberculous meningitis compared with a sensitivity of 43% for BACTEC culture and 43% for the older Xpert MTB/RIF.[44] WHO has recommended that the Xpert Ultra assay be adopted in settings with high rates of HIV and

TB such as sub-Saharan Africa. Given the lower specificity, there may be more false-positive results in low-HIV and low-TB settings.[45]

Another commercially available and FDA-approved NAAT assay that can be used directly on respiratory samples is the Amplified *M. tuberculosis* Direct (MTD) test (Hologic, San Diego, CA). The sensitivity is intermediate between acid-fast staining and culture. For smear-positive specimens, the sensitivity is 98% and the specificity is 99%. For smear-negative cases, sensitivity ranges from 60% to 80% and the specificity remains 99%.[46–48]

A number of other NAAT tests use novel technologies but are not FDA approved.[49] The COBAS TaqMan MTB assay (Roche Molecular Diagnostics, Pleasanton, CA) is a real-time PCR test that targets *M. tuberculosis* ribosomal RNA. The loop-mediated isothermal amplification assay (TB-LAMP; Eiken Chemical Company, Tokyo, Japan) does not require a thermal cycler or other sophisticated laboratory equipment. It can be performed manually in less than 1 hour, with results read with the naked eye.

Nucleic acid amplification testing complements but does not replace clinical judgment, acid-fast smear, and culture in the diagnosis of TB.[50] In sputum acid-fast smear-positive individuals, positive nucleic acid amplification indicates the presence of *M. tuberculosis* complex and confirms active TB. When there is a high clinical index of suspicion for pulmonary TB but with a negative acid-fast smear, a positive NAAT result is highly predictive of TB and allows early initiation of therapy. NAAT assays perform less well when the clinical index of suspicion for TB is low, in which case the frequency of false-positive tests may approach that of true positives.[51]

Detection of Mycobacterial Antigens in Urine

Detection of *M. tuberculosis* antigens in urine may have some usefulness in diagnosing TB in patients with advanced AIDS, particularly in countries where coinfection is highly prevalent. The Alere Determine lateral flow urine lipoarabinomannan (LF-LAM) assay (Abbott, Abbott Park, IL) is a commercially available point-of-care test for the diagnosis of active TB.[52] In a review of 12 studies of the LF-LAM test for TB diagnosis in HIV-infected patients, the pooled sensitivity was 45% and the specificity was 92%.[53] The combination of microscopy and urinary LAM testing provides incremental diagnostic sensitivity in HIV-infected adults. Sensitivity for TB in HIV-uninfected persons is less than 25%.

Speciation of Mycobacteria

Once mycobacteria have been identified in a clinical specimen, speciation is necessary for clinical diagnosis and epidemiologic investigation. For example, speciation may be important in immunocompromised patients at risk for nontuberculous mycobacterial infection, in localities where *M. bovis* transmission from animals to humans is possible, or in bladder cancer patients receiving bacillus Calmette-Guérin (BCG) immune stimulatory therapy. Speciation generally involves two steps: First, mycobacteria are identified as members of the *M. tuberculosis* complex (e.g., *M. tuberculosis, M. bovis, M. africanum*) or as *Mycobacterium* species other than tuberculosis (MOTT). Subsequently, if necessary, mycobacteria can be speciated within the *M. tuberculosis* complex. NAAT assays, growth in selective antibiotic media, nucleic acid probes, and high-performance liquid chromatography are all used to place mycobacteria within the *M. tuberculosis* complex.[54] Each has advantages and limitations that are detailed in Table 249.1. Identifying individual species within the *M. tuberculosis* complex is more challenging. *M. tuberculosis* grows slowly, lacks pigment, produces niacin, reduces nitrates, has weak catalase activity that is lost by heating to 68°C at pH 7.0, does not demonstrate monodrug resistance to PZA, is resistant to thiophen-2-carboxylic acid hydrazide, and prefers aerophilic conditions. Other members of the complex show different patterns with these tests. Next-generation sequencing technology is rapidly making WGS of clinical isolates routine and also enables identification of species within the *M. tuberculosis* complex.[55]

Genotyping of *Mycobacterium tuberculosis*

Characterizing the particular strain of *M. tuberculosis* is important for epidemiologic purposes, such as tracing transmission from person to person, distinguishing exogenous reinfection from endogenous reactivation in cases of recurrent TB, and identifying laboratory cross-contamination of cultures. The Centers for Disease Control and Prevention (CDC) offers free strain typing through the National Tuberculosis Genotyping Service based on four typing methods: restriction fragment length polymorphism (RFLP) analysis, spacer oligonucleotide typing (spoligotyping), mycobacterial interspersed repetitive unit (MIRU) analysis, and WGS.[56] In RFLP analysis, DNA cleavage fragments generated using *pvuII* are separated by means of electrophoresis and visualized with use of a probe to a repetitive DNA sequence, insertion sequence (IS) *6110.* Because numerous copies of IS*6110* are present at variable chromosomal locations in most *M. tuberculosis* isolates, identical RFLP patterns represent the same strain. Spoligotyping detects variability in the direct repeat (DR) region in *M. tuberculosis* genome. There are direct repeats of a conserved 36-bp sequence, separated by multiple spacer sequences. Different *M. tuberculosis* strains are distinguished by the presence or absence of 43 unique spacers. Each possible combination of spacers is designated by a unique numeric code that identifies a unique spoligotype strain. In MIRU analysis, 12 different DNA sequences, each of which can be tandemly repeated in the *M. tuberculosis* genome, are analyzed. The number of tandem repeats for each of the 12 sequences (or loci) is determined by means of PCR to create a 12-number code. Each code corresponds to a unique MIRU strain.

WGS of clinical isolates is rapidly supplanting prior typing technology. In the United States, many state public health laboratories and the National TB Molecular Surveillance Center routinely perform WGS on isolates from every TB case. Many other countries are developing similar systems. WGS provides data on species, strain type, and drug susceptibility (see later). The WGS bioinformatics pipeline and reporting system are being standardized, and clinicians should anticipate WGS reports on every culture-positive TB case in the near future.[57]

Drug Susceptibility Testing

Testing of *M. tuberculosis* isolates for drug susceptibility is important to guide therapy. There are two broad methods to test an *M. tuberculosis* isolate's drug susceptibility: phenotypic testing, which relies on culturing *M. tuberculosis* in media with varying concentrations of antibiotics, and genotypic testing, which correlates specific mutations in the isolate's genome with known drug susceptibility patterns.

In the United States, the agar proportion method is most commonly used to determine phenotypic drug resistance. The absolute concentration method and resistance ratio method are used less commonly. The agar proportion method compares growth of appropriately diluted inocula on drug-containing media versus growth on drug-free media and is reported as proportion resistant. For most drugs, resistance is significant when growth on drug-containing media exceeds 1% of control; 6% to 10% resistance or more indicates that the drug will add nothing to multidrug therapy. Liquid broth systems, such as BACTEC, can also be used and provide results in 5 to 14 days, but they do not give the proportion of resistant organisms.[58,59]

As noted earlier, the MODS method shows promise as an inexpensive and rapid method for culture and drug susceptibility testing.[26]

Molecular testing to detect *M. tuberculosis* chromosomal mutations associated with mycobacterial drug resistance is an exciting development.[32,60–63] Most commonly used are tests for RIF resistance, which predicts poor treatment outcomes and is a surrogate marker for MDR-TB. Assays detect mutations in the 81-base-pair *rpoB* gene, which encodes the β-subunit of RNA polymerase and correlates with greater than 96% of RIF resistance. Resistance to INH is more complex and is encoded by multiple genes, including the catalase peroxidase gene *katG,* the *inhA* gene involved in fatty acid biosynthesis, the *ahpC* gene, the *oxyR* gene, and the *kasA* gene.[64] Mutations associated with resistance to PZA, ethambutol (EMB), second-line injectable drugs, and fluoroquinolones have also been identified.

The GeneXpert MTB/RIF assay detects mutations in the *rpoB* gene and has a sensitivity of 95% and specificity of 98% for detection of RIF resistance in respiratory samples that are RIF resistant with culture techniques. However, use of the test in populations with high rates of HIV infection and drug resistance, such as in Swaziland, revealed that the test failed to detect a high-prevalence rpoBI491F outbreak strain.

This RIF-resistance–conferring mutation was present in 30% of MDR strains.[65] The drug-resistance assay is performed on sputum simultaneously with detection of organisms, and results are available within 2 hours. Three line probe assays are also commercially available: the INNO-LiPA Rif. TB kit (Innogenetics, Zwijndrecht, Belgium), which detects resistance to RIF in culture isolates; the Genotype MTBDRplus assay (version 2.0) (Hain Lifescience, Nehren, Germany), which detects resistance to INH and RIF in culture isolates and smear-positive sputum samples, and thereby can enable identification of MDR-TB; and the Genotype MTBDRsl assay (Hain Lifescience), which detects resistance to fluoroquinolones and second-line injectable drugs in culture isolates and smear-positive sputum samples and thereby can be used to identify XDR-TB.[66–69] WHO has recommended widespread use of these molecular assays.[70] The clinical impact of rapid diagnosis and drug-resistance detection has been reported from Tbilisi, Georgia, where the MTBDRplus assay was associated with selection of drug regimens that provided higher and more rapid rates of culture conversion at 24 weeks.[71]

WGS is also becoming a powerful tool for the detection of drug-resistance mutations in the *M. tuberculosis* genome.[72,73] Currently it can be performed only on culture isolates, and the bioinformatics pipelines, databases cataloguing drug-resistance mutations, and reporting systems are being standardized for routine clinical use.

EPIDEMIOLOGY

General Considerations

M. tuberculosis infects 1.7 billion people or approximately one-quarter of the world's population and caused 10.4 million new cases of TB and approximately 1.7 million deaths in 2016.[1,74,75] TB is the leading cause of death worldwide resulting from a single infectious agent, ranking above HIV since 2014.[76] Immunocompromise due to HIV infection is a risk factor for TB, and 374,000 TB deaths are in HIV-infected individuals. Drug-resistant TB is emerging globally, with approximately 490,000 new MDR-TB cases in 2016. Two factors essential for the rapid spread of *M. tuberculosis* are crowded living conditions and a population with little native resistance. In the 19th century, TB caused more than one-fourth of all adult deaths in Europe, eliminating those with the least native resistance. A downward trend had been established before the turn of the 20th century. Epidemiologists once believed the disease would eventually disappear based on the assumptions that 1 in 20 infections result in active cavitary disease of the lung (i.e., become contagious). Thus, each cavitary case would have to infect 20 persons for case rates to be maintained.[77] In Holland in the early 1900s, one infectious case produced only 13 new infections.[77] The annual decrement in mortality and morbidity from TB was approximately 5% in developed countries owing to progressively higher natural residual resistance in those who survived infection and to living conditions less conducive to airborne spread. This rate of decline approximately doubled after chemotherapy became widespread.

In the 1980s and 1990s, the high incidence of TB in Africa, Asia, Eastern Europe, and South America, the HIV coepidemic, and burgeoning MDR-TB demonstrated that predictions of the disappearance of TB were premature, and WHO declared TB a global public health emergency. Since then, tremendous gains have been made in reducing the number of new TB cases, now in decline for the past several years. The integration of multiple modalities, such as genotyping combined with a series of spatial analysis tools, might improve the efficiency of targeted transmission control.[78]

Recent Morbidity and Mortality Trends

In the United States, the incidence of TB has decreased steadily over the past 25 years, from 10.5 reported cases per 100,000 population in 1992 to 2.8 cases per 100,000 population in 2017, the lowest in recorded history.[2,79] Recent estimates of latent infection in the United States suggest a prevalence of latent infection in 2011–12 of 4.4% by the tuberculin skin test (TST) and 4.8% by the QuantiFERON-TB Gold In-Tube test (QFT-GIT; Cellestis Limited, Carnegie, Victoria, Australia).[80] In the United States the TB rate in foreign-born persons is 15 times higher than in US-born persons, and foreign-born persons now account for almost 70% of reported cases in the United States (Fig. 249.1).[79] This reflects increased immigration from high-prevalence countries, especially

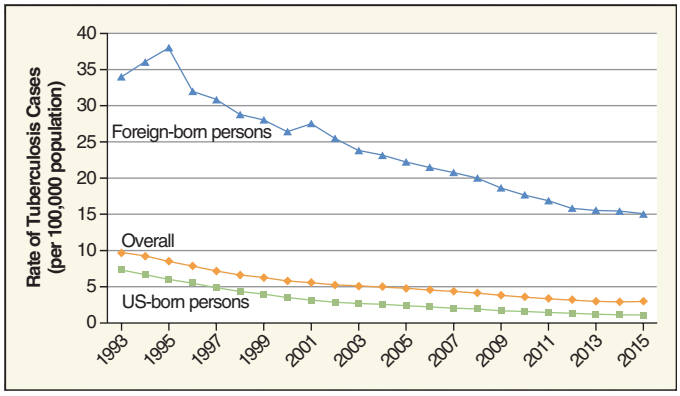

FIG. 249.1 Rates of tuberculosis cases among US-born versus foreign-born persons, United States, 1993–2015. *(Modified from Tuberculosis in the United States: National Tuberculosis Surveillance System highlights from 2015. Slide 17.* https://www.cdc.gov/tb/statistics/surv/surv2015/default.htm.*)*

Mexico, the Philippines, India, Vietnam, and China, from which immigrants account for more than half of the TB cases in foreign-born individuals.[81] Strain genotyping suggests that TB among foreign-born persons is from reactivation of latent infection acquired before arrival in the United States. Furthermore, the risk declines with duration of residency, also suggesting that most infections were acquired before immigration.[82] Screening of immigrants to the United States with a culture-based, rather than a smear-based, algorithm is justified by the high rate (54.4%) of smear-negative and culture-positive cases.[83]

TB has also become concentrated in certain ethnic and racial minorities and medically underserved populations, often occurring in contact-based microepidemics. In 2017, rates among US-born blacks was seven times higher than in non-Hispanic US-born whites; the rate in Native Americans was nine times higher than in whites.[79] A number of outbreaks have affected the urban poor, alcoholics, injection drug users, the homeless, migrant farm workers, and prison inmates.

The age distribution of TB reflects the degree of ongoing transmission in a given population. Disease in the elderly is generally due to reactivation of infection acquired in the remote past, whereas TB in young children indicates ongoing active transmission in the community. In this regard, 75% of childhood cases in the United States occurred in patients who had TB exposure through foreign-born parents or prior residence outside the United States.[84,85]

TB in the United States is most frequent in geographic regions and demographic groups where AIDS is prevalent, notably in urban blacks and Hispanics between 25 and 45 years of age.[86] Persons with active TB are more frequently HIV positive than is the general population. Approximately 8% of all TB cases in the United States occur in HIV-infected persons.[3]

Despite a predominantly urban epidemiology, large TB outbreaks have also affected small communities.[87,88] One well-characterized outbreak began in 1988 in a coastal Maine village where TB had not been reported in the previous 3 years.[88] A shipyard worker with cavitary TB was the source of 21 subsequent active cases and 697 new tuberculous infections. In retrospect, the source patient had repeatedly sought medical attention for cough, sore throat, and hoarseness during 8 months before TB was diagnosed and treated. This report highlights the need for vigilance regarding all segments of the population, not just those known to have high TB case rates.

The prevalence of positive TST results in US Navy recruits offers insights into trends of latent tuberculosis infection (LTBI) over time and risk factors for infection. From 1958 through 1969, more than 1 million US Navy recruits underwent TSTs, and in 5.2% the results were positive. In the 1980s and 1990s, the rate of tuberculin reactivity dropped to approximately 1.5% of new Navy recruits. The prevalence was greater in blacks (5%), Hispanics (5%), and Asian/Pacific Islanders (26%) than in whites (0.8%). Tuberculin positivity was more than 10-fold more prevalent among foreign-born recruits.[89–91] In a survey

TABLE 249.2 Reported Tuberculosis Case Rates in Immigrants According to Country of Birth: Stratified by Time Since Entry Into the United States

COUNTRY	CRUDE RATE (PER 100,000 PERSON-YEARS)[a] US ENTRY ≤2 YEARS	US ENTRY >2 YEARS
Somalia	889	179
Ethiopia and Eritrea	562	82
Vietnam	319	47
Cambodia	307	65
Philippines	283	38
Ecuador	194	31
Haiti	189	40
Honduras	177	28
Peru	159	32
Guatemala	111	21
India	106	33
China	74	26
El Salvador	73	11
Mexico	52	14
Korea	40	19
All foreign-born individuals	75	16

[a]Data provided for the 15 most commonly reported countries of birth.
Modified from Cain KP, Benoit SR, Winston CA, et al. Tuberculosis among foreign born persons in the United States. JAMA. *2008;300;405–412.*

TABLE 249.3 Estimated Incidence of Tuberculosis Cases in Countries That Accounted for 75% of Cases Worldwide, 2016

COUNTRY	CASES	RATE PER 100,000 POPULATION
India	2,790,000	211
Indonesia	1,020,000	391
China	895,000	64
Philippines	573,000	554
Pakistan	518,000	268
South Africa	438,000	781
Democratic Republic of Congo	425,000	323
Nigeria	407,000	219
Bangladesh	360,000	221
Myanmar	191,000	361
Ethiopia	182,000	177

Modified from World Health Organization. Global Tuberculosis Report 2017. http://www.who.int/tb/publications/global_report/gtbr2017_annex4.pdf.

of noninstitutionalized civilians in the United States, the prevalence of tuberculin reactivity among persons 25 to 74 years of age decreased from 14.4% in 1972 to 5.6% in 2000 and to 4.4% in 2011.[80,92]

Immigrants for the most part retain the tuberculin positivity and TB rates of their country of origin (Table 249.2).[93,94] Other groups, such as injection drug users, patients with end-stage renal disease or diabetes, health care workers in endemic countries, residents of institutions for the homeless, and, to a lesser degree, nursing home residents, demonstrate morbidity rates greatly in excess of the general population.[95–103]

On a global scale, TB has a devastating impact in lower- and middle-income nations, with 10 countries accounting for nearly 70% of all prevalent cases (Table 249.3).[104] In 1993, WHO declared TB a global public health emergency and intensified major initiatives to address the problem. An important aspect of this strategy is supervised treatment, which may include DOTS.[105] WHO subsequently reported decreasing incidence rates of TB in all six regions of the world, including Southeast Asia, the Western Pacific, and Africa. In China, access to DOT was rapidly expanded from 31% of TB cases in 2001 to 80% in 2005, and from 1990 to 2010 the prevalence of smear-positive disease decreased from 170 to 59 cases per 100,000, in a population of greater than 1.3 billion.[106,107] Similar progress has also been made in India, the country with the greatest number of TB cases.[108,109] Challenges remain; molecular epidemiologic data from China from 2009 through 2012 indicate that recent transmission still accounts for a substantial proportion of new cases and that sputum smear–negative cases may be responsible for 30% of secondary cases.[110] In 2014 WHO launched its End TB Strategy with the goal of reducing global TB deaths by 90% and TB incidence by 80% by 2030. Major expansions of current activities and new prevention and treatment strategies will be needed to achieve this goal.[1]

Over 35 million persons worldwide are now living with HIV/AIDS.[111] The potential for continued interaction between HIV and TB is therefore immense. In some developing countries where most persons harbor tubercle bacilli before adulthood, the prevalence of HIV infection becomes the only determinant of coinfection. The situation is worst in sub-Saharan Africa, where the incidence of TB has risen in parallel with the incidence of HIV infection. Between 1990 and 2005, the incidence of TB more than doubled, from 149 to 343 per 100,000 population. TB is the leading cause of death in HIV-infected people, and in 2016, 22% of the 1.7 million TB deaths were in HIV-coinfected people. Seventy-five percent of the world's HIV-positive TB deaths occurred in Africa.[1] The continued scale-up and integration of HIV and TB programs are necessary to decrease the deaths in these populations.

Drug-Resistant Tuberculosis

Drug-resistant TB poses an immense challenge for TB control. Resistance to antituberculous agents can be either *primary,* that is, present before initiation of therapy and due to transmission of a drug-resistant *M. tuberculosis* strain, or *secondary,* indicating emergence of resistance after antituberculosis therapy. Risk factors for infection with drug-resistant TB are listed in Table 249.4. Strains resistant to at least INH and RIF are defined as MDR-TB. Strains resistant to at least INH, RIF, a fluoroquinolone, and second-line injectable drugs are defined as XDR-TB.[112]

WHO has regularly reported global drug-resistance rates since 1994.[113–116] In the United States, the rate of primary resistance to any antituberculosis drug has remained stable at about 12%, with that of MDR-TB at about 1%.[115] Globally, 3.3% of new TB cases and 20.1% of previously treated TB cases are MDR.[116] In 2016, there were an estimated 490,000 new cases of MDR-TB worldwide. Parts of Eastern Europe and central Asia, including Belarus, Estonia, Latvia, the Russian oblasts of Ivanovo and Tomsk, and Henan Province in China, have rates of MDR in newly diagnosed patients with TB that exceed 18%.[114–118]

Prior antituberculosis treatment is the most important risk factor for drug-resistant TB. Additional historical clues that increase the likelihood of drug resistance include infection acquired in regions where resistance is prevalent and known contact with a drug-resistant case. One study from southern California recorded resistance in 71% of patients with TB who had been previously treated and had cavitary disease.[119] Of immense concern is transmission of XDR-TB.[112] Cases of XDR-TB have been reported in 105 countries worldwide, and it is estimated that 9.7% of MDR-TB is XDR-TB.[116]

Mode of Spread

Almost all infections with *M. tuberculosis* are due to inhalation of droplet nuclei—infectious particles from a person with pulmonary TB aerosolized by coughing, sneezing, or talking—which dry while airborne, remain suspended for long periods, and reach the terminal air passages. A cough can produce 3000 infectious droplet nuclei, talking for 5 minutes an equal number, and sneezing many more than that. Accordingly, the air in a room occupied by a person with pulmonary TB may remain

TABLE 249.4 Epidemiologic Circumstances in Which an Exposed Person Is at Increased Risk for Infection With Drug-Resistant *Mycobacterium tuberculosis*

- Exposure to a person who has known drug-resistant tuberculosis
- Exposure to a person with active tuberculosis who has had prior treatment for tuberculosis (treatment failure or relapse) and whose susceptibility test results are not known
- Exposure to persons with active tuberculosis from areas in which there is a high prevalence of drug resistance
- Exposure to persons who continue to have positive sputum smears after 2 months of combination chemotherapy
- Travel in an area of high prevalence of drug resistance

[a]This information is to be used in deciding whether to add a fourth drug (usually ethambutol) for children with active tuberculosis, not to infer the empirical need for a second-line treatment regimen.
From Centers for Disease Control and Prevention. Treatment of tuberculosis. American Thoracic Society, CDC and Infectious Diseases Society of America. MMWR Recomm Rep. *2003;52(RR–11):1–88.*

infectious for approximately 30 minutes even after his or her absence. Although in theory one droplet nucleus may be sufficient to establish infection, prolonged exposure and multiple aerosol inocula are usually required. Strains may vary widely in their transmissibility,[87] but infection does not generally occur outdoors because *M. tuberculosis* is killed by ultraviolet light. Although homes are the focus of TB contact investigations, evidence is mounting that in high-TB settings, approximately 85% of transmission occurs in other social spaces including medical facilities, public transportation vehicles, workplaces, schools, churches, bars, and other areas where people congregate.[120]

Large drops of respiratory secretions and fomites are unimportant in transmission, and special housekeeping measures for dishes and bed linens are unnecessary. Other modes of transmission are rare. Infection with *M. bovis* from ingestion of contaminated milk was once commonplace. Skin inoculation of *M. tuberculosis* from contamination of an abrasion occurs in pathologists and laboratory personnel (prosector's wart), and venereal transmission has been recorded. Although the source is pulmonary in the vast majority of cases, aerosolization of organisms during irrigation of cutaneous lesions or at autopsy has caused spread to health care workers.[121,122] The special case of organ-donor–transmitted infection should be noted because transplant recipients have a higher frequency of TB than the general population, and high mortality.[123] Because donor-derived disease develops late (>90 days) in the majority of cases, and many donors have identifiable risk factors for tuberculous infection, it has been proposed that screening protocols using donor histories that would heighten surveillance of recipients, in addition to cultures and smears, and testing for latent TB in donors should be undertaken.[124]

Risk for Infection

The most important determinants of infection of tuberculin-negative persons are closeness of contact and infectiousness of the source. From 2002 to 2011, 26 outbreaks in the United States were associated with index cases with a substantial burden of substance abuse, incarceration, and homelessness.[125] Cases with positive smears are highly infectious; those positive only on culture are less so. The degree of sputum positivity and pattern of coughing are important. Compared with measles, one case of which will infect 80% of susceptible casual contacts, TB is only moderately infectious in most circumstances. In the United Kingdom, a study of 111 cases with 825 contacts found that a shorter interval to liquid culture positivity identified patients at high risk of transmitting infection and was also superior to detection by means of smear.[126]

TB morbidity in a population is determined both by the risk for infection and the risk for acquiring active disease once infected. In Holland in the 1970s, 50% of newborn to 14-year-old household contacts of individuals with smear-positive cases became tuberculin positive, but only 5% did so when the contact case was culture positive but smear negative.[77] In the United States, approximately 27% of household contacts of individuals with smear-positive cases become infected, although rates as high as 80% occur in closed environments.[127] A large epidemiologic investigation in San Francisco from 1991 to 1996 estimated that 17% of new active TB cases arose from smear-negative, culture-positive index cases.

Persons coinfected with HIV do not appear to be more infectious than HIV-negative source cases and because they are more likely to be smear negative than are HIV-negative patients, they may be less infectious. In one large study from the Democratic Republic of Congo, household contacts of HIV-positive patients with pulmonary TB were no more likely to become infected with *M. tuberculosis* than were household contacts of HIV-negative TB patients.[128] A study in Uganda demonstrated that transmission from an HIV-infected index case to contacts was dependent on the index patient's sputum smear positivity and presence of a cavity on chest radiograph.[129] A meta-analysis of six studies involving exposed health care workers supports this finding, as does a study of household contacts in Peru.[130,131]

Influence of Chemotherapy on Spread of Infection

Patients receiving appropriate chemotherapy promptly become noninfectious as cough subsides and the concentration of organisms in sputum decreases. The time required to become noninfectious depends on the patient's burden of organisms, but there is indirect evidence that this occurs within 2 weeks in patients with drug-sensitive TB.[132] Thus, case finding and treatment comprise the most effective method of TB control.

Risk for Progression From Infection to Active Disease

In general, 3% to 4% of infected individuals acquire active TB during the first year after tuberculin conversion and an additional 5% do so thereafter, although the uniformity of these rates has been challenged in a study from Victoria, Australia, in which the cumulative hazard for progression to disease after infection was 14.5%, with most risk occurring within the first 5 months and greater risk in children younger than 5 years (50.6%).[133,134] These estimates are based on heavy exposures during disease-prone periods of life. Persons infected with small inocula or during disease-resistant periods probably have a much smaller risk,[135] whereas the risk for progression in immunocompromised persons is greater. In one study of 12,876 unvaccinated adolescents, 10.4% of those who converted their tuberculin tests acquired clinical TB, 54% of these within 1 year and 78% within 2 years.[77] The three periods of life during which infection is most likely to produce disease are infancy, ages 15 to 25 years, and old age. (The effect of age on disease progression is discussed in "Influence of Age on Tuberculous Infection.")

The likelihood of active disease developing varies with the intensity and duration of exposure. Persons with intense exposures are most at risk not only for infection but also for disease.[127] The degree of tuberculin positivity has some predictive value. Malnutrition, renal failure, and immunosuppression all favor progression of infection to active disease, but by far the strongest risk factor is HIV infection. Among tuberculin-positive, HIV-positive injection drug users in one methadone clinic population, 8% per year acquired active TB.[136]

Institutional Spread of Tuberculosis

Hospitals

TB has long been a recognized risk to health care workers and hospitalized patients. In the 1980s, numerous explosive outbreaks of TB occurred among HIV-infected patients in specialized wards and hospices in the United States and Europe.[137–141] In the first reported outbreak on an HIV ward, the index patient had fever, cough, a normal chest radiograph, and negative acid-fast smears, but a positive sputum culture for *M. tuberculosis*.[138] On the same ward, 39% of other HIV-positive patients acquired active TB within 60 days. Major factors contributing to these outbreaks included (1) delays in diagnosis, especially in HIV-infected patients with atypical chest radiographs; (2) inadequate negative-pressure ventilation inpatient rooms; (3) use of aerosol-generating procedures such as bronchoscopy and sputum induction; (4) rapid progression to active TB in HIV-positive patients; and (5) in the case of MDR-TB, prolonged infectivity despite antituberculous chemotherapy.[142] In high-income countries, decreased numbers of AIDS hospitalizations, decreased TB incidence, low rates of MDR, and improved hospital infection-control

programs have generally diminished these outbreaks. In middle- and lower-income countries, with higher rates of HIV- and TB-related hospital admissions and less resources for infection control, nosocomial transmission remains a major public health problem. An investigation of 404 cases of XDR-TB in South Africa demonstrated the continued importance of nosocomial transmission.[143,144]

In reaction to outbreaks of MDR-TB, the CDC in 1994 established very stringent criteria for removing from respiratory isolation patients who were suspected to have pulmonary TB and had not begun empirical treatment. These criteria now include three consecutive negative sputum smears on good-quality specimens obtained at least 8 hours apart.[145] Studies have demonstrated that two negative sputum Xpert MTB/RIF tests improve sensitivity and specificity for identifying patients who will be found to be culture and smear negative. Use of the Xpert MTB/RIF will decrease time in isolation and will be more cost-effective than use of three AFB smears.[146,147]

Shelters for the Homeless

Approximately 1% of the US population experiences homelessness in a given year, and these people account for a disproportionately high percentage (6%) of all the TB cases in the country annually. Poor nutrition, injection drug use, alcoholism, lack of access to TB screening and treatment, and crowding increase the risk for both endogenous reactivation of remote infection and acquisition of new (exogenous) infection in homeless shelter clients.[96] A review of cases between 1994 and 2003 showed that 6% of TB cases in the United States occurred in homeless individuals, of whom 87% were men and 34% were HIV positive and in whom alcohol and drug abuse was common.[148] A 2015 CDC-sponsored workshop with homeless shelter staff and public health officials from across the country defined key measures to prevent TB transmission in shelters including strict infection-control procedures, active case finding, screening for latent TB, cooperation between shelters and public health authorities, education of shelter staff and clients, data sharing, and prevention of stigma so that clients with symptoms will freely come forward.[149]

Correctional Facilities

The incidence of TB is markedly higher in incarcerated persons than in the general population.[150] In the United States, high-risk populations—including young black and Hispanic men, injection drug users, and HIV-infected persons—are overrepresented in prison populations.[151] Although most prison cases are due to reactivation of old infections, outbreaks of MDR-TB have shown that transmission of new (exogenous) infection also occurs. Although difficult for obvious reasons, preventive and curative services in correctional facilities are a high public health priority for everyone.[151,152] Transmission in prisons and jails may serve as an amplifier for spread to the community. In a study in a medium-size city in Brazil between 2009 and 2013, 25% of TB cases occurred among prisoners, who represented <1% of the city's population, and an additional 25% of the TB cases in the city were in ex-prisoners who had recently been released into the community. The remaining 50% occurred in community members. *M. tuberculosis* strain typing demonstrated clear clonal links between the prison cases, cases in ex-prisoners, and community cases.[153]

Controlling Nosocomial Spread

Spread of TB in the health care setting has raised justifiable concern. Tuberculin conversion rates as high as 50% among health care workers on HIV wards were reported early in the AIDS epidemic.[139] Delays in diagnosis and initiation of therapy are critical for both outcome and infectiousness to others.[142,154] Accordingly, TB must be considered in any HIV-positive patient with subacute or chronic pulmonary symptoms or symptoms compatible with extrapulmonary TB. Screening with NAAT tests such as Xpert MTB/RIF may expedite diagnosis.

Hospitalized HIV-positive patients with respiratory symptoms or people with suspected TB should be admitted to negative-pressure isolation rooms (so that air flows from the corridor into the room and is safely exhausted to the outside) with six air changes per hour. Procedures that stimulate coughing, such as sputum induction or bronchoscopy, should be carried out in negative-pressure rooms or special booths. The use of particulate respirator masks (N95), with appropriate training and fitting, further reduces risk and is recommended by the CDC. Ultraviolet irradiation of the air— either with the air pulled by a fan through a radiation chamber or with the ultraviolet beam directed into the uppermost parts of the room so as to avoid direct irradiation of personnel—is also advised. The CDC has published extensive guidelines for control of transmission of TB in diverse health care settings.[155] Further evidence from a guinea pig model, in which the animals breathed untreated air from a TB ward, supports the use of air disinfection based on ultraviolet treatment.[156] WHO has also published TB infection-control guidelines for health care facilities with strategies that may be attainable for low- and middle-income countries.[157]

IMMUNOLOGY

TB is the prototype of infections that require a cellular immune response for their control (see Chapter 6). An effective immune response against *M. tuberculosis* infection relies on $CD4^+$ T cells and the cytokines interleukin (IL)-12, interferon-γ, and tumor necrosis factor (TNF).[158] Conversely, *M. tuberculosis* has adapted to host immunity and likely depends on the cellular immune response to facilitate tissue damage, formation of pulmonary cavities, and its own aerosol transmission. WGS of *M. tuberculosis* shows that the 491 major human T-cell epitopes expressed by the mycobacterial genome are highly conserved, suggesting that *M. tuberculosis* is no longer evolving to evade the human immune response but rather has reached an equilibrium with it.[159]

After initial inhalation, droplet nuclei with *M. tuberculosis* must bypass mechanical barriers, ciliated respiratory epithelial cells, and mucins in the upper airways to arrive in the alveolar spaces.[160] In the alveoli, *M. tuberculosis* is phagocytized by the alveolar macrophage. Entry into macrophages involves interactions with complement receptors, mannose receptors, and Fc receptors. Various *M. tuberculosis* molecules are recognized by multiple pattern recognition receptors (PRRs) at the cell surface, in the phagosome, or in the cytosol of the macrophage. Other immune cells that participate in the initial host response include neutrophils, dendritic cells, λδ T cells, mucosal-associated invariant T (MAIT) cells, CD1-restricted T cells, and natural killer (NK) cells.[161]

The alveolar macrophage may successfully kill the mycobacteria through phagosome maturation, fusion with the lysosome, or autophagy. Alternatively the mycobacteria may release virulence factors that delay phagosome maturation or result in phagosome rupture. *M. tuberculosis* uses several strategies to survive within macrophage phagosomes while delaying or preventing effective immune responses. Mycobacterial urease helps prevent acidification of the phagosome, thus limiting the effectiveness of bactericidal enzymes. In addition, by remaining within the phagosome, the organism does not initially elicit T-cell responses via the proteosomal pathway of antigen presentation. The organism also secretes abundant superoxide dismutase, catalase, thioredoxin, and other antioxidants that detoxify reactive oxygen species generated by phagocytes. Microbial antioxidants not only provide direct protection against host-generated oxidants but also suppress early oxidant-mediated immune responses needed for efficient antigen presentation, including the activation and apoptosis of macrophages.[162] This both ensures the organism's continued survival within its host cell and delays the development of strong adaptive T-cell responses. The recent elucidation of such pathogenic mechanisms has fostered rational strategies toward vaccine development (see "Vaccination").

If the initial infection is successful, unrestrained replication proceeds for weeks, both in the initial focus and in lymphohematogenous metastatic foci. The development of adaptive cellular immunity is delayed and takes approximately 4 to 8 weeks and ultimately supervenes. Tissue hypersensitivity is florid in comparison with other intracellular infections, perhaps fueled by the adjuvant activity of mycobacterial lipids.

$CD4^+$ Th1 cells, which secrete interferon-γ, are central to the protective immune response against *M. tuberculosis*. *M. tuberculosis* antigen-specific $CD4^+$ Th1 cells are activated by dendritic cells via the IL-12 pathway in the lymphatic tissue, clonally expand, and then migrate to the site of infection. $CD4^+$ T-cell production of interferon-γ activates macrophages at the site of antigen. Activated macrophages accumulate high concentrations of lytic enzymes and reactive metabolites that greatly increase their mycobactericidal competence, causing a decrease in the

mycobacterial load. Activated macrophages also secrete regulatory molecules (e.g., TNF-α and transforming growth factor-β), which in concert with lymphocyte secretory proteins (e.g., interferon-γ, migration-inhibitory factor) determine the character of the pathologic and clinical response. Epithelioid cells, characteristic of the tuberculous granuloma, are highly stimulated macrophages. The Langhans giant cell consists of fused macrophages oriented around TB antigen with the multiple nuclei in a peripheral position, representing the most successful type of host-tissue response. Cytotoxic $CD8^+$ T cells are also generated during infection and may directly lyse infected mononuclear phagocytes.

When the population of activated lymphocytes reaches a certain size, cutaneous delayed reactivity to tuberculin manifests, generally within 3 to 9 weeks after initial infection. At the same time, enhanced macrophage microbicidal activity appears. The pathologic features of TB are the result of the degree of hypersensitivity and the local concentration of antigen. When the antigen load is small and tissue hypersensitivity is high, organization of lymphocytes, macrophages, Langhans giant cells, fibroblasts, and capillaries results in granuloma formation. Foci characterized by the resulting hard tubercles are said to be *proliferative* or *productive* and constitute a successful tissue reaction with containment of infection, healing with eventual fibrosis, encapsulation, and scar formation. When both antigen load and hypersensitivity are high, epithelioid cells and giant cells are sparse or entirely lacking; lymphocytes, macrophages, and granulocytes are present in a less organized fashion; and tissue necrosis may be present, a tissue reaction that has been called *exudative*. In the absence of necrosis, exudative lesions may heal completely or tissue necrosis may occur. Necrosis in TB tends to be incomplete, resulting in solid or semisolid acellular material referred to as *caseous* because of its cheesy consistency. The chemical environment and oxygen tension in solid caseous material tend to inhibit microbial multiplication. However, caseous necrosis is unstable, especially in the lungs, where it tends to liquefy and discharge through the bronchial tree, producing a tuberculous cavity and providing conditions in which bacterial populations reach very high titers. Cavities may contain 10^7 to 10^9 organisms compared with only 10^2 to 10^4 in areas of caseous necrosis.[163] Infectious material sloughed from a cavity creates new exudative foci in other parts of the lung (bronchogenic spread). A cross section of a pulmonary cavity demonstrates all these pathologic reactions, from the least to the most successful in terms of containment of infection. The central cavity, which contains myriad bacilli, is surrounded by a layer of caseous material with fewer organisms, a more peripheral layer of macrophages and lymphocytes with little organization and still fewer organisms, an area that is even more peripheral with epithelioid cells and giant cells in which the bacterial content is quite low, and, most peripherally, a bacillus-free layer of encapsulating fibrosis.

When the degree of hypersensitivity is very low, the tissue reaction may be nonspecific, consisting of polymorphonuclear leukocytes and mononuclear cells with huge numbers of tubercle bacilli, so-called *nonreactive tuberculosis.*[164] The immunologic spectrum from florid hypersensitivity to little or no specific tissue reaction is similar to that seen in leprosy and is recapitulated in HIV-infected persons as the $CD4^+$ T-cell count declines.[165]

Epidemiologic studies suggest that in a very small subgroup of individuals exposed to *M. tuberculosis,* the initial innate immune response may be able to prevent *M. tuberculosis* infection. These individuals have been termed "resistors" and likely represent <10% of the population.[166] Of those who become infected with *M. tuberculosis* and develop a cellular $CD4^+$ T-cell response, the adaptive immune response will be successful in containing the infection and preventing TB disease 90% to 95% of the time.[158] Active disease from *M. tuberculosis* does not generate a durable immunity against the occurrence of a second TB disease episode. To the contrary, a first episode of active TB is a significant risk factor for a second episode of TB.[167–169] Immune correlates of these successful and unsuccessful immune responses are not fully known and are an area of intense investigation.

Testing for Latent Tuberculosis Infection

Individuals infected with *M. tuberculosis* with no clinical evidence of disease have LTBI. They have been infected with *M. tuberculosis* but do not have TB disease. To test for LTBI, a skin or blood test is performed to detect a cellular immune response to tuberculous antigens, indicating prior infection. The CDC suggests testing people who are at increased likelihood for infection and progressing to active TB, and who would therefore benefit from preventive therapy. The CDC also recommends stratifying patients' risk of developing TB when interpreting TST results. The TST is the classic test, but blood interferon-γ release assays are increasingly recommended by expert panels.[170]

TUBERCULIN SKIN TEST

The TST is used to determine whether an individual is infected with *M. tuberculosis.* Koch's tuberculin (old tuberculin) was an extract of a boiled culture of tubercle bacilli. In 1934, Siebert made a simple protein precipitate (purified protein derivative [PPD]) of old tuberculin, which became the preferred reagent in most areas. In 1941, a large single lot was adopted as the biologic standard (PPD-S) to which other preparations are now standardized. A 5-tuberculin unit (TU) dose of PPD is equivalent to 0.0001 mg of PPD-S protein in 0.1 mL of solution.[171]

DOSAGE

The sensitivity and specificity of the 5-TU dose were derived in populations in which the incidence of TB was accurately known. A 5-TU dose of tuberculin clearly separated groups with 100% infection, such as sanatorium patients, from groups with a very low incidence of TB, such as infants from noninfectious environments. In the former, tuberculin reactions peaked at 16 to 17 mm; in the latter, 0- to 5-mm reactions were elicited.

Technical Aspects

The TST is performed by means of intradermal injection of 5 TU of PPD in 0.1 mL of solution, usually on the volar aspect of the forearm. The injection is made with a short, beveled 26- or 27-gauge needle with the bevel facing upward (Mantoux test). Correct injection produces a raised, blanched, 6- to 10-mm wheal. Deeper injections may be washed out by vascular flow, resulting in false-negative results. The loss of potency that occurs when PPD adsorbs to glass surfaces is prevented by the addition of the detergent polysorbate 80 (Tween 80). Tween-stabilized tuberculin in solution is light sensitive and must be refrigerated. The skin reaction is usually read in 48 to 72 hours. A positive test result is defined by the diameter of induration, not erythema, in response to 5 TU. The diameter should be read across the forearm and can be measured by viewing the reaction tangentially against a light background. An alternative is to use a medium-point ballpoint pen to draw a line starting 1 to 2 cm away from the skin reaction and moving toward its center. The pen is lifted when resistance is felt, the procedure repeated from the opposite direction, and the distance between opposing line ends measured.

Targeted Tuberculin Testing

The American Thoracic Society (ATS), Infectious Diseases Society of America (IDSA), and CDC guidelines for LTBI testing recommend targeted testing of persons at increased likelihood of infection and/or at high risk for developing TB and with the intent for treatment of LTBI if the test is positive.[170,172] This includes persons at high risk of infection (e.g., recent immigrants, household TB contacts) and persons with clinical conditions that increase the risk for TB disease (e.g., those with HIV/AIDS, organ transplant recipients, patients taking TNF inhibitors). Testing of persons at lower risk of infection and disease progression is discouraged. Initial testing is also recommended for persons whose activities place them at increased risk for exposure, such as employees at medical and correctional facilities.

Interpretation

Based on sensitivity and specificity of tuberculin skin testing, three cutoff levels have been recommended for defining positive reactions: 5 mm, 10 mm, and 15 mm (see "Treatment of Latent Tuberculous Infection").[170,172] The 5-mm cutoff is used for close contacts, children younger than 5 years, people who have HIV infection, those who are undergoing immunosuppressive therapy, those with an abnormal chest radiograph consistent with prior TB, and patients with silicosis. The 10-mm cutoff is used for people who are likely to be infected

but at are low-to-intermediate risk of disease progression. The 15-mm cutoff is for people at low risk, although current guidelines for targeted testing suggest that low-risk persons not be tested. Ninety percent of persons with 10 mm of induration and virtually all with greater than 15 mm of induration to 5 TU are infected with *M. tuberculosis*. Induration of less than 10 mm may reflect cross reactions caused by infection with other mycobacterial species or prior BCG vaccination. However, even 5- to 10-mm reactions are suggestive of tuberculous infection in geographic areas substantially free of other mycobacteria, such as the northeastern United States, and in persons with immune suppression, such as HIV-infected persons.[173,174] Because of the potential for false-positive TST results in people who have received BCG vaccine, the ATS, IDSA, and CDC recommend an interferon-γ release assay rather than the TST for people from countries that vaccinate with BCG.[170,175]

Booster Effect

Although tuberculin cannot sensitize an uninfected person, it can restimulate remote hypersensitivity that has deteriorated. This booster effect (a positive tuberculin test result after a negative one) develops within several days after a first injection and may be persistent. This causes interpretative problems, because a negative test result followed by a positive test result approximately 10 weeks later may be a product of either a recent infection or a booster effect. This problem is circumvented by retesting nonreactors 1 to 3 weeks after the initial test. If the second test result is positive, this indicates boosting rather than recent tuberculin conversion. In early rheumatoid arthritis patients, with baseline increased risk of TB compounded by the use of TNF-α inhibitor therapy, the use of a booster PPD skin test increased LTBI detection from 31.3% to 46.5% in early rheumatoid arthritis and 21.7% to 28.8% in late rheumatoid arthritis patients.[176]

False-Positive and False-Negative Reactions

False-positive reactions represent nontuberculous mycobacterial infection. False-negative reactions occur in at least 20% of all persons with known active TB. In one study, 25% of 200 patients with active TB were nonreactive to 5 TU and 10% were also nonreactive to 250 TU.[177] Most false-negative test results in patients with TB are attributed to general illness and become positive 2 to 3 weeks after effective treatment is initiated. Protein malnutrition diminishes all cutaneous delayed hypersensitivity reactions. Sarcoidosis may cause false-negative TST results. Intercurrent viral infections (including HIV-1 infection with <200 $CD4^+$ T cells/mm^3), vaccination with live-virus vaccines (measles, smallpox), reticuloendothelial disease, and corticosteroid therapy may cause false-negative tuberculin reactions. Attempts to correlate negative tuberculin test results with generalized anergy (e.g., negative skin test responses to mumps, *Candida,* and tetanus toxoid) have not been illuminating, and such "anergy testing" is therefore not recommended (see "Tuberculin Skin Testing and HIV Infection").[178] Intraobserver reliability in reading reactivity may vary by as much as 3 mm, causing some classification uncertainty if induration is close to the cutoff value.[179] TST results are negative during the first 3 to 9 weeks of initial infection.

Variant ("Delayed") Tuberculin Reactivity

An unusual form of tuberculin response (so-called delayed reactivity) has been described among Indochinese immigrants. This involves induration of less than 10 mm at 48 to 72 hours, which increases to greater than 10 mm when the skin test is read again at 6 days.

Loss of Tuberculin Reactivity

Earlier in the 20th century, lifelong tuberculin positivity was maintained by frequent reexposure to tubercle bacilli or continued active disease. However, a positive tuberculin test will revert to negative unless restimulated by new aerosol inocula or persisting infection. In one tuberculin survey, 8.1% of positive reactors reverted to true negative when retested 1 year later (Table 249.5).[180] Persons with a history of a positive skin test result can be safely retested. Two negative tests a week apart (to exclude boosting) indicate true negativity.

TABLE 249.5 Annual Tuberculin Conversion Rates (Positive to Negative) According to Age Groups, Victoria County, Canada, 1959–1962

AGE GROUPS	POSITIVE REACTORS RETESTED AFTER 1 YEAR	NO. OF REVERSIONS TO NEGATIVE	REVERSION RATE (%)
0–19	99	22	22.2
20–39	200	16	8.0
40–59	525	25	4.8
60 and older	377	34	9.0
TOTAL	1201	97	8.1

From Grzybowski S, Allen EA. The challenge of tuberculosis in decline: a study based on the epidemiology of tuberculosis in Ontario, Canada. Am Rev Respir Dis. *1964;90:707–720.*

Tuberculin Skin Testing and HIV Infection

During HIV infection, tuberculin reactivity decreases as the CD4 cell count falls. One study of patients with active TB demonstrated 10 mm or greater induration in response to 5 TU in only 60% of persons with HIV infection and in 35% of those with AIDS.[181] Induration of 5 mm in persons with HIV infection is sufficient to warrant treatment of LTBI (see "Treating Latent Tuberculous Infection in Persons With HIV Infection").[182] Testing simultaneously for cutaneous anergy with ubiquitous antigens such as mumps, tetanus toxoid, and *Candida* is not recommended. Because of lack of standardization and reproducibility, and variable risk for TB among anergic persons, cutaneous anergy does not predict *M. tuberculosis* infection, and responsiveness to control antigens but not PPD does not exclude tuberculous infection (see "Treatment of Latent Tuberculous Infection").

Interferon-γ Release Assays for Latent *M. tuberculosis* Infection

Three interferon-γ release assays are FDA approved to detect latent *M. tuberculosis* infection. These tests measure host cellular immune response to *M. tuberculosis* antigens in whole-blood samples. These tests overcome several limitations of the TST, including false-positive results from environmental mycobacterial exposure or BCG vaccination, operator-dependent variability in test placement and reading, and the need for a follow-up visit to examine skin induration. Unlike the TST, blood tests do not require a follow-up visit for determination of results. The CDC recommends that these tests be used preferentially for most populations rather than the TST to detect LTBI.[170,183] In a patient population at increased risk for tuberculous disease, such as candidates for organ transplantation, serial testing with interferon-γ release assays before transplant has revealed conversion and reversion rates of reactivity that undermine the ability to determine true-positive rates.[184] These conversion and reversion rates have also been studied in South African adolescents. Concordance with the development of disease was good for conversion but not reversion, and incident TB was eightfold higher in reverters than in those with consistently negative results.[185] In a study in 17 European centers, TST, QFT-GIT test, and T-SPOT.TB test (Oxford Immunotec, Abingdon, United Kingdom) (see later) were compared for their performance and comparability in immunocompromised patients (HIV infection, chronic renal failure, rheumatoid arthritis, solid-organ and hematopoietic stem cell transplant patients) versus immunocompetent controls. TB incidence was low but higher in HIV-infected persons with a positive TST result than with either interferon-γ release assay. Treatment was effective in preventing disease.[186]

The QFT-GIT test quantifies release of interferon-γ from lymphocytes in whole blood incubated overnight with three *M. tuberculosis* antigens: the early secretory antigen target-6 (ESAT-6), culture filtrate protein-10 (CFP10), and TB7.7. These three proteins are absent from BCG and from most other nontuberculous mycobacterial species. Blood must be tested within 12 hours of collection. The FDA has approved the QFT-GIT test, and the CDC has established guidelines for its use to detect latent

TB.[183] According to the CDC, the QTF-GIT may be used in all circumstances in which TST is used and is often the preferred test.

The next-generation QuantiFERON-TB Gold Plus (QFTPlus) test has been FDA approved and is starting to be rolled out in the United States and Europe. QTFPlus contains a fourth tube with short peptides from CFP-10, which are designed to elicit increased $CD8^+$ T-cell production of interferon-γ. Furthermore, the next generation assay does not use the TB7.7 antigen. Four milliliters of blood are divided into four tubes. After incubation, if either antigen tube produces more interferon-γ than the nil (no antigen) tube, the result is positive. If the mitogen tube does not produce more interferon-γ than the nil tube, the result is indeterminate. There are only a few studies comparing the QFT-GIT and QTFPlus, and these suggest comparable results or perhaps slightly improved sensitivity of the QTFPlus in elderly or immunocompromised populations.[187–189] Larger studies in diverse populations are needed.

Another assay, the T-SPOT.TB (Oxford Immunotec, Abingdon, United Kingdom) is an ELISPOT assay that also detects T-cell responses to *M. tuberculosis* antigens ESAT-6 and CFP10.[190] It has been approved for use by the FDA in the United States. In an investigation of a large school outbreak of TB in the United Kingdom, the ELISPOT had 89% agreement with the TST and correlated more closely with exposure to the index case than the TST. Its performance for health care worker screening in US hospitals demonstrates high concordance among serial tests and high test completion rates.[191]

Data on the performance of the interferon-γ release assays in children are limited, and guidelines differ on the optimal test. The ATS/IDSA/CDC guidelines recommend use of the same criteria as in adults for children aged 5 years and older. For children younger than 5 years, these guidelines recommend the TST, recognizing the limited data. Of note, 5 mL of blood is required for the interferon-γ release assay, which may be excessive for small children.[183] The American Academy of Pediatrics states that the TST is recommended for children younger than 2 years. Either the TST or an interferon-γ release assay is acceptable for children aged 2 years and older, but for BCG-vaccinated children aged 2 years and older the γ release assay is preferred.[192] Of note, a negative TST or γ release assay does not exclude active disease, and children are at high risk of rapid progression to TB disease.

PATHOGENESIS

Airborne droplet nuclei containing tubercle bacilli reach the terminal air spaces where multiplication begins. The initial focus is usually subpleural and in the midlung zone (the lower parts of the upper lobes and the upper parts of the lower and middle lobes), where greater airflow favors deposition of bacilli. (Very rarely, nonpulmonary initial foci will involve abraded skin, the intestine, the oropharynx, or the genitalia, all associated with foci in regional lymph nodes.)

The initial pulmonary focus is typically single, although multiple foci are present in about one-fourth of cases. The bacteria are ingested by alveolar macrophages, which may be able to eliminate small numbers of bacilli. However, bacterial multiplication tends to be mostly unimpeded, destroying the macrophage. Bloodborne lymphocytes and monocytes are attracted to this focus, the latter differentiating into macrophages, which ingest bacilli released from degenerating cells, and pneumonitis slowly develops. Infected macrophages are carried by lymphatics to regional (hilar, mediastinal, and sometimes supraclavicular or retroperitoneal) lymph nodes, but in the nonimmune host may spread hematogenously throughout the body. During this occult preallergic lymphohematogenous dissemination, some tissues favor retention and bacillary multiplication. These include the lymph nodes, kidneys, epiphyses of the long bones, vertebral bodies, and juxtaependymal meningeal areas adjacent to the subarachnoid space, but, most important, the apical-posterior areas of the lungs. Before the development of hypersensitivity (tuberculin reactivity), microbial growth is uninhibited, both in the initial focus and in metastatic foci, providing a nidus for subsequent progressive disease in the lung apices and in extrapulmonary sites, either promptly or after a variable period of latency.

Evolution of the Primary Infection

Tuberculin positivity appears 3 to 9 weeks after infection and marks the development of cellular immunity and tissue hypersensitivity. In most instances the infection is controlled, with the only evidence of infection being a positive skin test result. In a minority of cases, antigen concentration in the primary complex, consisting of the initial pulmonary focus (the Ghon focus) and the draining regional nodes, will have reached sufficient size that hypersensitivity results in necrosis and radiographically visible calcification, producing the Ranke complex (parenchymal and mediastinal calcific foci). Much less commonly, pulmonary apical and subapical metastatic foci contain sufficient bacilli that necrosis ensues with the onset of hypersensitivity, producing tiny calcific deposits (Simon foci) in which viable bacilli may persist.

The onset of tuberculin hypersensitivity may be associated with erythema nodosum or phlyctenular keratoconjunctivitis (a severe unilateral inflammation of the eye), although these manifestations are unusual in the United States. The primary complex may progress. In children, large hilar or mediastinal lymph nodes may produce bronchial collapse with distal atelectasis or may erode into a bronchus and spread infection distally. Also, typically in children but also in those infected in advanced age[97] and HIV-infected patients,[193] the primary focus may become an area of advancing pneumonia, so-called progressive primary disease, which may cavitate and spread via the bronchi. Again, typically in the very young, preallergic lymphohematogenous dissemination may progress directly to hyperacute miliary TB as a result of caseous material directly reaching the bloodstream, either from the primary complex or from a caseating metastatic focus in the wall of a pulmonary vein (Weigert focus). Hematogenous dissemination in the very young is often followed within weeks by tuberculous meningitis. In adolescents and young adults, the subpleural primary focus may rupture, delivering bacilli and antigen into the pleural space to produce serofibrinous pleurisy with effusion. Overwhelmingly, the most important consequence of preallergic lymphohematogenous dissemination is seeding of the apical-posterior areas of the lung, where disease may progress without interruption or after a latent period of months or years, resulting in pulmonary TB of the adult or reactivation-type TB (endogenous reinfection).

Primary (Childhood) and Reinfection (Adult) Tuberculosis

The traditional terms *primary* or *childhood pulmonary tuberculosis* and *reinfection* or *adult pulmonary tuberculosis* followed radiographic observations early in the 20th century when initial (primary) infection in childhood was believed to be universal.[194] Children's radiographs characteristically demonstrated large mediastinal or hilar lymph nodes with inconspicuous pneumonitis in the lower or middle lung field, whereas in adolescents and adults, apical or subapical infiltrates, often with cavitation and no hilar adenopathy, were the rule. These clinical and radiographic differences are due to age-related immunologic factors. Although many primary infections in adolescents and adults resemble primary infection in childhood, in others in this age group, an apical-posterior, metastatic pulmonary focus progresses within weeks to "adult"-type pulmonary disease, whereas the initial focus in the lower lung field and hilar nodes involutes undetected.

CHRONIC PULMONARY TUBERCULOSIS

Apical Localization

In adults, apical localization of pulmonary TB has often been attributed to the hyperoxic environment of the apices and the aerobic nature of the organism. A more plausible theory attributes it to deficient lymphatic flow at the lung apices, especially the posterior apices, where the pumping effect of respiratory motion is minimal. Deficient lymph traffic would favor retention of bacillary antigen and, when hypersensitivity ensues, tissue necrosis. Apical-posterior localization with a tendency to cavitation and progression is characteristic of pulmonary TB in adolescents and adults. In contrast, infection acquired by the elderly often causes nondescript lower lobe pneumonia similar to progressive primary infection of childhood.[97]

Endogenous Versus Exogenous Reinfection

In countries where the level of contagion is low, most cases of active TB reflect reactivation of latent foci.[194] However, when contagion is high, exogenous reinfection may be more common.[77,195] The temporal dynamics of relapse versus reinfection in high-prevalence settings suggest

that most relapse occurs early after completion of therapy, but reinfection becomes predominant 1 year after completion of therapy, accounting in total for at least half of recurrence.[196] In a large study in Malawi, 85% of recurrent TB cases in HIV-infected people were due to reinfections with a new *M. tuberculosis* strain, and HIV-infected adults were 20 times more likely to develop disease from reinfection than HIV-negative people.[197] Airflow in the apical-posterior areas of the lung is low, but when inhaled droplet nuclei reach that location, as is more likely with high levels of contagion, bacillary multiplication will be favored by the same local factors that enhance multiplication of bloodborne organisms. Support for this comes from a study from India that showed that disease in household contacts of active cases was most common in the middle-aged and elderly, who were certain to have been previously infected,[198] and from molecular epidemiology data.[96] Repeated inhalational exposures to tubercle bacilli maintain tissue hypersensitivity and cellular immunity, making superinfection more difficult; however, when the airborne inoculum is large, or in immunocompromised hosts, superinfection may occur.

Influence of Age on Tuberculous Infection

Many of the best clinical descriptions of TB come from the preantimicrobial era, when infection occurred early in life and cellular immunity was maintained by frequent exposure to tubercle bacilli. However, in industrialized countries, infection more often occurs later in life and cellular immunity may wane in the absence of restimulation. Accordingly, clinical patterns have changed. At one time, most patients were adolescents and young adults with apical cavitary disease. In developed countries, the incidence of TB (cases per 100,000) is now greatest in older persons, in whom hypersensitivity is less marked and in whom the clinical manifestations may be different and more subtle. Hypersensitivity and cellular immunity likely become less vigorous with age (see "Epidemiology").

Infection in Infancy and Childhood

Infection in infants often results in disease with local progression and dissemination (miliary-meningeal disease). The younger the patient, the greater the risk for progressive disease until the age of 5 years. From age 5 until puberty is a time of relative resistance to progressive disease, although not to infection. When disease occurs, it is usually the childhood type of pulmonary TB. Involvement of lymph nodes, bones, and, less commonly, other progressive extrapulmonary foci may develop, but TB confined to the lung in this age group usually heals spontaneously. The short-term prognosis in these individuals is good even if untreated, but there is a high frequency of relapse with chronic cavitary TB when the more disease-prone periods of adolescence and young adulthood arrive.[199]

Infection in Adolescence and Young Adulthood

Clinical disease developing after infection in adolescence or young adulthood may resemble childhood infection (lower lung field pneumonitis, hilar adenitis) but with less parenchymal and hilar calcification (Fig. 249.2). This is particularly the case in immunocompromised patients, including those living with HIV.[194] Rarely, the radiographic picture may be mixed, with features of childhood disease subsiding while chronic upper lobe (adult) disease progresses. However, disease in this age group frequently first appears as chronic upper lobe TB with no clinical manifestations of childhood disease. The tendency toward apical cavitation soon after the initial infection appears soon after puberty and is marked in young adults.[172] Evidence suggests that adolescents (and adults) may have a subclinical tuberculous pneumonia for months prior to the onset of overt disease.[200,201] Because most young people in industrialized countries are tuberculin negative (Fig. 249.3), most pulmonary TB in adolescents and young adults is due to recent initial infection rather than to late progression of childhood infection.

Infection in Midadulthood

Infection acquired during the middle years has a much better immediate and probably long-term prognosis than infection acquired in the teens and early 20s, presumably because of a reduced tendency to tissue necrosis.[199,202] One study demonstrated progression from infection to cavitary TB in 23% of patients infected from 15 to 19 years of age, 13% of those infected from 20 to 24 years of age, 4% of those infected from 25 to 29 years of age, and only 2% of those infected after 30 years of age. Progression occurred in 3 months in many and within 1 year in most.[203] (Elderly individuals were not included in the study.)

FIG. 249.2 Chest radiograph showing marked right hilar lymphadenopathy and lower lobe opacity in a 58-year-old woman with primary tuberculosis.

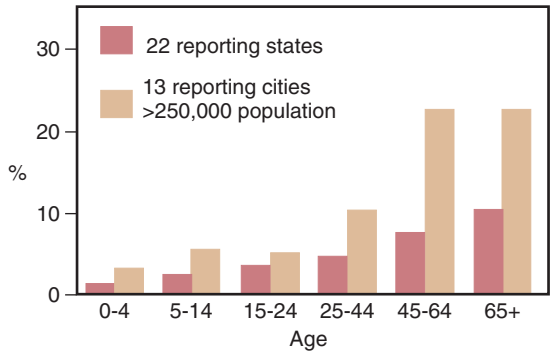

FIG. 249.3 Percentage of positive tuberculin reactors by age, selected areas, United States, 1979. *(From Centers for Disease Control and Prevention [CDC], Tuberculosis Control Division. Tuberculosis in the United States, 1979. Atlanta, GA: CDC; 1981:4–31.)*

Infection in Old Age

In the elderly, infection acquired years earlier can progress as age compromises immunity, producing typical apical-posterior disease. Studies of TB in nursing homes, however, have demonstrated that elderly patients are often tuberculin negative, either because they had never been infected or because remote past infection had been completely cleared, with a loss of tissue hypersensitivity. Such tuberculin-negative persons are susceptible to new infection; and if this occurs, they acquire active disease with a frequency similar to that of adolescents. This is typically a nondescript, poorly resolving pneumonitis in the lower or middle lobes or anterior segments of the upper lobes, sometimes with pleural effusion and resembling primary infection in children except with much less hilar-mediastinal lymphadenopathy.[97] Even with prompt diagnosis and treatment, TB after age 65 appears to be more frequently associated with death.

Late Hematogenous Tuberculosis

Chronic TB is probably always associated with recurrent abortive episodes of hematogenous spread. However, when aging or other factors compromise cellular immunity, such episodes may become progressively more frequent, producing the subtle and often fatal syndrome of late hematogenous or progressive generalized TB.

Intercurrent Events

General stress, poor health, and malnutrition favor progression of infection. Therapy with corticosteroids or other immunosuppressive agents compromises host defenses, as do hematopoietic-reticuloendothelial diseases, particularly malignancies. TB in complicating myeloproliferative disorders may cause confusion because disseminated TB can cause aplastic anemia, thrombocytopenia, leukopenia, and leukemoid reactions that may mimic leukemia. However, most patients with TB and hematologic findings that suggest leukemia will have both diseases. Inflammatory diseases such as rheumatoid arthritis and systemic sclerosis are often accompanied by immunologic derangements that may decrease immunocompetence even prior to the use of immunosuppressive therapies. Patients with systemic sclerosis in Taiwan had a significantly higher risk for TB and pulmonary TB, independent of systemic sclerosis treatment, compared with matched control subjects drawn from the National Health Insurance database (incidence rate ratios, 2.81 and 2.53, respectively).[204] Biologic TNF-α inhibitors (e.g., infliximab, etanercept, and adalimumab) that are prescribed for rheumatoid arthritis and other inflammatory diseases increase the likelihood of reactivation TB, including extrapulmonary and disseminated disease.[205–209]

The postgastrectomy state, jejunal-ileal bypass surgery, and end-stage renal disease are all risk factors for progression (see "Treatment of Latent Tuberculous Infection"). Viral illnesses, particularly in children, may predispose to progression of infection. Destructive local pulmonary processes such as lung abscess, carcinoma, cavitary histoplasmosis, and pulmonary resection occasionally are followed by activation of previously quiescent pulmonary foci. The development of bone and joint TB after physical injury and late generalized hematogenous TB after major trauma both illustrate that the balance between host and infection can be altered by both systemic factors and local physical disturbance.

Tuberculosis in People With HIV Infection

The earliest descriptions of TB with AIDS emphasized the very great risk for reactivation of remote infection as a result of progressively compromised cellular immunity. Among Haitians, all of whom were likely infected with *M. tuberculosis* in childhood, HIV infection was associated with development of active TB in 60%.[103] Subsequent studies of HIV-positive and tuberculin-positive methadone clinic patients in New York City showed that active TB developed in 8% yearly.[136]

TB remains the leading cause of death in HIV infection in reports from highly endemic areas, despite the introduction of ART.[210] As discussed in "Epidemiology," HIV-infected patients are predisposed not only to reactivation of remote infection but also to rapid progression of recently acquired infection.[137,138] It is unclear whether AIDS increases susceptibility to acquisition of new infection. Provision of ART restores immune function and decreases risk for TB, although not to levels seen among HIV-negative individuals.[211]

PULMONARY TUBERCULOSIS

Primary Tuberculosis in Childhood

The initial focus of pulmonary TB in children occurs most frequently in the midlung zones but may develop anywhere. At the time of tuberculin conversion, fever and lassitude and rarely erythema nodosum or phlyctenular keratoconjunctivitis may be present briefly. Clinical manifestations of the initial infection depend on the age of the patient. It is most often symptomatic in childhood because of an age-related tendency to extensive regional lymphadenitis. This may compress central bronchi, causing a brassy cough or atelectasis of a segment or lobe, or may rupture into a bronchus, seeding infection distally and causing pneumonia. In the very young, there is a tendency to progressive lymphohematogenous dissemination with miliary-meningeal disease. Uncommonly, again more in infants, local progression of the initial pneumonia results in progressive primary disease, which may spread via the bronchial tree or the bloodstream. However, most infections during the relatively disease-resistant period of childhood (ages 5–12 years) are usually nonprogressive, with healing by involution and encapsulation.[199] Progression, if any, occurs in extrapulmonary metastatic foci or with the development of apical-posterior pulmonary TB, usually when the patient reaches puberty or young adulthood.

Postprimary (Adult-Type) Pulmonary Tuberculosis

Primary infection in adolescents and adults (1) may occur without symptoms and signs, (2) may produce a typical primary complex, or (3) may result in typical chronic pulmonary TB without a demonstrable primary complex. Any pneumonic infiltrate, especially if associated with a hilar or mediastinal node, may represent primary infection. These lesions may undergo caseation, liquefaction, and bronchogenic spread just as with classic chronic pulmonary TB.

Postprimary pulmonary TB in adults is usually asymmetrical and characterized by caseation, fibrosis, and frequently cavity formation. It begins as a patch of pneumonitis in the subapical-posterior aspect of an upper lobe, usually just below the clavicle or first rib (Fig. 249.4). A less frequent location is the apex of the lower lobe, where it may be obscured by the heart and hilum on a chest radiograph but readily visible on a chest CT image. The inflammatory response in the sensitized host produces a fibrin-rich alveolar exudate containing a mixture of inflammatory cells. Serial radiographs may demonstrate waxing and waning and sometimes complete regression. If the process accelerates, however, an area of caseous necrosis surrounded by epithelioid cells, granulation tissue, and eventually fibrosis develops. This may arrest by inspissation of the caseous area, fibrous encapsulation, and healing. Caseation, however, tends to liquefy and drain into the bronchial tree, spreading bacillary contents by coughing. The cavity is prevented from collapsing by the fibrous capsule and the inelasticity of the surrounding lung. The pulmonary cavity favors bacillary multiplication to enormous titers, 5 to 6 logs greater than in noncavitary lesions. The progressive nature of pulmonary TB is due to (1) the tendency of apical caseous foci to liquefy, (2) the enormous concentrations of organisms in the resulting pulmonary cavities, and (3) spread of this bacilli-rich material through the bronchial tree. Progression from minimal infiltrate to far-advanced cavitary disease can occur within a few months (Fig. 249.5).

FIG. 249.4 **Chest radiograph showing a right apical infiltrate in a patient with moderately advanced postprimary tuberculosis.**

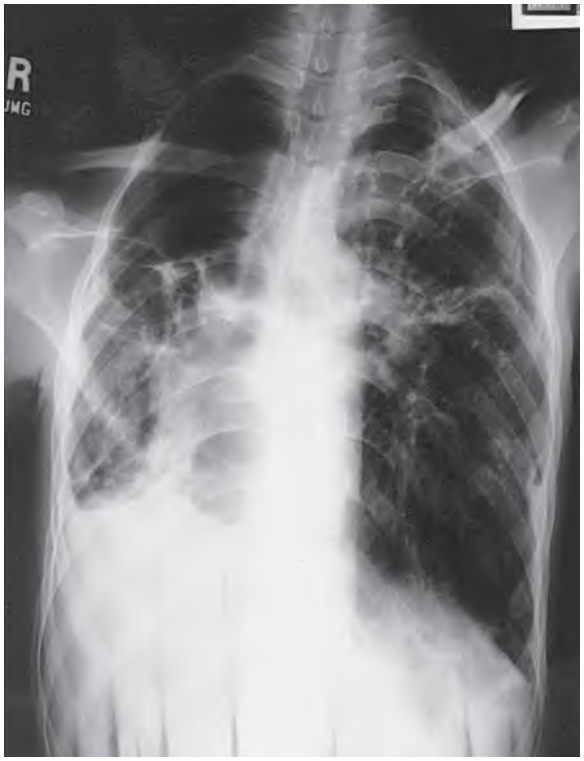

FIG. 249.5 Chest radiograph showing far-advanced bilateral apical cavitary pulmonary tuberculosis in a 32-year-old woman from Ethiopia.

Coughing aerosolizes infectious cavity secretions that may distribute widely throughout the lung (bronchogenic spread). New foci eventually develop that, in turn, may undergo caseation, fibrosis, and healing or slough, resulting in new cavities. The segment or lobe containing the initial cavity is typically involved first with scattered patchy disease, but the contralateral apex is often secondarily involved with progressive disease. Bronchogenic spread may establish foci of infection in the lower lobe and anterior portions of the upper lobe, producing a polymorphous mottling on a chest radiograph, but these are usually nonprogressive and heal with fibrosis. Although hematogenous spread from an established pulmonary focus can occur, it is usually limited by hypersensitivity-induced thrombosis.

The highly infectious secretions from a cavity always cause some degree of endobronchial inflammation and ulceration, which may be extensive. Ulcerative tuberculous laryngitis is an extension of this process, as is local disease throughout the upper airways, mouth, middle ear, and gastrointestinal tract.

Mechanisms of healing are the same whether spontaneous or under the influence of chemotherapy. Without drug therapy, solid caseous foci surrounded by contracting fibrous tissue occasionally arrest. However, viable bacilli almost always persist in such lesions and can later reactivate. Before drug therapy, healing of persisting cavities never occurred, and some large, thick-walled cavities in shrunken fibrotic lobes could persist for years with minimal symptoms while remaining highly infectious (chronic fibroid TB). With drug therapy, cavities may resolve or they may heal but remain open, sometimes with complete reepithelialization. The major risk for such persistent cavities is superinfection with organisms such as *Aspergillus* or nontuberculous mycobacteria.

Lower Lobe and Endobronchial Tuberculosis

These terms *lower lobe tuberculosis* and *endobronchial tuberculosis* are not appropriate for chronic pulmonary TB of the ordinary kind that happens to involve the apex of the lower lobes. In adults, *lower lung field tuberculosis* describes three different but often associated processes: (1) progressive lower lobe pneumonia in recently infected older individuals; (2) endobronchial TB, often with parenchymal consolidation-collapse; and (3) TB complicating AIDS. These three processes differ from postprimary TB radiographically, and the former two have a low bacterial content.

Progressive Lower Lobe Disease in Older Persons

TB in an older individual frequently causes a nonspecific, non-resolving pneumonitis in the lower or middle lobes or anterior segments of the upper lobes, similar to primary infection in childhood, except with less hilar and mediastinal adenopathy.[127] TB should be considered in any slowly or non-resolving pneumonitis in an older patient.

Endobronchial Tuberculosis

In the past, superficial endobronchial lesions resulting from infectious secretions were common, sometimes spreading to the larynx and beyond or causing obstructive atelectasis with collapse. These superficial lesions responded quickly to chemotherapy. Now endobronchial disease is most frequently caused by rupture of an adjacent node into the bronchial tree, or less frequently by direct spread from parenchymal TB.[212] The chest radiograph typically reveals collapse-consolidation but may be normal in as many as 20% of cases, although a chest computed tomography (CT) scan may be abnormal. Sputum smear results are usually negative, but the bronchial lavage result is frequently positive.[212]

The usual bronchoscopic findings are mucosal edema, ulceration, and narrowing, but in 30% of cases, bulky granulation tissue may resemble bronchogenic carcinoma. Endobronchial involvement is usual in lower lung field TB,[213] and endobronchial ulcers occasionally produce positive sputum smears with normal chest radiographs. Large parenchymal cavities may be present, at times associated with an air-fluid level resulting from intermittent obstruction and poor drainage. Bronchial perforation by tuberculous nodes with endobronchial mass formation and lower lobe consolidation has been observed in patients with AIDS.

Calcified nodes can erode into the bronchial tree and cause hemoptysis, expectoration of calcific material (lithoptysis), or spread of previously quiescent bacilli. The atelectatic pneumonitis, which may result with or without new active disease, is most frequently seen in the anterior segment of the upper lobe and medial segment of the middle lobe.

Pulmonary Tuberculosis in AIDS

TB as first described in persons with advanced AIDS was characterized by middle or lower lung field location, absence of cavitation, a greatly increased incidence of extrapulmonary disease, and usually a negative TST.[214,215] It resembled childhood TB except for a negative TST and less prominent hilar and mediastinal lymphadenopathy. A later study of TB in a much less ill population of persons in TB clinics unaware of their HIV infection found a clinical picture no different from ordinary reactivation TB in HIV-negative patients, with apical, often cavitary, disease and tuberculin positivity being the rule. The clinical picture of TB during HIV infection is determined by the degree of immunocompromise (Table 249.6). Although HIV-positive persons may have symptoms similar to those seen in HIV-uninfected persons, presentations can also be atypical or patients can be asymptomatic.[216]

HIV-positive persons may also acquire new infection from others in their environment, a risk that was first observed among patients with advanced AIDS living in HIV wards and domiciles. The clinical picture in these patients can include diffuse, rapidly progressive, noncavitary disease that is often fatal.[137,138] It is unclear whether HIV-infected persons are more likely to become infected after exposure to *M. tuberculosis* than HIV-uninfected persons, but once infected, they are more likely to progress to active disease. HIV-infected persons do not appear to be more likely to transmit *M. tuberculosis* than HIV-uninfected persons,[130] but TB disease, and therefore *M. tuberculosis* transmission, can occur even when the source patient has a normal chest radiograph or a negative acid-fast sputum stain.[217,218] The Cepheid GeneXpert MTB/RIF or the more recent Ultra version should assist in rapid detection of *M. tuberculosis* in sputum of such patients.

It is important to consider TB in HIV-positive individuals with respiratory failure in the intensive care unit. Patients may have adult respiratory distress or sepsis syndrome with multiple organ system failure. The diagnosis can be made readily by stain and culture of sputum or blood or both.

TABLE 249.6 Clinical Manifestations of Active Tuberculosis in Early Versus Late HIV Infection

	EARLY HIV INFECTION	LATE HIV INFECTION
Tuberculin test result	Usually positive	Usually negative
Adenopathy	Common	Unusual
Pulmonary distribution	Upper lobe	Lower and middle lobe
Cavitation	Often present	Typically absent
Extrapulmonary disease	10%–15% of cases	50% of cases

[a]For practical purposes, "early" and "late" may be defined as $CD4^+$ cell counts greater than 300 cells/mm^3 and less than 200 cells/mm^3, respectively.
HIV, Human immunodeficiency virus.

Tuberculomas

Asymptomatic rounded lesions may develop as the parenchymal residua of the initial infection or as an upper lobe caseous lesion encapsulates (Fig. 249.6). These are ordinarily static, but larger ones may cavitate to produce new spread of disease. In some persons, excessive fibrosis occurs with small caseous or granulomatous residua becoming surrounded by concentric layers of fibrous tissue, at times with central or concentric calcification resembling histoplasmomas. Most such lesions are stable, but important in that they can be confused with cancer.

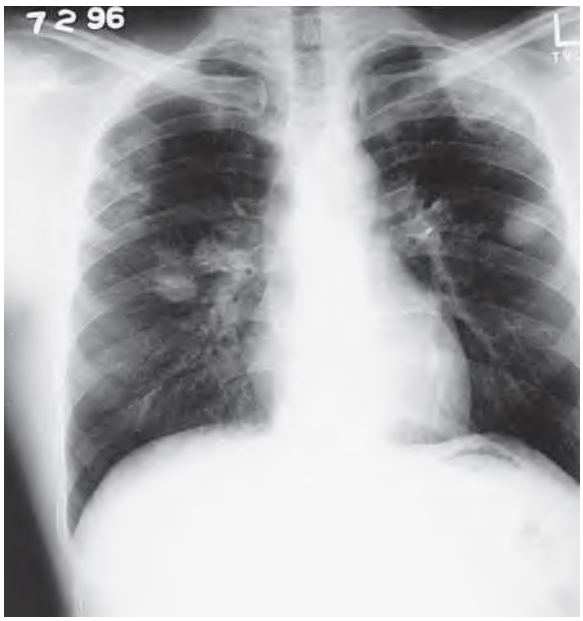

FIG. 249.6 Chest radiograph demonstrating multiple bilateral pulmonary tuberculomas in an asymptomatic 35-year-old man from Poland.

Symptoms

Initial infection with *M. tuberculosis* is usually asymptomatic, although some persons may have a relatively brief period of symptoms.[219,220] Early pulmonary TB is asymptomatic and may be discovered by chance on a chest radiograph. As the bacillary population grows, however, nonspecific constitutional symptoms such as anorexia, fatigue, weight loss, chills, fever, and night sweats may ensue. A productive cough is usually present. Coughing to clear cavitary secretions is usually mild and well tolerated but may become bothersome when bronchial involvement is extensive. The mucopurulent sputum is nonspecific, and both cough and sputum may be ignored by patients with chronic bronchitis. Hemoptysis resulting from caseous sloughing or endobronchial erosion is usually minor but connotes advanced disease. Sudden massive hemoptysis resulting from erosion of a pulmonary or bronchial artery by an advancing cavity (Rasmussen aneurysm) was an occasional terminal event in the predrug era but is now seldom seen. In inactive disease, brisk hemoptysis may be due to *Aspergillus* superinfection of residual cavities (aspergilloma). Chest pain is usually due to extension of inflammation to the parietal pleura. Pleural involvement adjacent to an established cavity tends to cause visceral-parietal pleural symphysis without effusion (dry pleurisy). Serofibrinous pleurisy with effusion is often an early postprimary event but may also complicate chronic pulmonary TB. Rarely, chest pain leads to discovery of tuberculous empyema. Symptoms often pertain to site of disease, such as painful pharyngeal ulcers; indolent and nonhealing ulcers of the mouth or tongue; hoarseness and dysphagia that are due to laryngeal involvement; tuberculous otitis media; gastrointestinal symptoms that are due to enteric ulceration, perforation, or mass formation; or anal pain that is due to tuberculous perirectal abscess and fistula formation. Lower lobe TB resulting from bronchial lymph node perforation may be associated with lithoptysis (stone spitting) and characteristically produces symptoms of severe endobronchial disease with serious cough and often hemoptysis.

Physical Examination

Physical findings are not specific, and in general do not reflect the extent of the illness and may be absent in spite of extensive disease. Dullness with decreased fremitus may indicate pleural thickening or fluid. Crackles may be appreciated only when the patient breathes in after a short cough (posttussive rales) and may persist long after healing, owing to permanent distortion of small airways. With large lesions, signs of consolidation with open bronchi (whispered pectoriloquy, tubular breath sounds) can be heard. Distant hollow breath sounds heard over cavities are called *amphoric,* like the sound made by blowing across the mouth of a jar (amphora).

Radiographic Findings

The chest radiograph is central to diagnosis, determination of the extent and character of disease, and evaluation of the response to therapy. Chest CT is a valuable adjunct to routine chest radiography. Certain patterns are highly suggestive, although not diagnostic, of TB. A patchy or nodular infiltrate in the apical- or subapical-posterior areas of the upper lobes or the superior segment of a lower lobe is highly suggestive of early chronic TB, especially if bilateral or associated with cavity formation (see Fig. 249.4). Cavities may be more apparent with CT or magnetic resonance imaging (MRI). On routine chest radiography, cavitation in the apical segment of the lower lobe may be obscured by the heart shadow and, in the lateral view, by the dorsal spine. Air-fluid levels are uncommon in upper lobe TB (less than 10%) but occur more frequently in lower lobe cavities. Fresh bronchogenic spread from recent spillage of infectious cavity contents appears as multiple, discrete, soft, fluffy infiltrates, or a confluent infiltrate adjacent to a cavity, or in the middle or lower lung field on the same or opposite side. These latter types of spread are seldom progressive and heal by rounding up into more discrete lesions with regular borders.

Both chronicity and histopathologic features can be estimated based on the chest radiograph. Granulomatous lesions tend to be small, nodular, and sharply defined, indicating few organisms and a good host response. Exudative lesions (pneumonic) tend to have soft, indistinct borders and are more unstable. Fibrotic scars have sharp margins and tend to contract. Caseation causes increased density. Healing exudative lesions first become smaller and less dense and then, as scarring develops, become more sharply defined. Lower lobe TB is nonspecific radiographically. Other patterns include poorly resolving pneumonia, atelectasis, mass lesions, and large cavities with air-fluid levels; initial misdiagnosis is the rule. Pneumonia associated with hilar adenopathy should always suggest primary TB, regardless of the lung fields involved and patient age. Pulmonary TB can also occur in persons with a normal chest radiograph; up to 6% of HIV-seronegative and 22% of HIV-seropositive persons with pulmonary TB have a normal chest radiograph.[217,221–223]

Laboratory Findings

Normocytic, normochromic anemia, hypoalbuminemia, and hypergammaglobulinemia are characteristic of advanced disease. The white blood cell count is usually normal but may be between 10,000 and 15,000

cells/mm^3. Many HIV-negative patients with active TB have CD4$^+$ T-cell counts much lower than 500 cells/L, which return toward normal with treatment.[224] Monocytosis is seen in less than 10% of cases. Hematuria or sterile pyuria should suggest coexisting renal TB. Hyponatremia with features of inappropriate secretion of antidiuretic hormone is characteristic of tuberculous meningitis but also occurs with isolated pulmonary involvement. Hyponatremia should also suggest associated Addison disease due to adrenal TB. Hypercalcemia is also seen during pulmonary TB, usually in the first weeks of therapy.

Diagnosis

A strong presumptive diagnosis can often be made based on the radiographic pattern. A positive sputum smear, usual in extensive disease, provides additional evidence in support of a diagnosis. However, an intercurrent cancer or lung abscess, particularly in the apices, may erode a quiescent focus of TB and cause brief shedding of tubercle bacilli without causing active disease. The best diagnostic sputum specimen is an early morning sample. Although two sputum specimens are sufficient in some settings, three specimens are recommended because of greater sensitivity.[225] Aspiration of gastric contents, obtained early in the morning to sample sputum swallowed during sleep, is an alternative when sputum is not produced. The specificity of gastric aspiration is diminished by the presence of nontuberculous mycobacteria but may be higher in children than adults. Sputum induction by hypertonic saline aerosols is also an effective substitute in ambulatory patients; the yield is comparable to that of fiberoptic bronchoscopy.[226] Pulmonary TB in patients with AIDS is often noncavitary and therefore may have a lower bacillary burden than in HIV-seronegative persons. The high prevalence of smear-negative TB in HIV-infected persons underscores the importance of obtaining sputum culture, even in resource-poor settings.[227] Positive sputum smears are much more likely to indicate *M. tuberculosis* than *Mycobacterium avium* complex, even in areas where both diseases are common.[228] NAAT, described previously, can provide a rapid distinction between the two infections in smear-positive respiratory secretions. (Additional diagnostic assays, including NAAT and testing for *M. tuberculosis* antigens in urine, are discussed under "Microbiology.")

A negative tuberculin reaction or interferon-γ release assay does not exclude TB; skin test anergy and negative assays can occur in the setting of active disease.[177,229,230] The TST and interferon-γ release assays are insensitive in immunocompromised persons, such as HIV-infected persons with less than 100 CD4$^+$ T cells/mm^3.[230,231] Granuloma formation at histologic examination, even with AFB, is still only strong presumptive evidence, because similar findings may be produced by MOTT. Granulomas in the absence of AFB can be seen with other infectious diseases (e.g., histoplasmosis) and noninfectious causes (e.g., sarcoidosis, autoimmune disease). Definitive diagnosis requires culture and speciation.

Fiberoptic Bronchoscopy

Diagnostic fiberoptic bronchoscopy with transbronchial biopsy and bronchoalveolar lavage should be considered when sputum tests are inconclusive and the suspicion of TB remains high. In AIDS patients with pulmonary TB but negative smears, bronchoscopy yields a rapid diagnosis (based on smears and histologic features) in only one-third of cases.[232–234] Thus, a negative acid-fast stain at bronchoscopy does not exclude TB, although such cases are certainly less contagious.

Tuberculosis Diagnosed at Autopsy

From 1985 through 1988, 5.1% of all reported TB cases in the United States were diagnosed at death.[235] Usually, the patient was elderly and had underlying diseases. Both nonresolving pulmonary processes and extrapulmonary TB, particularly chronic miliary and meningeal disease, are often present in such patients. The usual reason for failure to diagnose TB in such patients is failure to look for it; delays in TB diagnosis, as can occur when persons receive fluoroquinolones, can also contribute.[236]

Tuberculosis and Cancer

It has been estimated that 1% to 5% of TB patients also have cancer, most being male smokers. It is possible that cancer can arise in tuberculous scars, and it is certain that cancer can erode old quiescent tuberculous foci, causing active disease. However, in many patients the diseases will be anatomically remote. No one cancer cell type predominates.

When TB and cancer occur together, diagnosis of the latter is often difficult but should be kept in mind in older men with TB who smoke, and sputum cytologic studies should be performed. There are certain radiographic findings that suggest concomitant cancer, such as progression of one area while the remainder of the lesion is regressing, a large (>3 cm) mass lesion admixed with infiltrative disease, the presence of hilar nodes in adult chronic pulmonary TB, and postobstructive atelectasis.[237]

THERAPY

Before effective drugs were available, 50% of patients with active pulmonary TB died within 2 years and only 25% were cured.[238] With the advent of chemotherapy, successful treatment became a reasonable goal in all adults. In practice, failures occur because of drug resistance or an inappropriate regimen, or, most important, because of nonadherence to therapy. For this reason the responsibility for adequate treatment has been shifted from the patient to the prescribing physician and to the health department, emphasizing the importance of directly observed therapy (DOT).[239]

Antituberculous Drugs

Additional information on dosage, adverse effects, drug-drug interactions, and other aspects of the pharmacology of antituberculous drugs is provided in Chapter 39.

Isoniazid

INH is the cornerstone of therapy and should be included in all regimens unless the *M. tuberculosis* strain is INH resistant. Occasionally, when the *M. tuberculosis* strain is resistant to low-level INH but susceptible to higher INH levels, and there is resistance to other antituberculosis drugs, INH is included in the regimen (although not considered to have full activity). The most important adverse effect of INH is hepatitis, the risk for which increases with age and underlying liver disease. Although rare, this complication can be fatal.[240] INH continues to be a cause of significant drug-induced liver injury, which may be associated with a lack of adherence to guidelines that recommend cessation of therapy based on symptoms (nausea, abdominal pain, jaundice, or unexplained fatigue) or alanine aminotransferase levels. In one study, 70% of patients who died or underwent liver transplantation continued INH for more than 7 days after meeting stopping criteria.[241]

Rifampin

RIF is the second major antituberculous agent. The most important complication of RIF is hepatitis, which is usually cholestatic. Although the risk for hepatitis is lower with RIF than INH,[242,243] hepatitis occurs more frequently in regimens containing both INH and RIF than in those containing INH alone.[244]

Of special concern is that RIF, by inducing hepatic P-450 cytochrome oxidases, causes many drug-drug interactions. Examples of drugs whose levels are reduced in the presence of RIF include warfarin, hormonal contraceptives, azole antifungal agents, methadone, corticosteroids, cyclosporine, tacrolimus, nonnucleoside reverse transcriptase inhibitors, and HIV-1 protease inhibitors. This can result in subtherapeutic levels of these drugs, necessitating either increases in their dosage or use of an antituberculosis drug other than RIF. The interaction between RIF and HIV-1 protease inhibitors can lead to substantially lower HIV-1 protease inhibitor levels, inadequate control of viral replication, and emergence of drug-resistant virus. In this setting, RIF may be replaced by rifabutin, which has comparable antituberculous activity but is a weaker enzyme inducer.[245] Adjustment of antiretroviral drugs with treatment of TB is shown in Tables 39.3 and 39.5.

Rifapentine

Rifapentine is a rifamycin antibiotic with a longer half-life than RIF or rifabutin, which allows once-weekly administration.[239,246] Once-weekly therapy, together with INH or moxifloxacin, may be considered in HIV-seronegative persons in the continuation phase of TB treatment of noncavitary pulmonary disease[239,247]; however, the rifapentine-INH regimen is not generally recommended in the recent ATS/CDC/IDSA

guidelines.[239] Once-weekly rifapentine should not be used to treat HIV-infected persons with active TB owing to the high risk for acquired rifamycin resistance.[248]

Pyrazinamide

PZA is an essential component of 6-month regimens. Early studies of PZA using high doses recorded such serious hepatotoxicity that it was largely abandoned. At currently recommended doses, PZA is associated with higher rates of hepatotoxicity and rash than other first-line drugs.[249] Cohort and case-control analyses found that adding PZA to INH and RIF increased the risk for hepatotoxicity appreciably.[250] In addition, severe hepatic injury and deaths have been reported among predominantly HIV-negative adults receiving short-course RIF plus PZA for LTBI.[251] The beneficial effect of PZA is limited to the first 2 months in regimens containing both INH and RIF.[252] Additional side effects include hyperuricemia, mild nongouty polyarthralgias that respond to nonsteroidal antiinflammatory agents, and gout. *M. bovis* is uniformly resistant to PZA.[253]

Ethambutol

EMB is included in initial treatment regimens until drug susceptibility results are returned and resistance to the other first-line drugs has been excluded, at which time it can be discontinued. It is given at a daily dose of 15 to 20 mg/kg. At 15 mg/kg the risk for ocular toxicity is low, but assessment of visual acuity and color discrimination should be performed at baseline and monthly while the patient is on therapy.

Streptomycin

STM, the first major antituberculous drug, was promptly replaced by INH as the cornerstone of therapy. Its activity is similar to that of EMB when either drug is given with INH, RIF, and PZA. Its use is limited by relatively high rates of resistance (particularly in high-incidence countries), parenteral administration, nephrotoxicity, and ototoxicity.

Fluoroquinolones

In vitro activity and some favorable trial results suggest that fluoroquinolones, particularly later-generation agents such as levofloxacin and moxifloxacin, are effective antituberculosis drugs.[254–256] However, fluoroquinolones should not be used as first-line therapy but rather should be reserved for patients who are intolerant of first-line drugs or who have drug-resistant TB, as part of a well-designed multidrug regimen. In the treatment of INH-resistant infection, a retrospective cohort study found more frequent favorable outcomes with regimens that contained a fluoroquinolone, without regard to the other components of standard TB therapy.[257] In countries where fluoroquinolones are easily available, use of quinolones by persons with undiagnosed TB is likely contributing to increased resistance in *M. tuberculosis.* In a high-prevalence country such as India, rates of quinolone resistance are already high both in new and previously treated cases.[258] The potential role of fluoroquinolones as first-line antituberculosis therapy is currently under evaluation in clinical trials. A 6-month regimen in South Africa, Zimbabwe, Botswana, and Zambia using daily (2 months) and then weekly moxifloxacin in place of INH and weekly rifapentine was as effective as a control regimen.[247] A dose of moxifloxacin 10 mg/kg/day may be insufficient for children 7 to 15 years of age being treated for MDR-TB.[259]

Unfortunately, multiple phase III trials have not supported the use of fluoroquinolones in regimens meant to shorten the duration of therapy to 4 months. In sub-Saharan Africa, a 4-month gatifloxacin-containing regimen was inferior to standard therapy.[260] The previously referenced trial in South Africa, Zimbabwe, Botswana, and Zambia contained an arm based on 4-month therapy that was inferior to standard therapy, and a trial in nine countries on three continents also found that a 4-month regimen replacing EMB or INH with moxifloxacin was inferior to standard 6-month therapy.[247,261]

Bedaquiline

Bedaquiline (Sirturo) is a diarylquinoline; its mechanism of action is adenosine triphosphate synthase inhibition. It has potent activity against *M. tuberculosis.* In persons with MDR-TB, there were improved 2-month sputum culture conversion rates among those who received bedaquiline plus optimal background therapy, compared with optimal background therapy alone (48% vs. 9%, respectively).[262] Potential toxicities include nausea and QT interval prolongation. The terminal elimination half-life is 164 days; in one study almost all patients had detectable plasma levels 96 weeks after the last dose.[263] In December 2012, bedaquiline was approved by the FDA for treatment of MDR-TB, but with a black box warning because of a greater number of deaths in the bedaquiline arm compared with those who received optimal background therapy only. Safety will be monitored closely in future trials. A report of 35 French patients who received bedaquiline for at least 1 month did not encounter drug-associated deaths.[264] With data now reported in the follow-up of patients through 120 weeks from baseline, the addition of bedaquiline led to faster culture conversion and more conversions at the end of observation. There were 10 deaths in the 79-patient bedaquiline group compared with 2 in the 81-patient placebo group, although FDA analysis of these differences noted that both deaths in the placebo group and 5 in the bedaquiline group were due to progression of disease.[265,266]

A large retrospective observational study among 428 MDR-TB patients treated with bedaquiline noted good safety and tolerability, and only one death.[267] The recommended dosage for bedaquiline is 400 mg once daily orally for 2 weeks, followed by 200 mg three times a week for 22 weeks taken orally with food to maximize absorption. Pharmacokinetic analysis suggests that penetration into the CSF is poor.[268] High cost may be a significant barrier to use of bedaquiline. Drug interactions will require further study; phase I data indicate that RIF and rifapentine increase bedaquiline clearance (4.78- and 3.96-fold, respectively).[269] Interactions with HIV therapy that includes the potent CYP3A4 inhibitor ritonavir suggest that concomitant administration with bedaquiline might require dose adjustment.[270] A provisional guideline for use of bedaquiline has been published.[271]

Second-Line Agents

Second-line agents are less efficacious or more toxic, or both, than first-line drugs. These include ethionamide, cycloserine, terizidone (available overseas), amikacin, kanamycin, capreomycin, thiacetazone, para-aminosalicylic acid (PAS), and other agents discussed in Chapter 39.

Third-Line Agents

Third-line agents have even less activity against *M. tuberculosis* than second-line agents and are usually given only as adjunctive therapy to persons with XDR-TB. These drugs have generally not been evaluated in a systematic manner for the treatment of TB. Such drugs include amoxicillin-clavulanate, clarithromycin, and linezolid (see "Treatment of Multidrug-Resistant Tuberculosis" and "Therapy for Extensively Drug-Resistant Tuberculosis"). Clofazimine is also in this group, but is now being evaluated as a more prominent treatment option given its important role in shortening treatment of MDR-TB.[272,273]

Agents Under Development

There are several new drugs that are currently under investigation for potential use in MDR-TB. These include the oxazolidinones (e.g., sutezolid [Sequella] and LCB01-0371 [LegoChem Biosciences]), nitroimidiazoles (e.g., delamanid [Otsuka] and pretomanid [Global Alliance for TB Drug Development]), and diamines (e.g., SQ-109 [Sequella]).[274] Delamanid, when given with optimal background therapy for MDR-TB, was associated with significantly higher rates of 2-month sputum culture conversion.[275] However, it did not improve cure and survival compared with optimal background therapy in a phase III trial, so WHO has recommended that it be used when other, more effective drugs, cannot be used.[276] Of note, delamanid significantly prolongs the QT interval.[277] Pretomanid (PA-824) is a prodrug, as is delamanid, and in phase II trials seems to have had its greatest efficacy in combinations containing PZA.[277,278] A phase IIb trial in drug-susceptible and drug-resistant TB of a regimen of moxifloxacin, pretomanid, and PZA had an acceptable safety profile. Bactericidal activity was superior at the 8-week assessment, although the predictive utility of that end point remains controversial.[279]

Selecting a Drug Regimen

Before RIF was available, excellent results in drug-sensitive infections were obtained with INH plus either PAS or EMB given for 18 to 24

months, "reinforced" in extensive disease by STM for the first 6 to 12 weeks. Relapse rates were unacceptably high with shorter courses. However, demonstration that RIF was equal to INH in efficacy led to studies of shorter treatment regimens. In definitive studies, drug-sensitive TB responded as effectively to 9 months of INH and RIF as to 18- to 24-month regimens not containing RIF.[280,281] It was subsequently demonstrated that 6-month regimens based on an initial 2-month intensive "bactericidal phase" of INH, RIF, PZA, and either STM or EMB, followed by a "continuation phase" of INH and RIF for 4 more months, performed as well.[282–284] Next it was shown that neither STM nor EMB improved results over a three-drug regimen (INH, RIF, and PZA) during the first 2 months of intensive therapy when the isolate was fully susceptible.[282] This 6-month three-drug regimen is acceptable for drug-sensitive disease. However, given concerns about resistance, EMB should be included until susceptibility testing results are known. A 6-month continuation phase of INH and EMB is inferior to a 4-month continuation phase of INH and RIF.[285]

Standard Regimens Based on Isoniazid and Rifampin

The combination of INH (5 mg/kg; maximum 300 mg), RIF (10 mg/kg; maximum 600 mg), PZA (25 mg/kg, maximum 2 g), and EMB (15 mg/kg), all given once daily by mouth, should be initiated in persons suspected of having TB.[239,286,287] Therapy should be given daily throughout the entire course of treatment.[239] If intermittent therapy is considered, it should be no less frequent than three times per week, and given only in persons at low relapse risk.[239] Intermittent therapy should be provided under direct observation. These four drugs should be continued for 2 months; EMB can be discontinued when susceptibility results are received, noting that the infecting organism is susceptible to the other three drugs.

At the end of 2 months, PZA and EMB can be discontinued and INH and RIF continued to complete a 6-month course. Several treatment regimens have been endorsed by the CDC, ATS, IDSA,[239] and WHO.[288] Several well-studied regimens are presented in Tables 249.7 and 249.8.[239] As an alternative in persons with drug-susceptible disease, INH and RIF can be given daily during the first 2 months, followed by 7 months of either daily or intermittent therapy, with no less than thrice-weekly administration preferred.[239,289] When given thrice or twice weekly, the RIF dose remains the same and the INH dose is increased to 15 mg/kg (900 mg maximum). In persons with a cavity on initial chest radiograph and positive sputum cultures after 2 months of therapy, TB relapse risk is high[290]; INH and RIF should be continued for an additional 3 months (9-month total course) to decrease the relapse risk.[239]

In persons with resistance to or intolerance of INH, a 6-month regimen of RIF, PZA, and EMB can be used. Results of all 6-month regimens in patients with initial resistance to RIF are poor, and such cases probably require 18- to 24-month courses, as was the case before RIF was available.[291]

When hepatitis (defined as aminotransferase levels greater than five times the upper limit of normal regardless of symptoms or greater than three times the upper limit of normal in persons with symptoms of hepatitis) occurs in patients receiving INH, RIF, and/or PZA, all drugs should be discontinued until hepatic aminotransferase levels normalize and symptoms resolve. Drugs may then be cautiously reintroduced in a stepwise fashion while serum aminotransferase levels are monitored. If persons are intolerant of INH, a regimen of RIF, PZA, and EMB can be given to complete a 6-month course. If persons are intolerant of RIF, a more prolonged (18- to 24-month) regimen based on INH and at least one companion drug (e.g., EMB and possibly a fluoroquinolone) can be continued.

Directly Observed Treatment

Poor adherence to antituberculosis therapy over the entire course of treatment, with resultant development of drug-resistant TB and low rates of TB cure and treatment completion, has led to the recommendation to use DOT whenever feasible.[239] Important to note, DOT is

TABLE 249.7 Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

INITIAL PHASE			CONTINUATION PHASE			
REGIMEN[a,b,c]	DRUGS[d]	INTERVAL AND DOSES[e] (MINIMAL DURATION)	REGIMEN	DRUGS[d]	INTERVAL AND DOSES[e,f] (MINIMAL DURATION)	RANGE OF TOTAL DOSES (MINIMAL DURATION)
1	INH RIF PZA EMB	7 days/wk for 56 doses (8 wk) or 5 days/wk for 40 doses (8 wk)[g]	1	INH/RIF	7 days/wk for 126 doses (18 wk) or 5 days/wk for 90 doses (18 wk)[g]	182–130 (26 wk)
2	INH RIF PZA EMB	7 days/wk for 56 doses (8 wk), or 5 days/wk for 40 doses (8 wk)[g]	2	INH/RIF	3 times/wk for 54 doses (18 wk)	110–94 (26 wk)
3	INH RIF PZA EMB	3 times/wk for 24 doses (8 wk)	3	INH/RIF	3 times/wk for 54 doses (18 wk)	78 (26 wk)
4	INH RIF PZA EMB	7 days/wk for 14 doses (2 wk), then 2 times/wk for 12 doses (6 wk)	4	INH/RIF	2 times/wk for 36 doses (18 wk)	62 (26 wk)

[a]Regimen effectiveness is greatest for Regimen 1 to least for Regimen 4. Regimen 1 is preferred for newly diagnosed pulmonary tuberculosis. Regimen 2 is a preferred alternative regimen when more frequent DOT during the continuation phase is difficult to achieve. Regimen 3 should be used with caution in patients with HIV and/or cavitary disease; missed doses can lead to treatment failure, relapse, and acquired drug resistance. Regarding Regimen 4, twice-weekly regimens should be avoided in HIV-positive patients and patients with smear-positive and/or cavitary disease; if doses are missed, therapy is equivalent to once weekly, which is inferior.
[b]If the patient's isolate is susceptible to both INH and RIF, EMB is not necessary, and the intensive phase can consist of INH, RIF, and PZA only.
[c]Variations of the preferred regimen may be acceptable in certain clinical and/or public health situations, as described elsewhere.[239]
[d]Pyridoxine (vitamin B_6), 25–50 mg/day, is given with INH to all persons at risk of neuropathy (e.g., pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.
[e]When directly observed therapy is used, drugs may be given 5 days/wk and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.
[f]Patients with cavitation on an initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week) continuation phase.
[g]Five-day-a-week administration is always given by DOT.
DOT, Directly observed therapy; *EMB,* ethambutol; *HIV,* human immunodeficiency virus; *INH,* isoniazid; *PZA,* pyrazinamide; *RIF,* rifampin.
Modified from Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. *2016; 63:e147–e195.*

TABLE 249.8 First-Line Tuberculosis Medications

DRUG DOSE (MAXIMUM)	MAJOR ADVERSE REACTIONS	RECOMMENDED MONITORING	DOSAGE FORMS	COMMENTS
Isoniazid[a] (INH)				
Daily C: 10–15 mg/kg (300 mg) A: 5 mg/kg (300 mg) *Once weekly* C: Not recommended A: 15 mg/kg (900 mg) *Twice weekly* C: 20–30 mg/kg (900 mg) A: 15 mg/kg (900 mg) *Three times weekly* C: Not recommended A: 15 mg/kg (900 mg)	Hepatic enzyme elevation, peripheral neuropathy, hepatitis, rash, CNS effects, increased phenytoin, (Dilantin), and disulfiram (Antabuse) levels	Baseline hepatic enzymes Repeat monthly if baseline abnormal, risk factors for hepatitis, or symptoms of adverse reactions	*Scored tablets:* 50 mg, 100 mg, and 300 mg *Syrup:* 50 mg/5 mL *Aqueous solution (IV/IM):* Scarce and may not be available	Hepatitis risk increases with age and alcohol consumption. Overdose may be fatal. Aluminum-containing antacids reduce absorption. Pyridoxine (vitamin B_6) may decrease peripheral neuritis and CNS effects.
Rifampin[a] (RIF)				
Daily C: 10–20 mg/kg (600 mg) A: 10 mg/kg (600 mg) *Once weekly* C: Not recommended A: Not recommended *Twice weekly* C: 10–20 mg/kg (600 mg) A: 10 mg/kg (600 mg) *Three times weekly* C: Not recommended A: 10 mg/kg (600 mg)	Hepatitis, fever, thrombocytopenia, flulike syndrome, rash, gastrointestinal upset, renal failure Reduces levels of many drugs, including methadone, warfarin (Coumadin), birth control pills, theophylline, dapsone, ketoconazole, PIs, and some NNRTIs Orange discoloration of secretions (sputum, urine, sweat, tears) and may permanently stain soft contact lenses	CDC no longer recommends routine monitoring tests; however, many clinicians continue to order baseline CBC, platelets, hepatic enzymes Repeat if baseline abnormal, risk factors for hepatitis, or symptoms of adverse reactions	*Capsules:* 150 mg and 300 mg *Syrup:* can be formulated from capsules by pharmacy *Aqueous solution (IV/IM):* Scarce and may not be available	Patients on methadone will need an increased dose of methadone (average 50%) to avoid opiate withdrawal. Interaction with many drugs leads to decreased levels of one or both. May make glucose control more difficult in diabetics. Contraindicated for patients taking PIs and some NNRTIs. Women on birth control pills need a barrier method while on rifampin.
Pyrazinamide (PZA)				
Daily C: 15–30 mg/kg (2 g) A: 15–30 mg/kg (2 g) *Once weekly* C: Not recommended A: Not recommended *Twice weekly* C: 50 mg/kg (2 g) A: 50–70 mg/kg (4 g) *Three times weekly* C: Not recommended A: 50–70 mg/kg (3 g)	Gastrointestinal upset, hepatotoxicity, hyperuricemia, arthralgias, rash, gout (rare)		*Scored tablets:* 500 mg	May complicate management of diabetes mellitus. Treat increased uric acid only if symptomatic. Most common reason for TB patients experiencing GI upset.
Ethambutol[b] (EMB)				
Daily C: 15–20 mg/kg (1000 mg) A: 15–25 mg/kg (1600 mg) *Once weekly* C: Not recommended A: Not recommended *Twice weekly* C: 50 mg/kg (2.5 g) A: 50 mg/kg (4 g) *Three times weekly* C: Not recommended A: 25–30 mg/kg (2400 mg)	Decreased red-green color discrimination, decreased visual acuity (optic neuritis), rash	Baseline tests of visual acuity and color vision Monthly testing for patients taking >15–25 mg/kg, for those taking EMB for >2 mo, and for patients with renal insufficiency	*Tablets:* 100 mg and 400 mg	Optic neuritis may be unilateral; check each eye separately. Not recommended for children too young for monitoring of vision unless drug resistant. Use lowest possible dose in range (except for drug-resistant patients). EMB should be discontinued immediately and permanently if any signs of visual toxicity occur.
Rifabutin (RBT)				
Daily C: Not recommended A: 5 mg/kg (300 mg) *Once weekly* C: Not recommended A: Not recommended *Twice weekly* C: Not recommended A: 5 mg/kg (300 mg) *Three times weekly* C: Not recommended A: 5 mg/kg (300 mg)	Hepatitis fever, thrombocytopenia, neutropenia, leukopenia, flulike symptoms, hyperuricemia Orange discoloration of secretions (sputum, urine, sweat, tears) and may permanently stain soft contact lenses Reduces levels of many drugs, including methadone, warfarin (Coumadin), birth control pills, theophylline, dapsone, ketoconazole, PIs, and NNRTIs With increased rifabutin levels, severe arthralgias, uveitis, leukopenia occur	Baseline hepatic enzymes Repeat if baseline values abnormal, risk factors for hepatitis, or symptoms of adverse reactions	*Capsules:* 150 mg	Patients on methadone may need an increased dose to avoid opiate withdrawal. Interaction with many drugs leads to decreased levels of one or both. May make glucose control more difficult in diabetics. Women on birth control pills need to use a barrier method while on rifabutin. In combination with NNRTIs or PIs, dosages change significantly.