Tuberculosis: An Update

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
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Faculty

Marilyn Fuller Delong, MA, BSN, RN, received her basic nursing education at St. Luke's School of Nursing in Cedar Rapids, Iowa, her BSN from Coe College and her MA from California State University, Long Beach. She has worked throughout the United States both clinically and as an educator. Her continuing education classes have focused on the case management aspects of the care of orthopedic and pulmonary patients, with particular focus on the long-term care needs of the elderly and disabled.

John M. Leonard, MD, Professor of Medicine Emeritus, Vanderbilt University School of Medicine, completed his post-graduate clinical training at the Yale and Vanderbilt University Medical Centers before joining the Vanderbilt faculty in 1974. He is a clinician-educator and for many years served as director of residency training and student educational programs for the Vanderbilt University Department of Medicine. Over a career span of 40 years, Dr. Leonard conducted an active practice of general internal medicine and an inpatient consulting practice of infectious diseases.

Faculty Disclosure

Contributing faculty, Marilyn Fuller Delong, MA, BSN, RN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Contributing faculty, John M. Leonard, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planners

Ronald Runciman, MD
Jane C. Norman, RN, MSN, CNE, PhD
Randall L. Allen, PharmD

Director of Development and Academic Affairs

Sarah Campbell

Division Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for all healthcare workers who may have contact with a patient with tuberculosis, including hospital staff and community healthcare providers.

Accreditations & Approvals

In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the learner to earn credit toward the CME and Self-Assessment requirements of the American Board of Surgery's Continuous Certification program. It is the CME activity provider's responsibility to submit learner completion information to ACCME for the purpose of granting ABS credit.

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 5 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

A complete Works Cited list begins on page 32.

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NetCE designates this continuing education activity for 5 ANCC contact hours.

This activity was planned by and for the healthcare team, and learners will receive 5 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 6 hours for Alabama nurses.

NetCE designates this continuing education activity for 5 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

NetCE designates this activity for 5 hours ACPE credit(s). ACPE Universal Activity Numbers: JA4008164-0000-22-015-H01-P and JA4008164-0000-22-015-H01-T.

Individual State Nursing Approvals

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Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

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Course Objective

Although tuberculosis has declined in the United States, the annual number of reported cases is in excess of 7,500 and the incidence rate remains disproportionately high among foreign-born, immunocompromised, and minority groups. The purpose of this course is to provide healthcare professionals with updated information regarding the pathogenesis, transmission, diagnosis, and treatment of tuberculosis in order to improve patient outcomes and promote the public health goal of eventual eradication of this infection.

Learning Objectives

Upon completion of this course, you should be able to:

1. Discuss the historical background of tuberculosis.
2. Describe the modes of transmission for tuberculosis.
3. Identify the three stages of tuberculosis.
4. List the signs and symptoms of pulmonary tuberculosis.
5. Identify persons at high risk of contracting pulmonary tuberculosis.
6. Describe the methods of diagnosis used for suspected tuberculosis, including the necessity of a translator for assessing non-English-proficient patients.
7. Characterize the important forms of extrapulmonary tuberculosis.
8. Discuss the suggested treatment options for pulmonary tuberculosis.
9. Describe approaches to chemoprophylaxis of tuberculosis.
10. Identify patient teaching goals that help the patient understand and cope with the diagnosis of tuberculosis.

Pharmacy Technician Learning Objectives

Upon completion of this course, you should be able to:

1. Discuss the history, transmission, and presentation of tuberculosis, including persons at risk for infection.
2. Describe the methods of diagnosing and treatment tuberculosis and considerations for prevention.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

HISTORICAL BACKGROUND

Tuberculosis (TB), also historically called the "white plague" and "consumption," is a disease that has plagued the citizens of nearly every nation in the world for centuries. It has produced acute, chronic, and latent diseases involving every organ in the body, although the lungs remain the primary site of infection. The disease is caused by a group of similar bacilli, most commonly *Mycobacterium tuberculosis*, which is often abbreviated as *M. tuberculosis* or as MTB.

Evidence of TB dating back 6,500 years has been found in archaeologic digs. There are signs of the organism in the remains of mummified Egyptians and mention of it in ancient Chinese and Sanskrit written records. Hippocrates made the first clinically detailed description between 460 and 375 B.C.E. He called the disease "phthisis." During the 16th to the 19th centuries, TB was epidemic in Europe, causing the death of as many as one in four persons.

Starting in Northern Europe more than 500 years ago, the disease spread steadily across the continent but did not move into Russia until the late 1800s. New Guinea, the last place left uninfected, developed TB for the first time in the 1940s.

Historically, epidemics of TB have been lengthy, lasting as long as centuries in some cases. At one time, it was thought that the illness was brought on by generalized weakness or starvation and that only artists, writers, or alcoholics would become infected. In time, as people of higher station in life were seen to develop TB, this idea was abandoned [12].

TB has been prevalent in America since colonial times, and the United States has waged a public health campaign against TB for more than 150 years. Until the early part of the 20th century, TB was largely a disease of the poor. It spread quickly through the industrial northeastern states due to poor nutrition and close living and working quarters, which encouraged cross-infection in those with very little resistance. Northern Europeans, who had been exposed for generations, had developed some resistance, but hundreds of thousands of others who had not quickly became infected. Despite public health measures, periodic epidemic spikes in the incidence of infection occurred often up until the 1930s.

In 1882, one of the most significant accomplishments in the history of medicine occurred when Dr. Robert Koch identified the tubercle bacillus. Public health officials developed strict rules of cleanliness, and many people were forced to go to "consumptive prison." Unfortunately, this resulted in a common prejudice directed toward TB victims and their families. In 1906, immigration laws were written denying admission to this country by anyone with active TB. In 1912, laws were enacted preventing patients with TB from attending schools or renting apartments.

Eventually, sanitaria were opened to provide a more humane form of quarantine, and this proved to be an effective means of decreasing the incidence of disease. The success of sanitarium care was not so much because it provided a cure for this difficult disease, but because it effectively segregated infected persons from the general public. At the sanitaria, many forms of treatment were tried, including surgical pneumothorax and lobectomy. Some patients even had ping-pong balls inserted into infected pulmonary cavities in a desperate attempt to control progression and effect a cure.

Christmas Seals, which originated in the early 1900s, helped to pay for the treatment of those with TB and for education to help prevent the disease. In 1944, Dr. Selman Waksman discovered that streptomycin, the first of the aminoglycoside antibiotics, was effective in treating TB. This understandably raised much hope at the time, and Dr. Waksman eventually was awarded the Nobel Prize in Medicine for his discovery. Soon, however, isolates of the organism began to show resistance to streptomycin, limiting its effectiveness. Para-aminosalicylic acid (PAS) was added, and while it was effective for a time, the organism once again mutated sufficiently to resist treatment.

In the 1950s, two major developments greatly advanced the treatment and control of TB. First, the discovery of isoniazid (INH) provided the first highly effective, inexpensive, and safe drug able to regularly produce a clinical cure. Second, the use of a multidrug regimen (with INH) was shown to enhance the therapeutic effect, to reduce the risk of developing drug resistance on therapy, and to render patients noninfectious within a relatively short period of time. As a consequence, sanitaria soon began to close their doors.

Systematic surveillance of TB was introduced in the United States in 1953. In the decades following, the reported yearly incidence of new cases declined steadily until 1985, at which time it leveled off, then rose slightly to a peak in 1992 [23; 31]. In response, the U.S. Public Service pooled local, state, and federal resources in an effort to identify the causes for the increase, enhance surveillance, and establish treatment guidelines. This trend, which proved to be transient, could be attributed to several factors: the advent of the human immunodeficiency virus (HIV) outbreak, the high prevalence of poverty and homelessness, and the influx of foreign-born persons into the country, particularly from Latin America, Asia, and the Pacific Islands [23; 24].

As a nationally notifiable disease, the health departments of all 50 states and the District of Columbia electronically report all TB cases to the Centers for Disease Control and Prevention (CDC). Federal funds are designated for TB control, including treatment, and administered through state health departments. Fortunately, and in part as the result of current treatment and public health control measures, the incidence of TB has decreased by almost 79% between 1993 and 2020 [10]. Additionally, a steep reduction in TB incidence from 2019 to 2020 occurred (20% fewer cases versus 2% to 3% fewer in each previous year) and is thought to have been due to COVID-19 infection control measures and/or reduced detection [24]. Ongoing diligence is nevertheless required, as the incidence of multidrug-resistant tuberculosis (MDR-TB) has become a serious threat to elimination of the disease [23].

EPIDEMIOLOGY

In a global perspective, the effect of TB on the health and economy of the world is staggering. It has been estimated that 2 to 3 billion people worldwide are infected with *M. tuberculosis* and are therefore at risk for developing active clinical disease within their lifetime. This represents approximately one-third of the world's population. According to the World Health Organization (WHO), TB caused an estimated 10 million new cases of active clinical disease and 1.5 million deaths in 2020 [14]. TB ranks as a leading cause of death among individuals with human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS) worldwide, and about 214,000 TB deaths in 2020 were among HIV-positive individuals. Even among immunocompetent people with latent TB, 5% to 10% will develop active tuberculosis disease [14].

In 2018, a total of 9,029 TB cases were reported in the United States, for an incidence rate of 2.8 cases per 100,000 persons [54]. This represented a 1.3% decrease from 2017, continuing the gradual decline in the incidence of TB for more than 20 years. As discussed, 2020 saw a significant, yet anomalous, reduction in reported TB cases [24]. In 2021, a total of 7,860 TB cases were reported in the United States, for an incidence rate of 2.4 cases per 100,000 persons [70]. Although this represents a 9.4% rise in cases from 2020, it is still a 12.6% decrease compared with 2019. A reduction of TB cases was also observed globally during the coronavirus pandemic [70]. It remains likely that underdetection (due to disruptions in healthcare access), less migration from countries with high TB transmission, and increased health precautions (e.g., distancing, masking, quarantine, hygiene) all contributed to the unusual decrease in new TB cases in the United States throughout the COVID-19 pandemic.

The reported incidence varied significantly among states in 2021, from 0.27 cases per 100,000 population in Montana to 7.92 cases per 100,000 in Alaska, with a median national rate of 2.37 [70]. Ten states (Alaska, California, Delaware, Hawaii, Maryland, Massachusetts, New Jersey, New York, Texas, and Washington) and the District of Columbia reported TB incidence above the national rate. For the past two decades, four states (California, Florida, New York, and Texas) have accounted for approximately half of the annual reported cases of TB in the United States [54].

Conditions that are believed to be catalysts for the persistence of TB are [54; 70]:

- Increased poverty, injection drug use, and homelessness
- Increased numbers of residents in long-term care facilities
- Foreign-born persons originating from countries where TB is endemic
- Immunocompromised individuals, particularly those with HIV/AIDS
- Failure of patients to complete TB drug treatments

Records show that foreign-born persons and racial/ethnic minority populations continue to be affected disproportionately. The rate among U.S.-born and non-U.S.-born persons is 0.79 and 12.16 (per 100,000), respectively [70]. Pulmonary TB is also seen commonly among people living in overcrowded housing with poor sanitation. Due to air travel and immigration, disease that is prevalent in developing countries often spreads worldwide. Of the 7,860 cases reported in 2021, 71% occurred in foreign-born persons, whereas 29% occurred in persons born in the United States [70]. In 2020, five countries of origin accounted for more than 50% of foreign-born persons with newly reported TB: Mexico (19%), the Philippines (12%), India (10%), Vietnam (8%), and China (6%) [24; 54].

ETIOLOGY

Of the species in the genus *Mycobacterium*, several have been grouped as the *Mycobacterium tuberculosis* complex: *M. tuberculosis*, which is the causative agent for nearly all the TB in humans; *M. bovis*, found in cattle, which is rare in the United States because of laws requiring the pasteurization of milk; *M. africanum*, a disease primarily in equatorial Africa, may also be found in those who have immigrated from Africa; and *M. microti*, which is not pathogenic for immunocompetent humans. Within the last 20 years, five additional species belonging to the complex, *M. suricattae*, *M. pinnipedii*, *M. canettii*, *M. caprae*, and *M. mungi*, have been identified [36; 37; 38; 39; 56].

Tubercle bacilli are slender rods with a slight curve, measuring 2 – 4 microns in length. They are aerobic, non-spore forming, non-motile, and weakly gram-positive.

The cell wall of *M. tuberculosis* grows in snake-like cords and is the most complex of all bacteria. By electron microscopy, three layers are visible. The innermost layer, which is next to the cell membrane, consists of cross-linked peptidoglycans that give the cell its shape and rigidity. The middle layer is an arabinogalactan polymer laced with long-chain fatty acids, called mycolic acids. The outermost layer is composed of mycosides. The mycolic acids of the various species of mycobacteria are unique to that particular species, which allows differentiation of characteristic fatty acid fingerprints, identifiable by chromatography and DNA testing [22].

TB is often referred to as having been caused by an "acid-fast bacillus." The bacilli are difficult to stain because of the high lipid content of their cell walls, and once stained, they resist discoloration with acid-alcohol. There are other bacteria that are weakly acid-fast, but only *M. tuberculosis* is so strongly stained. Because of this, the acid-fast stained sputum smear is the traditional method for preliminary detection of pulmonary TB. It is easy to perform, inexpensive, and widely used around the world. The specificity

of a positive smear in a patient with compatible symptoms and x-ray findings is nearly 100%, but the sensitivity is only about 30% to 50% in specimens of sputum that are later cultured as positive for *M. tuberculosis*.

PATHOGENESIS, TRANSMISSION, AND RISK FACTORS

Although primarily affecting the pulmonary system, TB may spread to other organs. *M. tuberculosis* is acquired by inhalation of droplets containing bacteria aerosolized from infected persons with active (usually cavitary) lung disease who are untreated or undertreated.

Inhaled droplet nuclei containing tuberculous bacilli accumulate in the alveoli of the middle or lower lobes of the lung. They replicate and gain access to regional lymphatic channels, mediastinal lymph nodes, and thence to the thoracic duct and bloodstream, by which they are disseminated throughout the body. In response, the immune system targets these scattered vascular foci of infection, first with macrophages that surround and engulf the organisms, then lymphocytes, and finally a characteristic, focal inflammatory reaction termed a granuloma. A healthy granulomatous reaction terminates active infection, usually before the person is symptomatic, though it does not eliminate all bacilli. In time, the granuloma becomes encapsulated, effectively sealing off any remaining viable organisms. Encapsulated granulomas are termed tubercles. With age, they usually calcify, and larger ones are visible later by chest x-ray and tissue scans. Most healthy persons remain asymptomatic throughout life, the only evidence of prior infection being the calcified granuloma or positive skin test.

As indicated, infected but asymptomatic individuals may harbor viable organisms within macrophages contained by inactive granulomas, maintaining this dormant state (latent TB) for decades. Many new active cases of TB are considered to actually represent reactivation of latent infection under conditions of impaired host cellular immunity. As such, these cases are referred to as reactivation TB. Infection in healthcare workers often occurs from exposure to patients with cavitary pulmonary TB prior to diagnosis [7].

Risk factors for progressive primary infection or reactivation TB include the following:

- Extremes of age (i.e., the very young and the elderly)
- Inanition and malnutrition caused by social deprivation, injection drug use, or malignancy
- Conditions leading to impaired cellular immunity, such as corticosteroid therapy or HIV/AIDS

Most communicable diseases are transmitted in a variety of ways. They may be passed from person to person through blood or other body fluids, via fomites, or by air droplets. For years, those caring for patients with TB were careful to dispose of or decontaminate the clothing, linens, eating utensils, and other belongings of patients with TB. However, it was discovered that TB is spread almost entirely through the inhalation of aerosolized droplet nuclei carrying the live *M. tuberculosis* bacillus.

Infected droplet nuclei, released by coughing, originate from cavitary foci within the lung or from ulcerative lesions in the tracheobronchial tree or oropharynx. Pulmonary cavitation develops gradually from localized inflammation and necrosis of lung tissue that follows reactivation of latent TB. Pooled secretions and retained debris impede clearance, and cavitary lesions become an oxygen-rich environment that facilitates multiplication of bacilli. The clinical consequence is a chronic cough, and with each cough there is potential risk for transmission of infection as large numbers of bacilli are released into the nearby atmosphere. In persons with open cavitary disease, simple coughing, sneezing, laughing, or singing can release a myriad of infected particles into the air.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The World Health Organization recommends that respiratory hygiene (including cough etiquette) in people with presumed or confirmed TB is recommended to reduce *M. tuberculosis* transmission to health workers, persons attending healthcare facilities, or other persons in settings with a high risk of transmission.

(https://apps.who.int/iris/bitstream/handle/10665/311259/9789241550512-eng.pdf. Last accessed September 22, 2022.)

Strength of Recommendation/Level of Evidence: Strong recommendation based on low certainty in the estimates of effects

However, compared with other infectious diseases, TB is not easy to contract. The average time of exposure until acquired infection is about two months. There have been reports of infection occurring in much less time. In one well-reported incident, a passenger on an airline was very ill with TB and coughed throughout the entire flight. Later, it was learned that fellow passengers on the plane had become infected with TB [7]. This is a rare occurrence, but it serves as a reminder to those in the healthcare professions. Caring for patients with TB can be a health risk, and proper isolation techniques for prevention must be employed when working with known or suspected cases of active infection [7].

The incidence of TB varies in relation to socioeconomic conditions, immigration status, and prevalence of HIV/AIDS. Compared to the general population, rates of active infection are disproportionately high among African Americans, Hispanics, and immigrants from Asia, perhaps in part because of crowded living conditions and poor access to health care [54]. One report stated that as many as 18% of persons living in homeless shelters test positive for TB [13]. Institutionalized individuals and migrant farm workers are also at increased risk for TB due to crowded housing conditions.

TB is generally a problem at the extremes of life in the United States. Pediatric TB cases comprise about 5% of the total number of reported cases [25]. While the risk of disseminated TB is higher in children younger than 4 years of age, children in the United States who are younger than 14 years of age have the lowest incidence rate (0.9 per 100,000) [24; 25]. Elderly patients at greatest risk are those residing in nursing homes or other group settings [21]. These people are at risk not only for primary TB from direct transmission, but also for reactivation TB.

STAGES AND TYPES OF TUBERCULOSIS

There are three stages of infection seen in persons with pulmonary TB: primary or initial infection; latent or dormant (asymptomatic) infection; and secondary or reactivation infection. All three must be considered and treated when patients present with TB-specific symptoms.

PRIMARY INFECTION

When droplet nuclei containing live *M. tuberculosis* are inhaled, they will most likely be deposited on the bronchial mucosa. The bacilli may then be swept out of the respiratory tract by mucociliary action or move on to the terminal bronchioles and alveoli. If this occurs, the bacteria will begin multiplying and develop a focus of infection. This usually takes place in the middle or lower lobes of the lung, where ventilation is greatest.

As indicated, the characteristic pathologic lesion in TB is the granuloma, composed of macrophages and lymphocytes in varying degrees of active phagocytosis and degeneration. When the inflammatory reaction is prolonged and progressive, as with poorly contained or reactivation infection, the granuloma becomes sizable and undergoes central necrosis. On pathologic examination, this central necrotic debris is often described as "caseous" because it resembles crumbling cheese.

The initial, small focal granulomatous pneumonitis associated with primary infection, while contained, often calcifies in time and is a visible coin-shaped lesion on chest x-ray. This calcified focus carries the term Ghon lesion; when seen in association with calcification of the adjacent mediastinal lymph node, it is referred to as the Ranke or primary complex—a finding highly specific for prior TB infection.

In the course of primary infection, *M. tuberculosis*-laden macrophages migrate from hilar and mediastinal lymph nodes through the thoracic duct and into the bloodstream. The resultant bacillemia leads to multiple small foci of infection scattered throughout the body, especially in oxygen-rich organs such as kidney, liver, spleen, vertebra, and the epiphyses of long bones. Usually, cell-mediated immunity develops and stops further growth and spread. If that fails, the infection progresses and the illness may assume a chronic, active, disseminated form (miliary TB) that can, in time, lead to central nervous system involvement and meningitis.

In the early postprimary infection period, weeks to months after the development of effective cell-mediated immunity, a tuberculous pleural effusion may develop, even in apparently healthy young adults. The pathogenesis is considered to be a delayed hypersensitivity reaction to mycobacterial antigens released into the pleural space from the rupture of a subpleural, poorly-contained granuloma. Tuberculous pleural effusion may be caused by relatively few bacilli, making diagnosis difficult. In young, otherwise healthy adults, this form of TB may remit spontaneously (without treatment); however, it does portend an increased risk for reactivation TB later in life.

LATENT/ASYMPTOMATIC PULMONARY INFECTION

If the immune process works well and stops the proliferation of bacilli after the initial primary infection, healing occurs in the lungs, in the lymph nodes, and in the metastatic sites of infection. Depending upon the patient's age and presence of other infections, a latent period ensues. This period lasts a lifetime in 85% to 90% of those infected. During this asymptomatic phase, the only evidence of infection with *M. tuberculosis* may be skin-test reactivity to tuberculin [22]. Some patients will have fine, linear scarring in the lung or a focal calcification (Ghon lesion) visible usually in a middle or lower lobe, a sign of the struggle between *M. tuberculosis* and the cellular immune response.

SECONDARY OR REACTIVATION TB

It is estimated that 13 million persons in the United States are infected with the latent or asymptomatic form of TB [57]. Recurrence of the active disease occurs in 10% to 15% of infected patients, half of whom reactivate within the first two years after the primary infection. The cause for the reactivation is usually a breakdown in the patient's immune system rather than reinfection from newly inhaled bacteria. In the United States, the highest frequency of recurrent or reactivation TB is in middle-aged and older adults and immigrants [3].

VARIATIONS IN IMMUNE RESPONSE

The diagnosis of TB may be missed, or not even considered, because of the uncommon presentation it makes in some persons. For example, an elderly person may develop what is thought to be community-acquired lower lobe pneumonia. Diagnosis is confirmed by chest x-ray, but the infection may not respond to the usual antibiotic treatments. The "pneumonia" may actually have occurred as the result of a lymph node rupturing into a bronchus, a consequence of TB.

In another scenario, a patient with AIDS develops a lower lobe infiltrate. The chest x-ray reveals no granuloma and no cavities, so TB is not entertained as a possible diagnosis. This occurs because the inflammatory response is so blunted in AIDS that rapid proliferation and spread of *M. tuberculosis* within the involved lobe occurs before an established, healthy granulomatous reaction can develop. It is important, therefore, to consider TB as a possible diagnosis, even when the symptoms and radiographic signs do not fit the typical scenario.

PULMONARY TUBERCULOSIS

SIGNS AND SYMPTOMS

The early symptoms of active pulmonary TB are often so subtle as to be missed at first by most patients. Because of this, they will frequently have difficulty pinpointing exactly when their illness began. Some patients without obvious symptoms are diagnosed solely by a routine chest x-ray. For those who do have symptoms, the most common manifestations are gradual onset and progression of fever, malaise, cough, anorexia, and weight loss. The fever is one that is not so high as to be noticed or to be disquieting. When the fever breaks during the early morning hours, it is often associated with "night sweats." Weight loss may result from the infectious process itself, or it can be a sign that malnutrition and depletion of immune reserves preceded, and to some extent caused, the infection.

Cough is generally nonproductive at first, then later productive of purulent sputum. With progressive cavitation in the lung, the patient develops hemoptysis. Bleeding results from the necrosing walls of cavitary lesions in the lungs or from the rupture of small venules in the walls of inflamed bronchi.

Chest pain, usually pleuritic in nature, arises from infection of the pleural surface and the resulting effusion. If there is extensive lung destruction, dyspnea will also occur, which eventually leads to respiratory failure and death.

In most cases, physical examination is not a helpful diagnostic tool, as the clues are simply not specific enough to pinpoint TB. Rales and other breath sounds may or may not be heard. When fever is out of proportion to respiratory symptoms and the chest x-ray findings are nonspecific, especially if there is lymphadenopathy or hepatosplenomegaly, one should consider extrapulmonary, disseminated TB.

METHODS OF DIAGNOSIS

Chest x-ray provides the best early clue to diagnosis, as it is nearly always abnormal in patients with active pulmonary TB. The progression of TB can also be monitored by chest x-rays, as the films have a different appearance at different stages of the disease. Pleural effusions are common during the post-primary phase of infection, particularly in adolescents and young adults. Hilar and mediastinal adenopathy are prominent, especially in children. In progressive primary TB, the chest x-ray shows infiltrates with consolidation in the lower- and mid-lung areas. After the primary infection heals, there are often apical changes, and calcification may appear in the lungs and lymph nodes [50].

Reactivation TB often presents as upper lobe infiltrates and cavitation in the apical and posterior segments of the upper lobes. It is rare to have the disease occur in the anterior segment. Reactivation TB may also appear in the superior segments of the lower lobes. As the disease progresses, infection spreads to adjacent areas of the lung, and the x-ray may show "fluffy" patches of infiltrate [50]. Computed tomography (CT) and magnetic resonance imaging (MRI) may also be used in assessing the areas affected by the disease. CT scans may provide a more sensitive evaluation of changes in the lungs. Magnetic resonance and positron emission tomography (PET) are more helpful with extrapulmonary TB.

Laboratory findings in TB are much the same as with any other chronic infection. There is normochromic normocytic anemia, the white blood cell count may be normal or mildly elevated, and commonly, one finds reactive thrombocytosis. Pancytopenia, disseminated intravascular coagulation (DIC), and elevated hepatic transaminases may occur in miliary TB. Urinalysis shows pyuria without bacteriuria if there is renal TB. Hyponatremia may result from the syndrome of inappropriate antidiuretic hormone secretion (SIADH), either as a result of pulmonary or central nervous system infection. Hypercalcemia may or may not be present, but when it is, usually it is mild.

HIGH-RISK GROUPS TO SCREEN FOR TUBERCULOSIS
Persons with HIV infection
Close contacts of persons with active, infectious TB
Persons with conditions that weaken their immunity, thereby putting them at greater risk for contracting the disease (includes chronic renal failure, diabetes, prolonged steroid use, immunosuppressive therapy, malnutrition, gastrectomy)
Injecting drug users
Residents and employees of long-term care facilities, prisons, mental institutions, homeless shelters, or other group homes
Emergency medical personnel
Firefighters
Persons spending time in countries with a high prevalence of TB
Foreign-born persons originating from countries with a high prevalence of TB

Source: Compiled by Author *Table 1*

TUBERCULIN SKIN TEST
When applying a skin test using the Mantoux technique, the injection should be made with a single-use, disposable tuberculin syringe. Draw up 0.1 mL of PPD, containing 5 tuberculin units (TU). The skin should be cleansed, as with any injection, and the skin stretched taut.
Using a 26- or 27-gauge needle, the tuberculin syringe should be held close to the skin so the needle hub touches it as the needle is inserted into the skin, with the bevel up. This decreases the needle angle at the skin surface and helps to ensure the fluid is injected just beneath the surface of the skin into the dermis to form a wheal, taking care not to inject subcutaneously.
The site of the injection should be circled with a pen and the location documented on the patient's medical record (in case the pen circle should wash off).
Examine the site of the Mantoux intradermal injection within 48 to 72 hours of injection. Always use sufficient lighting to examine the area. Use a pen to outline the diameter of induration (firm-to-hard zone of elevation or swelling). The area of erythema (redness) is not measured, and erythema without induration is of no significance. Use a standard centimeter rule or a clear plastic ruler that has been marked with circles of various diameters. Place the ruler over the outlined induration to measure its diameter. The presence and degree of induration is an indicator of prior TB infection and, to some extent, the probability of current active TB.
A reaction of <5 mm is negative. Reactions >10 mm are "positive." An intermediate reaction of 5–10 mm is suspicious for prior infection in high-risk persons.

Source: Compiled by Author *Table 2*

TB Screening

Screening for TB infection should include those persons identified as high risk (***Table 1***). It is also important to screen any others who may potentially come into contact with those in high-risk groups; this would include emergency medical personnel, firefighters, and those employed in prisons, homeless shelters, or other group housing facilities. Other low-risk groups may be required to be assessed for risk factors and/or tested for TB, including daycare center workers, teachers, and U.S.-born students [63]. There are currently two testing methods available for TB screening in the United States: the Mantoux tuberculin skin test and interferon gamma release assays (IGRAs). Healthcare providers should select the appropriate detection method based on the reason for testing, test availability, and cost [51].

Tuberculin Skin Testing

One way to perform mass TB screenings is to use the Mantoux method of skin testing (***Table 2***) [51]. The test indicates those who have been infected with the organism as soon as 2 to 10 weeks after exposure.

PPD, also called tuberculin, is available in three strengths: 1 tuberculin unit (TU), 5 TU, and 250 TU. The weakest is 1 TU, which is rarely used except in persons suspected to be at risk for a strongly positive reaction. The 5-TU strength is the standard for routine skin tests, in part because at this dose, the Mantoux test delivers a defined, well-controlled dose of antigen that is most reliable.

With the Mantoux technique, 0.1 mL of PPD, containing 5 TU, is injected intradermally into the volar or dorsal surface of the forearm. In 48 to 72 hours, the results are measured and recorded. The 250-TU strength may be useful for selected patients in whom the 5-TU test is negative. However, at the higher TU strength, a positive result is less specific; mildly positive reactions may represent previous vaccination against TB or prior infection with nontuberculous mycobacteria.

When the skin test is positive in a person previously known to have been negative, the person is said to have "converted." The reaction is measured in millimeters of induration, not by redness at the site. Generally, the larger the induration, the greater the likelihood of TB; however, this does not always hold true. More importantly, a negative reaction does not rule out latent or active infection. Someone whose immune system has been weakened by disease, age, or drugs may have a weak or negative reaction even though they are infected. It is important to remember that the test is primarily used for assessing the probability of exposure to *M. tuberculosis* in the past and the possibility of latent infection, not the presence of active disease [11; 18].

Older persons who were infected many years previously may have sustained a natural waning of immunity, resulting in a false-negative skin test. Because of this, a two-step procedure is often done on those older than 50 years of age who are suspected of being infected. If the first test is negative, then it is repeated one or two weeks later. If the second test is positive, it means the initial dose stimulated the latent cellular immunity, resulting in a positive reaction to repeat antigenic exposure. This is often referred to as the "booster phenomenon."

In suspected cases, the significance of a negative tuberculin skin test can be further assessed by testing for anergy. A control test is done using antigens to which virtually all adults have been previously exposed to determine if there is any cellular immune response. The antigens most commonly used as controls are *Candida albicans*, *Trichophyton*, mumps virus, and tetanus. They are administered using the same Mantoux technique. An induration occurs if a person has been sensitized to the antigen and has an intact, healthy cell-mediated immune response. Failure to obtain a reaction from a control site is an indicator of depressed immune system (or anergy). There is some controversy among physicians regarding anergy testing, and studies have brought the usefulness of the testing into question. At this time, routine anergy testing is not recommended [29; 40].

Interferon Gamma Release Assay (IGRA)

In 2007, the FDA approved the QuantiFERON-TB Gold In-Tube test (QFT-GIT), a third-generation IGRA [6]. This test quantifies the immune response to peptides that imitate TB proteins not found in either the bacille Calmette-Guérin (BCG) vaccine or in non-tuberculosis mycobacteria [6]. In 2008, the FDA approved another IGRA for the rapid detection of TB: the T-SPOT.TB test (also referred to as T-Spot) [49]. This test can detect increases in the number of cells that secrete interferon gamma after stimulation with antigen as compared to the media control [49]. As of 2022, these two TB blood tests are the only approved, commercially available

IGRAs in the United States [6]. According to the manufacturers' instructions, a blood sample is drawn from the patient, the fresh blood is mixed with antigens and controls, and the interpretation is based on the amount of IFN-g that is released (QFT-GIT) or on the number of cells that release IFN-g (T-Spot). Results from these tests are available within 24 hours. IGRAs can usually be used in place of tuberculin skin testing and may be preferable, as they require only one patient visit. The CDC guidelines for the use of IGRAs are available online at https://www.cdc.gov/mmwr/pdf/rr/rr5905.pdf [48].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America recommend performing an interferon-γ release assay (IGRA) rather than a tuberculin skin test in individuals 5 years of age or older who are likely to be infected with *M. tuberculosis*, who have a low or intermediate risk of disease progression, and in whom it has been decided that testing for LTBI is warranted.

(https://academic.oup.com/cid/article/64/2/111/2811357. Last accessed September 22, 2022.)

Strength of Recommendation/Level of Evidence: Conditional recommendation, moderate-quality evidence

Sputum Smear and Culture

When skin testing, chest x-rays, or clinical symptoms suggest TB, the next step is to obtain sputum specimens for smear and culture. This will help confirm the diagnosis and rule out other similar diseases.

Sputum specimens must be properly obtained in order to be useful. The technique used must produce the best specimen and must also prevent the care provider from exposure to the tubercle bacillus. Effective specimens can help the practitioner to confirm a diagnosis of pulmonary TB, determine an infection's susceptibility to drugs, and assess the response to treatment. Acid-fast bacilli should decline in number after treatment has begun, and sputum smear and culture become negative in a matter of a few weeks. If this does not occur, it may signify lack of compliance or the development of MDR-TB. For diagnostic purposes, morning sputum samples are collected daily for three to five days. This increases the opportunity for finding the *M. tuberculosis* organism.

Procuring Sputum Specimens

When procuring a sputum specimen, it is important that patients understand the instructions so that their cooperation is obtained. If they speak a language other than English, it will be necessary to find a translator. A good indicator of patient understanding is to have them repeat the instructions to the practitioner. If the patient has difficulty learning the steps to the procedure, they may need to be instructed on each step as it occurs.

The optimal time to collect a specimen is early morning, after the patient has had nothing by mouth for about eight hours. The mouth should be rinsed with water to reduce contamination of the sample with the normal flora of the mouth, but the teeth should not be brushed prior to the collection.

Patients are provided a sterile container with a screw-top lid. They should avoid putting the rim of the jar inside their lips, but rather hold it below their bottom lip. Specimens should not be saliva or nasopharyngeal secretions, but should come from the lungs after a deep cough. A sample of 5–10 cc (1–2 teaspoons) of sputum is adequate. Patients should be instructed to notify the practitioner as soon as the sample has been obtained so it can be sent to the laboratory promptly.

In some cases, a patient may not have adequate secretions to produce a specimen or there may be reason to need an immediate specimen. In those instances, sputum may be obtained by induction. This procedure carries a higher risk of contamination because an aerosol is used. The procedure should be done only in an acid-fast bacillus isolation room or sputum induction booth that meets the 2005 CDC guidelines [33; 35]. Staff should wear high efficiency particulate air (HEPA) or N95 (or better) respirators that have been certified by the National Institute of Occupational Safety and Health (NIOSH), which meet CDC guidelines for personal protection against TB. Access to the room is customarily restricted for one hour after the procedure is completed, allowing an adequate air exchange (six complete exchanges) to clean the air of all TB particles.

Sputum by induction is also best obtained early in the morning, as in normal sputum collection. A solution of 3% saline is introduced through a nebulizer for 15 to 20 minutes or until a specimen is produced. Hand-held ultrasonic nebulizers are most effective at maximizing the aerosol delivery and produce the best specimens.

If a patient has a history of asthma, a bronchodilator may be administered before the procedure to protect against bronchospasm. If not successful, the process should not be repeated until the patient has been given an opportunity to rest.

Comatose patients, others who are unable to cough, and children may require gastric aspiration to check for acid-fast bacilli in the stomach through nasotracheal or tracheostomy suctioning. When these procedures are done, the same protective measures should be followed as those described for the induction procedure. A positive smear is not as meaningful in this case because other acid-fast organisms may reside in the stomach, but a culture growth will confirm diagnosis [15].

DNA Probes

There are two U.S. Food and Drug Administration (FDA) approved, commercially available nucleic acid amplification tests (NAATs) for use in confirming *M. tuberculosis* in procured specimens [71]. The Xpert MTB/RIF Assay, which is able to detect the presence of *M. tuberculosis* organisms as well as resistance to rifampin, is an automated, cartridge-based system (GeneXpert platform) that requires a sputum sample [55]. Results are available within two hours. The second approved probe is the amplified *M. tuberculosis* direct (Hologic Amplified MTD) test, which uses transcription-mediated amplification in order to identify and magnify the RNA target. Results are generally available within three to four hours. This test is approved for the detection of tuberculosis in both smear-positive and smear-negative cultures [26]. Non-FDA approved NAATs (often called "in-house" tests) may be used to diagnose TB and to test for drug-resistant TB [46; 58]. The Xpert MTB/RIF Ultra and the Xpert MTB/XDR tests are two examples, the latter of which is a drug susceptibility test that can identify resistance to isoniazid, fluoroquinolones, second-line injectable drugs (e.g., amikacin, capreomycin, kanamycin), and ethionamide [72].

These tests are able to differentiate the DNA of different species of *M. tuberculosis*, also called DNA fingerprinting or genotyping. Because most strains of bacteria share patterns, it has been difficult to follow the person-to-person transmission of certain strains. Using genotyping, researchers have shown that each strain has a distinct DNA fingerprint and that all samples sharing the same DNA fingerprint were isolated from people who live together. This will help track the path of transmission and aid public health researchers to pinpoint patterns of infection, which in turn helps to plan prevention programs that target the areas of heightened infection rates.

A task force supported by the CDC and pulmonary/infectious disease subspecialty societies recommends that a NAAT should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established and for whom the test result would alter case management or TB control activities [46].

Other Tests

Mycobacterial antigens can be found in the cerebrospinal fluid (CSF) of patients with tuberculous meningitis, making immunoassay an attractive diagnostic tool. Biochemical tests using gas chromatography and mass spectrometry are sensitive and accurate, but the equipment costs make widespread use impractical. Most research into immunoassay for diagnosis of TB has focused on blood testing. In 2007, a study of immunoassay of bronchoalveolar lavage fluid found that the technique had the potential to be a useful tool [45]. However, a 2010 study of the Diagnos TB AG immunoassay found that the test was not helpful in the rapid diagnosis of TB [47]. Another immunoassay, SD BIOLINE TB Ag MPT64, has been developed to quickly discern between *M. tuberculosis* and other mycobacteria. More research is necessary to evaluate the efficacy and validity of such tests. CSF can also be tested with IGRA or the Xpert MTB/RIF test [73].

EXTRAPULMONARY TUBERCULOSIS

Although primarily seen as a pulmonary disease, TB can affect any organ in the body. Historically, TB of the tonsils, lymph nodes, abdominal organs, bones, and joints was common. In the past, this was often related to ingestion of milk contaminated by *M. bovis*. Since pasteurized milk became an industry standard, the threat of that sort of extrapulmonary TB has not been seen.

Often, in cases of extrapulmonary TB, local trauma, aging, or an acquired immunodeficiency results in the breakdown of a latent tuberculous granuloma in a distant organ such as lymph node, bone, liver, or spleen. This can lead to a sustained, progressive local organ infection, often complicated by periodic bacillemia and generalized (disseminated) tuberculosis.

TB OF THE CENTRAL NERVOUS SYSTEM

Central nervous system tuberculosis is among the least common but most devastating of extrapulmonary forms of infection. It develops in the setting of sustained bacillemia that may follow primary or late reactivation tuberculosis, in the course of which bacilli, and in turn fresh tubercles, are distributed throughout the brain and meninges. The chance location, progression, and rupture of a meningeal tubercle into the subarachnoid space initiates meningitis. The onset and progression of illness follows three stages over three to five weeks: a prodrome of malaise, fever, and vague headache; followed by severe headache, neck discomfort, nausea, vomiting, and cranial nerve signs; then drowsiness, stroke-like signs, stupor, and coma. Early clinical diagnosis and empiric therapy before confirmation of the diagnosis is critical. The diagnosis is made by smear, culture, and NAAT of serial CSF specimens. On occasion, central nervous system TB produces an abscess or large granulomatous mass lesion (tuberculoma) within the brain without meningitis. As with other brain "tumors," these patients present with headache, seizures, and/or focal weakness.

RENAL TB

The kidney is the most common site for extrapulmonary TB. From there, the bacilli spread to the bladder and, in men, to the prostate, seminal vesicles, and epididymis. Often, the first sign of the infection is an enlarging scrotal mass. Pyelography will then often reveal a cavitary lesion of the renal parenchyma and irregularities of the ureters. Diagnosis is easily confirmed by urine smear and culture.

GENITOURINARY TB

After the onset of menarche, the fallopian tubes become quite vascular, making them vulnerable to hematogenous secondary TB salpingo-oophoritis. Systemic symptoms are lacking; the condition usually presents as a chronic pelvic inflammatory disease, with tubal scarring and infertility. Urine cultures often are not effective in diagnosis of genital TB in women; generally, a laparoscopy, laparotomy, or uterine scrapings are required.

TUBERCULOUS PERITONITIS

Tuberculous peritonitis arises from the rupture of an abdominal lymph node into the peritoneal space or by spread from a tuberculous salpingo-oophoritis. Symptoms range from fatigue and abdominal pain and tenderness to an acute abdomen. Diagnosis is usually made from paracentesis and peritoneal needle biopsy.

TUBERCULOUS PERICARDITIS

TB infection of the membrane surrounding the heart usually results from a spread of the infection from a mediastinal lymph node or tuberculous pleuritis to the pericardial sac. The illness begins insidiously and results largely from chronic inflammatory constriction of the pericardium that limits cardiac function. Symptoms include intermittent fever and chest pain, signs of heart failure, venous jugular distention, and distant heart sounds, occasionally by a pericardial friction rub. Surgical pericardiectomy is usually required for diagnosis and effective management.

TUBERCULOUS LYMPHADENITIS

Tuberculous lymphadenitis presents with malaise, low-grade fever, and enlarged superficial or deep lymph node enlargement. Clinical signs include mildly tender, slowly progressive swelling of the involved nodes. A classic form is cervical tuberculous lymphadenitis (also known as scrofula) in which patients have developed slowly enlarging matted nodes that are palpable and in time visible, with distortion of the overlying skin. Untreated, draining skin fistulas may develop, from which organisms can be seen on smear and cultured.

TB OF BONES AND JOINTS

TB affecting the bones occurs easily in children because the epiphyses are open and the blood supply is rich, facilitating dissemination of the bacilli to the long bones and vertebrae. Infection may also spread into the articular capsule. The joints most commonly involved are those that bear weight, but bones of the wrist, hand, and elbow also may be involved. Diagnosis is made by biopsy and/or synovial fluid analysis.

GASTROINTESTINAL (GI) TB

TB infection of the GI tract occurs only after an extended period of time and characteristically takes the form of a localized inflammatory mass, most often in the terminal ileum or right colon. Imaging studies show changes suggestive of Crohn disease or colon cancer. The diagnosis is often made only after surgical intervention. Treatment usually involves resection of the involved area, followed by antituberculous chemotherapy.

HEPATIC TB

TB of the liver is found in patients with advanced pulmonary TB or miliary TB. There are tubercles in the liver that can spread to the gallbladder, leading to obstructive jaundice. When the primary site of infection (lung or other site) is treated and cured, the liver will also return to a normal state.

MILIARY TB

Under conditions of poor immune function or trauma, previously quiescent TB foci may destabilize, releasing viable bacilli into the bloodstream. Unchecked, this leads to a sustained, active systemic infection with small metastatic lesions throughout the body. Although not immediately evident on chest x-ray, eventually the films will show multitudes of small nodules spread throughout both lungs, having the appearance of millet seeds. Prominent symptoms include chronic fever, night sweats, weakness, malaise, weight loss, and dyspnea. Bone marrow and liver biopsies are often taken to complete the diagnosis.

TREATMENT OF DRUG-SUSCEPTIBLE TUBERCULOSIS IN ADULTS		
Drug	**Daily Dose (Adult)**	**Adverse/Toxic Reactions**
First-Line Drugs		
Isoniazid	5 mg/kg PO/IM (up to 300 mg)	Hepatotoxicity, hepatitis, peripheral neuropathy, hypersensitivity, flu-like symptoms
Rifampin	10 mg/kg PO/IV (up to 600 mg)	Orange discoloration of urine and other secretions, nausea, vomiting, hepatitis, hepatotoxicity, fever, purpura
Rifabutin	5 mg/kg PO (up to 300 mg)	Rash, GI disturbance, neutropenia Not approved by FDA for treatment of TB
Rifapentine	10–20 mg/kg	Red-orange stain on body fluids, hyperuricemia, abnormal liver function tests
Ethambutol	800 mg PO (40–55 kg), 1,200 mg PO (56–75 kg), or 1,600 mg PO (76–90 kg)	Optic neuritis, decreased visual acuity, color blindness, skin rash
Pyrazinamide	1,000 mg PO (40–55 kg), 1,500 mg PO (56–75 kg), or 2,000 mg PO (76–90 kg)	Hepatotoxicity, hyperuricemia, skin rash, arthralgias, GI irritation
Second-Line Drugs		
Streptomycin	15 mg/kg IM/IV	Ototoxicity, nephrotoxicity, hypokalemia
Ethionamide	15–20 mg/kg PO (usually 250–500 mg once or twice daily)	GI disturbance, hepatotoxicity, depression, drowsiness, hypothyroidism, metallic taste
Para-aminosalicylic acid	8–12 g PO (typically 4,000 mg in two to three divided doses)	GI disturbance, sodium load, hepatotoxicity
Amikacin/kanamycin	15 mg/kg IM/IV (up to 1 g) or 15 mg/kg dose three times per week for decreased renal function	Auditory and renal toxicity, hypokalemia, vestibular toxicity Not approved by FDA for treatment of TB
Cycloserine	10–15 mg/kg PO (usually 250–500 mg once or twice daily)	Psychosis, personality changes, rash, impaired coordination, convulsions, depression
Capreomycin	15 mg/kg IM/IV	Auditory and renal toxicity, vestibular toxicity, hypokalemia
Moxifloxacin	400 mg daily PO/IV	Nausea, diarrhea Not approved by FDA for treatment of TB

Source: [30; 32; 34; 42] *Table 3*

PEDIATRIC TREATMENT FOR TUBERCULOSIS		
Drug	**Daily Dose**	**Comments**
Isoniazid	10–15 mg/kg in one to two divided doses	Not to be given to children younger than 1 year of age Not to exceed 300 mg/day
Rifabutin	10–20 mg/kg	Not to exceed 300 mg/day
Rifapentine	—	Not recommended for children younger than 13 years of age
Rifampin	10–20 mg/kg	Not to exceed 600 mg/day
Streptomycin	10–20 mg/kg	Not to exceed 1 g/day
Ethambutol	15–25 mg/kg	Not to exceed 1 g/day
Pyrazinamide	30–40 mg/kg	Not to exceed 1 g/day
Ethionamide	15–20 mg/kg in one or two divided doses	Not to exceed 1 g/day
Para-aminosalicylic acid	200–300 mg/kg in two to three divided doses	Not to exceed 10 g/day
Cycloserine	15–20 mg/kg in one or two divided doses	Not to exceed 1 g/day
Amikacin/kanamycin	15–20 mg/kg	—
Capreomycin	15–20 mg/kg	Not to exceed 1 g/day

Source: [30; 32; 34; 42] *Table 4*

TREATMENT

Some form of antituberculous chemotherapy has been in existence since the 1940s. With appropriate antibiotic treatment, TB can be cured in most people. Six drugs are rated as first-line because they are frequently effective and have low toxicity for most patients with TB. A successful treatment outcome depends greatly on patient compliance with the prescribed combination of drugs (***Table 3*** and ***Table 4***). Patient noncompliance with the prescribed regimen may lead to failed resolution, early relapse, and the emergence of resistant strains (MDR-TB). Some research indicates that involving a pharmacist on the healthcare team improves rates of treatment completion [66]. Successful treatment of MDR-TB is difficult and involves the use of less effective, potentially more toxic medications that must be administered for as long as two years. Even more severe is extensively drug-resistant TB (XDR-TB), which is caused by a strain that resists even the second-line agents [5; 9]. The effort continues to discover new antituberculous agents that are inexpensive and well-tolerated. This is especially important given the increasing prevalence of multi-drug resistant strains worldwide [2; 4].

The CDC and specialty organizations provide updated guidance for the treatment of tuberculosis [30]. Therapy may be initiated on the basis of strong clinical (or laboratory) suspicion, without waiting for culture confirmation of the diagnosis. The recommended strategy is to use a multi-drug regimen administered in a two-step process: an initial four-drug intensive phase for eight weeks, followed by a maintenance phase regimen to complete a total six- to nine-month course of therapy.

The recommended intensive phase regimen consists of isoniazid, rifampin, pyrazinamide, and ethambutol. This approach covers the possibility that infection is caused by a resistant strain and provides a quick "knockdown" effect designed to maximize the rate of clinical improvement, eliminate the risk of transmission, and prevent the emergence of resistant strains. After 8 weeks, when the initial results of sputum culture and sensitivity are known and drug-sensitive infection is known or presumed, pyrazinamide and ethambutol are discontinued and isoniazid and rifampin are continued for an additional 18 to 24 weeks [30].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America state that the preferred regimen for treating adults with TB is a regimen consisting of an intensive phase of two months of isoniazid (INH), rifampin (RIF), pyrazinamide, and ethambutol, followed by a continuation phase of four months of INH and RIF.

(https://academic.oup.com/cid/article/63/7/853/2197067. Last accessed September 22, 2022.)

Strength of Recommendation: Strong (Most individuals should receive the intervention.)

Customarily, chemotherapy for six to nine months is sufficient to cure pulmonary TB. Treatment for less than six months most often results in relapse. After one month of therapy, patients should have a follow-up sputum smear and culture. Then, another sputum check should be undertaken at the conclusion of the intensive phase of therapy and at least monthly until two consecutive specimens are negative. The continuation phase treatment regimen should be extended to 28 weeks for patients who have cavitation pulmonary disease and positive sputum cultures after two months of treatment [30].

Conversion to a smear-negative state occurs in 90% of patients after three months of treatment. Lack of conversion raises the question of compliance and/or presence of drug-resistant organisms. A follow-up sputum check is also done six months after completion of treatment in order to screen for the 1% to 3% of patients who relapse.

FIRST-LINE DRUGS

Isoniazid

Isoniazid, or isonicotinoylhydrazine (INH), is bactericidal, easily permeates infected cells as well as the CSF, and has proved to be highly effective for the treatment of TB. It has been available since 1952 and is still the most useful and least expensive drug used in the treatment of TB. It is the drug of choice for prophylactic treatment as well as for active cases. Therapeutic efficacy is greatly enhanced when INH is used in combination with rifampin.

Adverse reactions can be severe with INH. Reversible liver damage occurs in 1% to 2% of patients younger than 65 years of age, 4% to 5% in patients older than 65 years, and is even higher in patients with alcoholism. Patients should always be alerted to the symptoms of liver toxicity, such as anorexia, nausea, vomiting, and jaundice. If these symptoms occur, INH should be stopped immediately and liver function studies done.

If liver function studies are greatly elevated beyond the normal range, INH should not be continued. If only mildly elevated, the patient is often given a half dose for two or three days. If this is tolerated, the full dose may be restarted with close monitoring for symptoms. Allergic reactions to INH include rash, drug fever, anemia, and agranulocytosis.

INH interferes with GI absorption of the vitamin pyridoxine; its use over weeks to months can lead to a deficiency state manifested as peripheral neuropathy. This is more apt to occur in persons poorly nourished, pregnant, or dependent on alcohol, but it is a risk for anyone on long-term INH therapy.

It is recommended that all patients receiving INH take a daily supplement of 25–50 mg pyridoxine throughout the period of treatment.

INH is normally given at 300 mg per day for adolescents and adults; 10–15 mg/kg/day in one to two divided doses is appropriate for infants and children, with a maximum of 300 mg/day [42]. INH is taken as a single dose in the morning, and treatment continues for six to nine months in most cases. INH may be prescribed during pregnancy.

Rifampin

Rifampin is bactericidal, well absorbed, and penetrates readily into cells and the CSF. Rifampin is active early against rapidly dividing organisms, yet it also retains good activity against semidormant, intracellular bacilli, an advantage in achieving late resolution of granulomatous foci of infection.

The usual dose is 600 mg/day; the dose is 10–20 mg/kg/day in a single dose for infants and children, with a maximum of 600 mg/day [42]. A combination of 300 mg rifampin and 150 mg INH is available as a single capsule under the brand name Rifamate [42]. Toxic effects are jaundice, fever, thrombocytopenia, and renal failure. Because the liver complications are similar to those with INH, attempts to reintroduce the drugs should occur one at a time, so it can more accurately be determined which drug is causing the problem.

Rifampin has several drug interactions. It accelerates metabolism of anticoagulants, oral contraceptives (effectively inactivating them), digitoxin, corticosteroids, oral hypoglycemic agents, and methadone. It also causes a decrease in vitamin D concentration. This can be problematic because vitamin D is essential to the function of macrophages, which protect against M. *tuberculosis*. It may be indicated to give supplements of vitamin D. Rifampin is safe to use during pregnancy.

Rifabutin

Rifabutin, a rifamycin drug, is currently only approved by the FDA for the prevention of Mycobacterium avium disease in HIV-seropositive patients. Generally, rifabutin is used in first-line treatment of TB in patients with unacceptable reactions to rifampin. The usual dosage is 300 mg/day in a single administration for adults. The appropriate dosage for children is 10–20 mg/kg/day with a 300 mg/day maximum [30; 42]. Adverse effects are commonly mild and include hematologic toxicity, hepatotoxicity, and rash. An orange/red discoloration of skin, sweat, and mucus is a universal result of the medication and resolves upon discontinuation of treatment.

Ethambutol

A bacteriostatic agent, ethambutol inhibits the transfer of mycolic acids into the cell wall. It penetrates into most tissues, but does not always enter the CSF. It works equally well in both intracellular and extracellular organisms.

Ethambutol is safe to use in pregnant patients and is generally well tolerated by most adult patients. Adverse reactions include damage to the ocular nerve, symptoms of which include color blindness, scotomas, constricted visual fields, and blurred vision. Discontinuing the drug usually eliminates the symptoms. However, continued use can cause permanent visual impairment. It is standard practice to do a baseline examination of visual acuity before beginning treatment. The risk of ocular toxicity is about 1% at the lower recommended dose of 15 mg/kg/day. Because it is often difficult to judge these changes in a child, ethambutol is generally not given to children unless the child's TB is drug resistant.

Normal dosage for adults is 800–1,600 mg/day based on weight [30]. Some patients are given 50 mg/kg twice weekly and seem to tolerate the change in dosage without problems. Patients who have renal insufficiency should have their dosage reduced to 10 mg/kg/day. The normal dosage for children is 15–25 mg/kg to a maximum of 1 g/day [30]. This drug is fully dialyzable [30; 32].

Pyrazinamide (PZA)

Pyrazinamide (PZA) is bactericidal and highly active against intracellular organisms. It penetrates readily into tissue, including the CSF. It is catabolized in the liver and excreted in the urine.

The major adverse reactions of PZA are hepatitis and hyperuricemia, which only rarely cause symptoms of gout. Other adverse reactions include skin rash, joint pain, and gastrointestinal distress. Because of its propensity to cause hepatotoxicity with prolonged use, PZA is primarily used in combination with INH, rifampin, and ethambutol during the first eight weeks of intensive therapy only. The usual dose of PZA for adults is 1,000–2,000 mg (based on weight) given in a single daily dose, with a maximum dose of 2 g/day [30; 42]. For children, the normal dosage is 30–40 mg/kg, not to exceed 1 g/day. The drug is contraindicated in pregnancy because of the risk of adverse effects to the fetus [30; 32]. A capsule containing 120 mg rifampin, 50 mg INH, and 300 mg PZA (brand name Rifater) may be taken to improve compliance with complex, multidrug regimens [42].

Rifapentine

A newer addition to the treatment of TB, rifapentine (RPT) is only used in combination with other drugs to which the isolate is susceptible. RPT is not approved for use in children younger than 12 years of age for active TB treatment but is FDA approved for those 2 years of age and older with latent TB [42]. The adverse effects are similar to those experienced with rifampin.

In February 2022, the CDC released interim guidance recommending a daily four-month (vs. daily 6-month) regimen, consisting of RPT 1,200 mg, moxifloxacin (MOX) 400 mg, INH 300mg, and PZA 1,000 –2,000 mg (weight-based), for drug-susceptible pulmonary TB in patients at least 12 years of age and weighing at least 40 kg, with no contraindications to this treatment [75]. After the eight-week intensive phase, PZA is discontinued, and the remaining three drugs (RPT, MOX, and INH) are given daily for another nine weeks (continuation phase) at the same dosages. The four-month regimen can be used in patients with HIV (if CD4 counts ≥100 cells/mcL and if patients are receiving or planning to initiate efavirenz as part of the antiretroviral therapy regimen) [75].

It is important to note that with all of the rifamycin drugs outlined here, the known drug interactions are constantly and rapidly changing. For the most up-to-date information, please consult the CDC website at https://www.cdc.gov/tb.

SECOND-LINE DRUGS

Streptomycin

In the past, streptomycin had been greatly effective in treating many patients with TB. However, it is no longer used routinely because of the risk for nephrotoxicity and the availability of newer alternative drugs.

The drug is given intramuscularly at about 15 mg/kg/day for adults and 15–20 mg/kg/day for children, with a maximum dose of 1 g/day for both children and adults [30; 42]. In patients older than 59 years of age, the dosage is 10 mg/kg/day, with a maximum of 750 mg/day [30]. CSF penetration is poor.

Adverse reactions include renal tubular damage, hypokalemia, vestibular damage, and ototoxicity. Patients receiving streptomycin should have their hearing, balance, and serum creatinine levels monitored regularly. Allergic reactions include skin rash, drug fever, agranulocytosis, and serum sickness. Streptomycin is contraindicated in pregnancy because it is reported to damage the eighth cranial nerve in the fetus.

Ethionamide

Chemically related to INH, ethionamide is effective in controlling the tubercle bacilli but has such major side effects that as many as one-third of all patients taking it are unable to continue. These side effects include nausea, vomiting, diarrhea, excessive salivation, metallic taste, hepatotoxicity, peripheral neuropathy, and headaches. The dose is 15–20 mg/kg/day in one to two divided doses for children and adults, with a maximum dose of 1 g/day [30; 42].

Para-Aminosalicylic Acid

At one time used in combination with INH, para-aminosalicylic acid has effectively been replaced by ethambutol. Nearly all patients suffer from gastrointestinal symptoms, including dyspepsia, nausea, vomiting, and diarrhea. Other patients may develop hypersensitivity reactions including fever, rash, and hepatitis. The drug has a large amount of sodium, which increases fluid retention in some patients. The dose is 200–300 mg/kg/day in two to four equally divided doses for children and 8–12 g/day in two to three equally divided doses for adults [30; 42].

Kanamycin and Amikacin

Amikacin is a less toxic, semisynthetic derivative of kanamycin. Similar to streptomycin in its action and side effects, most organisms that are resistant to streptomycin are susceptible to kanamycin and amikacin.

Side effects include auditory toxicity and severe nephrotoxicity. Dosage for kanamycin is 15–20 mg/kg in divided doses every 8 to 12 hours for children and 15 mg/kg in divided doses every 8 to 12 hours (maximum: 15 mg/kg/day) for adults [42]. Amikacin is not currently approved by the FDA for treatment of TB.

Cycloserine

Because cycloserine inhibits cell-wall synthesis and is a small molecule, it enters all body fluids. Dosage is 10–15 mg/kg/day given orally but should not exceed 1 g/day for adults; the dosage for children is 15–20 mg/kg/day in two divided doses, with a maximum dose of 1 g/day [30].

Adverse reactions include severe neurotoxicity, which can cause headaches, tremors, irritability, depression, anxiety, psychosis, and seizures. Discontinuing the drug may cause the symptoms to disappear, but full resolution usually takes several weeks. Understandably, cycloserine is not recommended for patients who have mental illness.

Capreomycin

A tuberculostatic, the usual adult dosage of capreomycin is 15 mg/kg/day intramuscularly; in children the dosage is 15–20 mg/kg/day). Side effects include nephrotoxicity and ototoxicity. It is excreted in the urine, so the dosage must be reduced when there is renal failure [30; 42].

Levofloxacin

Although not FDA-approved for the treatment of TB, levofloxacin is recommended by the CDC as a second-line agent for patients who do not tolerate first-line therapies [30]. The usual dose for adults with susceptible disease is 500–1,000 mg/day. Levofloxacin is not approved for long-term use in children and adolescents due to concerns regarding bone and cartilage growth. However, the CDC recommends that the drug be considered in children with TB resistant to both INH and rifabutin; the dose for children is 15–20 mg/kg [30]. It is favored over the other available quinolone antibiotics moxifloxacin and gatifloxacin due to its more acceptable safety profile.

Potential adverse reactions include hepatotoxicity and gastrointestinal effects (taste disturbance, nausea, diarrhea, constipation, abdominal pain, dyspepsia, and vomiting) [42]. The FDA has issued a warning for all quinolone antibiotics, including levofloxacin, stressing the risk of tendon inflammation and/or rupture in some patients; the risk is higher for those who are older than 60 years of age, organ transplant recipients, and patients on long-term corticosteroid therapy [42].

SURGICAL TREATMENT

The role of surgery for the adjunctive management of pulmonary TB has diminished considerably with the advent of antituberculous chemotherapy. It is now used only rarely, for the following indications, usually in reference to large cavitary disease:

- Unsuccessful drug therapy
- Removal of destroyed lung tissue
- Persistent bronchopleural fistula
- Intractable hemorrhage
- Repair of postsurgical complications

On occasion, when there are conglomerate lesions in the lung and no clear diagnosis, surgery is performed to establish a definitive diagnosis and to rule out other possibilities, such as malignancy.

DRUG-RESISTANT TB

Drug-resistant TB constitutes a public health crisis in areas of the world with a high burden of tuberculous infection. The WHO estimates that, worldwide in 2017, 558,000 persons developed TB that was resistant to rifampin; of these, 82% were infected with a strain resistant to two or more first-line drugs [14]. MDR-TB is defined as TB that is resistant to the two most effective first-line therapeutic drugs—isoniazid and rifampin. Less common, but exceedingly more problematic, are MDR-TB strains that are also resistant to most effective second-line drugs as well, designated as XDR-TB. Three countries account for almost half of the world's cases of MDR-TB: India (24%), China (13%), and the Russian Federation (10%).

During the 1950s and 1960s, only 2% to 3% of TB cases in the United States were resistant to antituberculous drugs. In the 1990s, that number had increased transiently to 10%. Perhaps not coincidentally, this increase occurred along with the closing of TB sanatoriums, which greatly reduced the number of patients receiving direct supervision of their treatment. There have also been outbreaks of drug-resistant TB among groups of patients infected with HIV, immigrants from epidemic areas, and the homeless. Of the 6,684 TB cases reported in 2017 with available drug-susceptibility testing results, 128 (1.9%) were MDR-TB [54]. Of this subset of MDR-TB cases, 110 (85.9%) were in foreign-born persons. Three cases of XDR-TB were reported, all of which occurred in foreign-born persons.

Outbreaks of MDR-TB can cause havoc on immunocompromised patients. These individuals already are unable to fight infections adequately when they acquire an organism with extraordinary resistance to treatment. This is most often seen in patients with HIV. The mortality rate for these patients is 70% to 90%, with death commonly occurring only 4 to 16 weeks after diagnosis [17].

Part of the problem is that it takes millions of dollars and many years to develop a drug from research to the point that it can be distributed to patients in need. By that time, the specific organism in question could have mutated even further and may no longer resemble the prototype for which the drug was created [17].

In 2007, much attention was given to the case of an American diagnosed with XDR-TB who flew on six international flights, with the potential for exposing hundreds of people to the disease. Fortunately, XDR-TB is relatively rare, and cultures obtained from the individual later demonstrated that he actually had a form of MDR-TB. However, many learned through the media coverage of this event that the government does have the power to enforce isolation or quarantine [9; 16]. Also in 2007, a man with active TB was jailed because he refused to wear a mask when he was around others [28]. This serves as a

CDC GUIDELINE FOR THE TREATMENT OF MDR-TB IN ADULTS		
Pattern of Resistance	**Suggested Regimen**	**Duration of Treatment**
Isoniazid (with or without streptomycin)	Rifampin, pyrazinamide, and ethambutol (A fluoroquinolone may strengthen the regimen for patients with extensive disease.)	6 months
Isoniazid and rifampin (with or without streptomycin)	A fluoroquinolone, ethambutol, pyrazinamide, and an injectable agent[a], possibly with an alternative agent	18 to 24 months
Isoniazid, rifampin (with or without streptomycin), and ethambutol or pyrazinamide	A fluoroquinolone (and ethambutol or pyrazinamide if disease is active), an injectable agent[a], and two alternative agents	24 months
Rifampin	Isoniazid, ethambutol, and a fluoroquinolone, supplemented with pyrazinamide for the first two months (An injectable agent[a] may be included for the first two to three months for patients with extensive disease.)	12 to 18 months
[a]Injectable agents include aminoglycosides (such as streptomycin, kanamycin, and amikacin) or capreomycin.		
Source: [60; 61; 62]		*Table 5*

reminder that careful attention to patient education and consistent adherence to basic precautions are always important.

For clinical and epidemiologic purposes, TB drug resistance may be classified as "primary" or "secondary." Primary resistance denotes a case in which the resistant strain is isolated from a patient who has never before been treated with antituberculous medication, indicating that the infection had been acquired from contact with a person having drug-resistant TB. Secondary resistance denotes a case in which resistance emerges on therapy, meaning that the initial culture yielded a sensitive isolate but later cultures, on treatment, are positive for a strain resistant to one or more of the drugs in the treatment regimen. The usual cause for secondary resistance is an insufficient or interrupted course of treatment. This could result from a suboptimal regimen or dosage error, lack of compliance with the prescribed regimen, or failure to sustain a course of treatment for the prescribed duration. Some patients share their medications with family members, thinking they are saving money, but actually harm themselves and their family members, as neither receives an adequate amount of treatment [17].

Treatment of MDR-TB

It is difficult and expensive to treat patients with MDR-TB. The per-patient cost of hospitalization and treatment is approximately $150,000 for MDR-TB and $482,000 for XDR-TB, compared with $17,000 for non-MDR-TB [59]. The usual plan is to administer at least four drugs that have not been previously used to treat the patient or other members of the family (***Table 5***). If chemotherapy fails, it is sometimes necessary to surgically resect that portion of the lung that is infected [4].

In 2012, the FDA approved the first new medication to treat MDR-TB, bedaquiline. This agent represents the first new class of medications (diarylquinolines) approved to treat TB in more than 40 years [53]. It acts by inhibiting a mycobacterial enzyme necessary for replication of the mycobacteria. The drug is specifically approved as part of combination therapy to treat MDR-TB or XDR-TB when other alternatives are ineffective or unavailable [61]. Bedaquiline is associated with significant adverse effects, including an increased risk of mortality, hepatotoxicity, and QT interval prolongation leading in some instances to death [53]. Therefore, it should be prescribed with caution. The provisional CDC guidelines recom-

mend the use of bedaquiline as part of a multidrug regimen in laboratory-confirmed MDR-TB when genotypic or phenotypic resistance to INH and rifabutin has been shown and when other effective drug combinations cannot be provided [60; 61]. The CDC recommends that molecular drug resistance testing be performed for patients suspected or at high-risk for MDR-TB [58].

A promising new drug is pretomanid, a nitroimidazole compound with bactericidal activity against all tested drug-resistant clinical isolates of *M. tuberculosis*. Pentremanid received FDA approval in August 2019 for use in combination with bedaquiline and linezolid in adults with XDR-TB or non-responsive MDR-TB [64]. The efficacy of this three-drug regimen was demonstrated in a preliminary report of a clinical trial in South Africa; of 107 patients with XDR-TB, 89% were considered cured at six months of therapy [64]. This appears to be a major advance in treatment prognosis for a subset of XDR-TB that has, to this juncture, been almost uniformly fatal.

As of 2022, the CDC recommends the use of pretomanid 200 mg daily for 26 weeks in the treatment of adults with pulmonary extensively drug-resistant, pre-extensively drug-resistant (i.e., resistant to isoniazid, rifampin, and at least one fluoroquinolone or injectable medications) or treatment-intolerant/nonresponsive multidrug-resistant TB when a safe and effective treatment regimen cannot otherwise be provided and when administered in combination with bedaquiline and linezolid as the BPaL regimen [74]. The 26-week BPaL regimen can be used for adults with HIV but has not been studied in children or in pregnancy.

A 2022 clinical trial, the ZeNix trial, set out to identify the optimal dose and duration of linezolid for the BPaL regimen, as a previous trial (the Nix-TB trial) found a high incidence of significant adverse events (e.g., peripheral neuropathy, myelosuppression, optic neuropathy) with a 1,200 mg daily dose for 26 weeks [77]. The ZeNix trial studied 1,200 mg of linezolid for 26 weeks or 9 weeks and 600 mg for 26 weeks or 9 weeks in a total of 181 participants. The incidence of adverse events decreased with lower dose and/or shorter treatment duration, while the incidence of bacteriologic relapse was similar in each of the four study arms (the highest dose/duration had no relapse, while the lowest dose/duration had one relapse). Analysis of the trial data published in the *New England Journal of Medicine* suggests that a bedaquiline, pretomanid, and linezolid regimen including linezolid 600 mg daily for 26 weeks has the most favorable risk-benefit ratio [77].

CHEMOPROPHYLAXIS FOR TUBERCULOSIS

Certain individuals who have latent TB (e.g., positive skin test) and others having significant exposure to someone with open cavitary TB are at heightened risk for developing active disease unless they receive a course of preventive treatment. The CDC has established guidelines for the use of chemoprophylaxis based on individual risk considerations [52; 76].

The goal of TB prophylaxis is to prevent progressive primary infection or late reactivation disease in those with latent TB. Therefore, persons with known recent exposure, and those at high risk for reactivation disease, should be evaluated for tuberculin skin test reactivity or have a skin test performed. Those who are positive should then be considered for preventive therapy.

CANDIDATES FOR PREVENTIVE THERAPY

Preventive therapy is recommended for the all persons, regardless of age, with a positive TB blood test (IGRA) [57]. Persons in the following risk groups should be given high priority for preventive therapy if their reaction to the tuberculin skin test result is 5 mm or greater [57]:

- Persons with HIV infection
- Close contacts of a TB case
- Patients who have had organ transplants and other immunosuppressed patients (receiving the equivalent of ≥15 mg/day of prednisone for at least one month)
- Persons with fibrotic changes on chest radiograph consistent with old TB disease

Persons in the following risk groups should be given priority for preventive therapy if their reaction to the tuberculin test is 10 mm or greater [57]:

- Recent arrivals to the United States (within the last five years) from high-prevalence countries
- Persons who inject illicit drugs
- Residents and employees of high-risk congregate settings
- Mycobacteriology laboratory personnel
- Children younger than 4 years of age, or children and adolescents exposed to adults in high-risk categories

Persons with no known risk factors may be considered for preventive therapy if they have a positive tuberculin test result of 15 mm or greater or a positive IGRA test result [57]. However, testing for TB should generally only be performed among high-risk groups.

LATENT TB THERAPY

There are four approved preventive treatment regimens for adults and children with latent TB infection (***Table 6***) [52]. While all regimens are effective, the CDC recommends that providers prescribe the more convenient shorter regimens when possible. Additional considerations in choosing the appropriate regimen include:

- Drug-susceptibility results of the presumed source case (if known)
- Coexisting medical illness
- Potential for drug-drug interactions

The CDC has updated the recommendations for use of once-weekly isoniazid-rifapentine for three months to include persons who have HIV infection, including those with AIDS, and children 2 to 17 years of age [65]. For children, the refapentine dosage is shown in ***Table 6*** and the INH dose is 25 mg/kg for those 2 to 11 years of age or 15 mg/kg for those 12 years of age and older (900 mg maximum) [65].

For individuals at particularly high risk for conversion to active TB disease and suspected of nonadherence to a medication regimen or with an intermittent dosing regimen, directly observed therapy should be considered.

VACCINATION

Although not recommended or routinely used in the United States, many other countries, particularly developing countries with limited financial resources, have used the BCG vaccine to control TB [20]. The WHO estimates that more than 1 billion people have received BCG, making it one of the most widely used vaccines in the world. Studies have shown BCG to have variable efficacy against all TB strains. Analysis of these studies is difficult due to the fact that several different strains of the vaccine are used worldwide. There are serious concerns about its use in immunocompromised patients [20].

Generally, the vaccine is given to infants and children who have (1) a negative tuberculin skin test; (2) are at high risk of continuing exposure to persons with infectious TB; (3) cannot be placed on long-term preventive therapy; or (4) are continually exposed to persons with INH- or rifampin-resistant disease. As BCG is a live, attenuated vaccine, administration will cause a person to convert from a negative TB skin test to a positive one, requiring any subsequent skin testing to be confirmed by blood test.

Several novel TB vaccines are in clinical trials, including a recombinant form of BCG [44; 67]. One candidate, M72/AS01$_E$, is a subunit vaccine comprised of an immunogenic fusion protein derived from two *M. tuberculosis* antigens and a proprietary adjuvant [68]. A phase IIb trial of the vaccine found the efficacy at month 36 was 49.7%, and the infection rate in the treatment group was approximately half that of the control group [69]. Another experimental vaccine, ID93+GLA-SE, is temperature stable, which could improve its availability in vulnerable populations compared to BCG, which must be stored and transported refrigerated [78].

LATENT TB INFECTION TREATMENT REGIMENS				
Drug(s)	**Duration**	**Dose**	**Frequency**	**Total Doses**
Isoniazid (INH)	Nine months	Adults: 5 mg/kg Children: 10–20 mg/kg[a] Maximum dose: 300 mg	Daily	270
		Adults:15 mg/kg Children: 20–40 mg/kg[a] Maximum dose: 900 mg	Twice weekly[b]	76
	Six months	Adults: 5 mg/kg Children: 10–20 mg/kg[a] Maximum dose: 300 mg	Daily	180
		Adults: 15 mg/kg Children: 20–40 mg/kg[a] Maximum dose: 900 mg	Twice weekly[b]	52
INH and rifapentine (RPT)	Three months	Adults and children older than 12 years of age: INH[c]: 15 mg/kg, rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT[c]: 10.0–14.0 kg: 300 mg 14.1–25.0 kg: 450 mg 25.1–32.0 kg: 600 mg 32.1–49.9 kg: 750 mg ≥50.0 kg: 900 mg maximum Children 2 to 11 years of age: INHc: 25 mg/kg; 900 mg maximum RPTc: Same as for older patients	Once weekly[b]	12
Rifampin (RIF)	Four months	Adults: 10 mg/kg[d] Maximum dose: 600 mg Children: 15–20 mg/kg[e] Maximum dose: 600 mg	Daily	120
INH and RIF	Three months	Adults: INH[c]: 5 mg/kg; 300 mg maximum RIF[c]: 10 mg/kg; 600 mg maximum Children: INH[c]: 10–20 mg/kg; 300 mg maximum RIF[c]: 15–20 mg/kg; 600 mg maximum	Daily	90

[a]The American Academy of Pediatrics recommends an isoniazid (INH) dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice weekly regimen.

[b]Intermittent regimens must be provided via directly observed therapy (i.e., healthcare worker observes the ingestion of medication).

[c]INH is formulated as 100-mg and 300-mg tablets. RPT is formulated as 150-mg tablets in blister packs that should be kept sealed until usage.

[d]In the United States, the recommended regimen for treatment of latent TB infection in children is a nine-month course of INH. For the treatment of latent TB infection in infants, children, and adolescents when INH could not be tolerated or the child has had contact with a case patient infected with an isoniazid-resistant but rifamycin-susceptible organism, the American Academy of Pediatrics recommends six months of daily rifampin (180 doses) at a dosage of 10–20 mg/kg

[e]The American Academy of Pediatrics acknowledges that some experts use RIF at 20–30 mg/kg for the daily regimen when prescribing for infants and toddlers.

Source: [52] *Table 6*

CHILDREN AND TB

Children are vulnerable to TB for a variety of reasons. Many children who live in poverty do not receive sufficient nutrition to adequately build their immune systems. They are also less aware of hygiene, so are often exposed to coughs, sneezes, laughs, and other risks from those who are infected. If their parents or other family members are infected with TB, it is almost impossible for the child not to become infected as well.

Young infants may not cough, which is often the main symptom associated with TB. In older children (3 to 15 years of age), TB is typically asymptomatic but is discovered due to a positive skin test or chest x-ray. Older children and adolescents have symptoms similar to adults and are also more likely to develop a more severe case of the disease, with cavitation and TB of other organs.

Tuberculous meningitis is a frightening complication that is experienced most often in developing countries. If the child lives in an area where drug therapy can begin promptly, their life may be saved. Otherwise, there is a very high mortality rate for children who develop tuberculous meningitis.

Prophylactic treatment for children of patients with TB is highly recommended. The treatment regimens most effective for children are limited, compared with those used for adult patients with TB. However, the once-weekly, three-month regimen of isoniazid-rifapentine is now approved for use in children 2 to 17 years of age, thereby permitting a relatively brief and more manageable course of antituberculous prophylaxis [65]. Nine-month treatment with INH alone has proved to be successful in most children and is also recommended [52]. Children taking INH do not seem to develop the transient elevation of liver enzymes seen in adults, so liver function does not have to be monitored unless the patient has a history of other liver disease. When INH is not tolerated, the American Academy of Pediatrics recommends six months of daily rifabutin at a dosage of 10–20 mg/kg [52]. As noted, ethambutol is usually avoided in children younger than 7 years of age because it is difficult to properly monitor visual acuity and color perception in children that young. It is rare for children to develop drug-induced hepatitis, so monthly follow-ups do not include liver function studies, as in adults. Good indicators of improvement are increased appetite, weight gain, and lower evening temperatures.

Studies have shown that 50% of infants born to mothers with active TB develop the disease during their first year of life. It is therefore recommended that these children receive prophylactic drug therapy. Newborn infants whose mothers have positive skin tests and no evidence of disease should be skin tested. The first test is applied at 4 to 6 weeks of age, then at 3 to 4 months of age, and again at one year [18]. Unfortunately, studies have indicated that positive skin tests are rare in congenital TB cases. It is important, therefore, to recognize the signs and symptoms of the disease, including abnormal chest radiography, abdominal distension, skin lesions, ear discharge, hepatosplenomegaly, respiratory distress, and fever [27].

TUBERCULOSIS DURING PREGNANCY

When a pregnant woman is diagnosed with TB, treatment may be postponed until after the first trimester due to concerns about the use of medications during pregnancy and the risk of hepatotoxicity [22]. However, the CDC recommends initiating antitubercular therapy as soon as infection is detected, as there is very low potential for teratogenic effects with first-line agents (with the exception of PZA) in spite of their ability to cross the placenta [30]. Preventive therapy is considered both safe and appropriate for women who are breastfeeding. Most antituberculous drugs are excreted in breast milk, but there are no studies showing that this causes any harm to the infant [30; 43]. Some feel it is safest to have the mother take her medications after breastfeeding and substitute a bottle for the feeding immediately following dosing.

CARE OF THE PATIENT WITH TB

Hospital admission requirements are based on actual symptoms that support the medical necessity of acute hospitalization, not merely by the diagnosis of TB. This usually, but not exclusively, includes severe shortness of breath with abnormal arterial blood gases, undiagnosed fevers of unknown origin, invasive procedures in a debilitated patient, and establishment of a drug regimen. Patients with TB are more likely treated on an outpatient basis.

INPATIENT CARE

One of the most important actions healthcare providers can take is to prevent the spread of TB in their own facilities. The CDC has identified several environmental factors that increase the risk of TB transmission in healthcare settings [35]:

- Exposure to TB in small, enclosed spaces
- Inadequate local or general ventilation that results in insufficient dilution or removal of infectious droplet nuclei
- Recirculation of air containing infectious droplet nuclei
- Inadequate cleaning and disinfection of medical equipment
- Improper procedures for handling specimens

Patients with known or suspected TB should be admitted into private rooms with negative air pressure, with air being exhausted directly outside six times per hour. Air from that room should not be circulated into any other rooms in the hospital. The goal of this environmental control is to reduce the concentration in and to remove the airborne infectious droplets from the room [35]. Entry into airborne infection isolation rooms should be strictly controlled.

Some hospitals do not have AII rooms, and if that is the case, ultraviolet germicidal lights and HEPA filters or portable HEPA filtration units should be used to increase equivalent air changes per hour. Germicidal lamps kill many bacteria, including the tubercle bacilli. They can be placed in ceiling or wall fixtures or within the air ducts of recirculating ventilation systems. HEPA filters remove particles greater than 3 microns in diameter. Healthcare workers and visitors entering the room should wear respirators (at least N95) that have been certified by NIOSH.

It is crucial to maintain good hand hygiene when caring for a patient with tuberculosis. Avoid unnecessary touching of surfaces in close proximity to the patient to prevent the transmission of pathogens to other surfaces or clothing, even when gloves are worn [35]. Visitors should be cautioned against unnecessary touching, and antimicrobial soap or alcohol-based hand sanitizer should be used after leaving an isolation room. If the patient needs to leave the airborne infection isolation or isolation room, they should be instructed on proper respiratory hygiene and cough etiquette procedures or, preferably, wear a well-fitting surgical or procedure mask [35].

Ineffective Breathing Pattern

In cases of ineffective breathing, the patient may have decreased lung volume and lung capacity due to the TB. Increased metabolism may also be a factor if there have been high fevers. Some patients may have a frequent productive cough and hemoptysis. These issues are defined by increased respiratory rate, the use of accessory muscles to breathe, retractions, diaphoresis, and tachycardia.

The anticipated outcome is that the patient's breathing pattern returns to normal with a regular respiratory rate and pattern. As part of the initial evaluation, the medical professional should:

- Assess depth, rate, and character of respirations
- Check for increased work of breathing
- Assess the cough
- Assess the secretions (include color, amount, and consistency)
- Monitor vital signs
- Auscultate the lungs for breath sounds
- Monitor arterial blood gases as indicated

The therapeutic interventions are to administer oxygen as necessary, push fluids and promote hydration to liquefy secretions, and maintain semi-Fowler's position to ease breathing.

Acute Infection

Active pulmonary TB causes high fevers and purulent or bloody sputum. The desired outcome in these cases is that the infection is treated effectively, thereby reducing the risk of spreading the disease to others. This is evidenced by resolution of fever and negative follow-up acid-fast bacilli smear and culture.

Ongoing assessments include:

- Assessing the secretions for amount, color, and consistency
- Monitoring temperature at least every four hours
- Monitoring sputum smear and culture

Therapeutic interventions include:

- Maintaining respiratory isolation
- Disposing of secretions properly
- Teaching patient handwashing techniques
- Administering medications as ordered

Knowledge Deficit

Many patients will not be knowledgeable about the disease process or the current and most effective treatment modalities. They may be aware only of the stigma that was associated with TB years ago. Healthcare professionals may become aware of this knowledge deficit by hearing patients verbalize incorrect information, ask many questions, or be noncompliant.

Therapeutic interventions include:

- Teaching patients about TB (detection, transmission, signs and symptoms of relapse, treatment, prevention, and compliance)
- Teaching patients how to follow their regimen after they are discharged from acute hospitalization
- Reinforcing isolation technique
- Explaining the importance of maintaining good nutrition
- Encouraging patients to stop smoking

Other possible afflictions that may be present in patients with TB, depending upon the seriousness of their disease, include anxiety, ineffective airway clearance, impaired gas exchange, alteration in comfort (pain), ineffective individual coping, ineffective family coping, sleep pattern disturbance, ineffective management of therapeutic regimen, activity intolerance, fatigue, alteration in nutrition, or spiritual distress.

Case Management

Case management of patients with TB is one of the most rapidly growing and highly effective methods of care available. The case manager can maintain close ties with the patient and family, participating in directly observable therapy, counting pills, and/or other methods to maintain compliance for the necessary length of time. Some case managers are working for the insurance carrier, others for a home health agency, still others for a public health service clinic or other outreach program. All of these settings provide the opportunity for the case manager to assess the needs of the patients and provide those services that will best help meet those needs.

OUTPATIENT CARE

The home health professional or other outpatient caregiver has a major investment in the patient with TB. He/she will hopefully have a long association with this patient, as therapy can last nine months or longer. During this time, there are many topics that need attention, primary among them is compliance with the drug regimen.

It is important for healthcare professionals to give both the patient and the caregiver explicit verbal and written instructions outlining which medications should be taken and how often. Some even make a poster with sample tablets glued to it, so the patient has a constant visual reminder of what needs to be taken. These instructions should also include the name and telephone number of a physician or nurse to call if questions arise.

Patients' health literacy is typically low, and an inability to follow a prescription is the foremost problem associated with poor health literacy [19]. Patients whose primary language is not English, racial/ethnic minorities, and patients older than 60 years of age have the lowest health literacy, which is unfortunate given that most cases of TB occur in these populations [19; 23; 54]. Many patients report that the clinician did not provide information in words they could understand, and some individuals feel shame about their lack of understanding and fail to ask for clarification due to embarrassment. Non-English-proficient patients require a professional translator (i.e., not a family member) to be present at each visit. It is vital that the patient understand the importance of precisely following the drug regimen.

Patients and caregivers should be taught the signs and symptoms of drug toxicity and side effects, such as those with rifampin, which causes feces, saliva, tears, and urine to be a red-orange color. It is important to strongly reinforce that they must not stop taking the medications without permission.

Some patients may have financial hardships as a result of paying for the continuing prescriptions, but not all will feel comfortable mentioning that fact. Depending upon the type of insurance coverage the patient has, the cost of the medications can range from minimal to major. There is also the cost of lost wages, hospital care, and physician's fees to consider. Because of this, it is important that all patients be given information about where they can obtain financial assistance or free medications in the community.

The home should be assessed for anticipation of possible problems. If the home is located in an area with significant air pollution, for example, it can be expected that the patient's condition would not improve as rapidly as if he or she were living in a cleaner environment. Dietary recommendations are usually for a high-protein, low-glycemic index diet that is well balanced and excludes alcohol. If necessary, the patient may do better with several small meals a day, as the large number of medications being taken often suppresses the appetite.

The diagnosis of TB has a major impact on the patients who receive it and upon their families. There is a change in their lifestyle, an economic impact, and emotional issues to confront. Frequent medical appointments will probably mean absences from school and/or work, again adding stressors to the family. Successful management of these problems requires extensive education and a commitment from the staff as well as the family. The attitude of the healthcare professional interfacing with the patient and family will greatly influence the compliance of the patient. Additionally, children being treated are more likely to have a positive attitude if their parents thoroughly understand the seriousness of the disease and the importance of treatment.

Patients should be encouraged to verbalize their fears and concerns, which helps them to confront and resolve them. For example, some patients still believe there is a social stigma attached to the development of TB. They are embarrassed to be infected and angry that they have this burden in their life. Simply talking about their concerns can dispel some of the worry. Still others do better in support groups formed by the hospitals and clinics.

CASE STUDY

Patient A is a registered nurse, 40 years of age, working in southern California at a large medical center. The hospital is located in an area with a large population of immigrants from southeast Asia, so she has cared for many of these patients during her 12 years of work on the surgical floor.

However, she decides to transfer to the hospital's home health agency to work with hospice patients. She had suffered through her mother's death from breast cancer only months before, and she is also hoping to get more regular hours to be able to spend more time with her teenage son.

About the same time, her husband is "downsized out" of his job as an aerospace engineer. It is a difficult time for the entire family, but Patient A feels perhaps the greatest stress of all. She is trying to overcome her grief for her mother; give attention to her father, son, and husband; do well in her new position; and work extra hours when necessary to help with their financial woes. There never seems to be any time for her to relax.

In December, Patient A gets a cold that develops into bronchitis and seems to hang on forever. She is often awake at night, either coughing or having drenching night sweats. Finally, in April, she goes to her family practice physician to have it checked.

Her chest x-ray shows questionable cavitary lesions in her right upper lobe. Although Patient A's first panicky fear is that she has cancer, her physician investigates further, ordering a TB skin test and sputum for acid-fast bacilli. Both tests are positive.

She is started on INH (300 mg/day), RIF (600 mg/day), ethambutol (800 mg/day), and PZA (1,000 mg/day). She is shocked by her diagnosis and embarrassed to tell her friends that she, a nurse who should know good universal precautions technique, would develop a contagious disease.

Patient A, however, is the perfect candidate for infection. Working in a community with a large immigrant population from underdeveloped countries means she had a greater risk for exposure than other nurses. Although she worked on a surgical unit, many of the patients were possibly infected.

Her healthy immune system successfully suppressed the initial infection, but when the stressors in her life mounted, a breakdown occurred. Perhaps the combined effect of a parent's death, change in financial status, family concerns, new job demands, and lack of sufficient rest led, in time, to a subtle depression in immune function and reactivation of latent TB. Any of these alone might have been insufficient to cause the immune system to fail, but grouped together, it was only a matter of time until the latent infection re-emerged. On antituberculous chemotherapy, proper nutrition, and a brief period of rest, she recovers without complication.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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