Inside: Continuing Medical Education for U.S. Physicians and Nurses

CORE CURRICULUM ON TUBERCULOSIS

What the Clinician Should Know

Fourth Edition, 2000

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention
National Center for HIV, STD, and TB Prevention
Division of Tuberculosis Elimination

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

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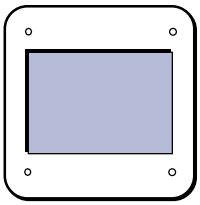

The *Core Curriculum on Tuberculosis* is accompanied by a slide series for use in presentations and training programs. The text boxes in this publication are based on that slide series; the number below each of the graphics corresponds to the number of the slide in the series. Missing slide numbers correspond to the chapter titles or supplemental information.

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Contents

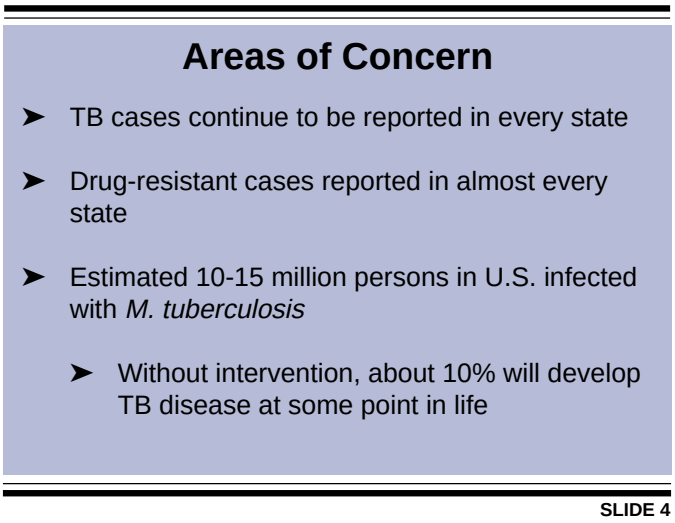
Chapter One

Introduction

In 1989, the Centers for Disease Control and Prevention (CDC) announced the goal of eliminating tuberculosis (TB) from the United States by the year 2010. The *Strategic Plan for the Elimination of Tuberculosis in the United States* was published at that time, and reassessed in 1999, to identify the actions necessary to achieve elimination. In 1992, a special federal task force was convened to address the problem of increasing case rates and outbreaks of drug-resistant TB. This task force developed the *National Action Plan to Combat Multidrug-Resistant Tuberculosis*, which enhanced the original Strategic Plan. Both plans stress the need to increase clinical knowledge about TB disease and infection.

Since 1993, TB case rates have been declining, suggesting that the nation is recovering from the resurgence of TB that occurred in the mid-1980s, and is back on track toward TB elimination. While the decrease in TB case rates is encouraging, there are several areas of concern that will require expanded efforts:

- TB cases continue to be reported in every state
- Drug-resistant TB cases continue to be reported in almost every state
- An estimated 10 to 15 million persons in the U.S. are infected with *Mycobacterium tuberculosis*. Without intervention, about 10% of these persons will develop TB disease at some point in life.



SLIDE 4

An update on TB for clinicians is critical today. The occurrences of several outbreaks of multidrug-resistant TB have pointed to the need for new treatment regimens and the more effective use of current ones. New methods of diagnosis have been introduced, and guidelines for patient management and public health practice have been revised.

This curriculum was designed to present basic information about TB for health care professionals. It is intended for use as a reference manual for clinicians caring for persons with or at high risk for TB disease or infection. In addition, it was designed to be useful in developing educational programs. ***It is not meant to provide detailed answers to all public health or clinical questions about TB, nor is it meant as a substitute for any specific guidelines.*** Information contained in this document is current as of April 2000.

In preparing this document, our aim was to meet the following goals:

- To increase clinicians' knowledge of the current TB trends.
- To assist clinicians with identifying those at highest risk for TB infection and disease.
- To increase clinicians' index of suspicion for TB in high-risk patients.
- To increase clinicians' use of treatment for high-risk persons with latent TB infection.
- To increase clinicians' knowledge about appropriate and effective treatment regimens.
- To increase clinicians' use of directly observed therapy (DOT) and other adherence-promoting methods.
- To assist clinicians with identifying appropriate measures to prevent TB transmission in health care settings.
- To assist clinicians with identifying resources for patients with TB.

This document was originally developed by the 1989 National Tuberculsosi Training Initiative [1] cosponsored by the American Thoracic Society and CDC. Because the guidelines for treating and controlling TB continue to evolve, it has been necessary to periodically revise this curriculum. The current document is the fourth edition of the *Core Curriculum on Tuberculosis*.

Endnotes

1. Reichman L. The National Tuberculosis Training Initiative. Ann Intern Med 1989;111:197-198.

Continuing medical education (CME) credits, continuing nursing education (CNE) credits, and **continuing education unit (CEU) credits** are available for this publication. See page 127 for information on how to obtain continuing education credits.

This curriculum is based on the following documents published by the American Thoracic Society, the Advisory Council for the Elimination of Tuberculosis, the American Academy of Pediatrics, and the CDC. We recognize that documents prepared by other professional organizations may contain minor differences in recommendations. Each reference is also listed in the appropriate chapter.

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Centers for Disease Control and Prevention. Recommendations for prevention and control of tuberculosis among foreign-born persons. MMWR 1998; 47(No.RR-16).

For more information on TB, contact the following organizations:

- Your state or local health department TB program
- Your state or local American Lung Association or American Thoracic Society
- CDC's TB Web site at www.cdc.gov/nchstp/tb
- The CDC Fax Information Service at (888) CDC-FAXX (232-3299)
- The CDC Voice and Fax Information System at (888) CDC-FACT (232-3228)
- The New Jersey Medical School National Tuberculosis Center at (800) 482-3627
- The Francis J. Curry National Tuberculosis Center at (415) 502-4700

Chapter Two

Transmission and Pathogenesis

Summary. TB is a communicable disease caused by *Mycobacterium tuberculosis*, or the tubercle bacillus. It is spread primarily by tiny airborne particles (droplet nuclei) expelled by a person who has infectious TB. If another person inhales air containing these droplet nuclei, transmission may occur. Some bacilli reach the alveoli, where they are ingested by macrophages. Infection begins with the multiplication of tubercle bacilli within these alveolar macrophages. Some of the bacilli spread through the bloodstream when the macrophages die; however, the immune system response usually contains the bacilli and prevents the development of disease. Persons who are infected but who do not have TB disease are asymptomatic and not infectious; such persons usually have a positive reaction to the tuberculin skin test. About 10% of infected persons will develop TB disease at some time in life, but the risk is considerably higher for persons who are immunosuppressed, especially those with HIV infection. Although the majority of TB cases are pulmonary, TB can occur in almost any anatomical site or as disseminated disease.

Objectives

After working through this chapter, you will be able to

- Describe how TB is spread;
- List at least 10 conditions that increase the risk that TB infection will progress to TB disease;
- Define primary and secondary drug resistance;
- Describe the classification system for TB.

In the United States, the vast majority of TB cases are caused by *Mycobacterium tuberculosis*, sometimes referred to as the tubercle bacillus. *M. tuberculosis* and three very closely related mycobacterial species (*M. bovis*, *M. africanum*, and *M. microti*) can cause tuberculous disease, and they compose what is known as the *M. tuberculosis* complex. *M. bovis* and *M. africanum* are very rare causes of disease in the United States; *M. microti* does not cause disease in humans. Mycobacteria other than those comprising the *M. tuberculosis* complex are called nontuberculous mycobacteria. Nontuberculous mycobacteria may cause pulmonary disease resembling TB.[1]

Transmission

Transmission of *M. tuberculosis*

- Spread by droplet nuclei
- Expelled when person with infectious TB coughs, sneezes, speaks, or sings
- Close contacts at highest risk of becoming infected
- Transmission occurs from person with infectious TB disease (not latent TB infection)

SLIDE 6

TB is spread from person to person through the air. When a person with pulmonary or laryngeal TB coughs, sneezes, speaks, or sings, droplet nuclei containing *M. tuberculosis* are expelled into the air. Depending on the environment, these tiny particles (1-5 microns in diameter) can remain suspended in the air for several hours.

If another person inhales air containing droplet nuclei, transmission may occur. The probability that TB will be transmitted depends on four factors: (1) the infectiousness of the person with TB (the number of organisms expelled into the air), (2) the environment in which exposure occurred, (3) the duration of exposure, and (4) the virulence of the organism. (See *Infection Control in Health Care Settings*, p. 87, for more information on infectiousness.)

Probability TB Will Be Transmitted

- Infectiousness of person with TB
- Environment in which exposure occurred
- Duration of exposure
- Virulence of the organism

SLIDE 7

The best way to stop transmission is to isolate patients with infectious TB immediately and start effective TB therapy. Infectiousness declines rapidly after adequate therapy is started, as long as the patient adheres to the prescribed regimen.

Persons at the highest risk of becoming infected with *M. tuberculosis* are close contacts — persons who had prolonged, frequent, or intense contact with a person with infectious TB. Close contacts may be family members, roommates, friends, coworkers, or others. Data collected by CDC since 1987 show that infection rates have been relatively stable, ranging from 21% to 23% for the contacts of infectious TB patients.[2]

Among contacts of persons with drug-resistant TB, infection rates seem to be similar. However, because they may have a poor response to treatment, persons with drug-resistant disease are often infectious for longer periods and therefore have the potential to infect more contacts. HIV-positive persons with TB disease are not considered more infectious than HIV-negative persons with TB disease.

Extrapulmonary TB is rarely contagious (except for laryngeal TB); however, transmission from extrapulmonary sites has been reported during aerosol-producing procedures, such as autopsies and tissue irrigation.[3,4,5]

Pathogenesis

When droplet nuclei are inhaled, most of the larger particles become lodged in the upper respiratory tract, where infection is unlikely to develop. However, smaller droplet nuclei containing the tubercle bacilli may reach the alveoli, where infection begins.

The tubercle bacilli that reach the alveoli are ingested by alveolar macrophages; the majority of these bacilli are destroyed or inhibited. A small number multiply intracellularly and are released when the macrophages die. These bacilli can spread through the lymphatic channels to regional lymph nodes and then through the bloodstream to more distant tissues and organs, including areas in which TB disease is most likely to develop: the apices of the lungs, the kidneys, the brain, and bone. Extracellular bacilli attract macrophages from the bloodstream. The immune response kills most of the bacilli, leading to the formation of a granuloma. At this point the person has TB infection, which can be detected by using the tuberculin skin test. It may take 2-10 weeks for the infected person to develop a positive reaction to the tuberculin skin test. Immune responses soon develop to kill the bacilli. Within 2 to 10 weeks after infection, the immune system is usually able to halt the multiplication of the tubercle bacilli, preventing further spread.

Persons who are infected with *M. tuberculosis*, but who do not have TB disease cannot spread the infection to other people. TB infection in a person who does not have TB disease is not considered a case of TB and is often referred to as latent TB infection (LTBI).

In some people, TB bacilli overcome the defenses of the immune system and begin to multiply, resulting in the progression from TB infection to TB disease. This process may occur soon after or many years after infection. In the United States, unless they are treated, approximately 5% of persons who have been infected with *M. tuberculosis* will develop TB disease in the first year or two after infection and another 5% will develop disease sometime later in life. Recent infection (within the past 2 years) with *M. tuberculosis* is therefore an important risk factor for progression to TB disease. In all, in approximately 10% of persons with normal immune systems who are infected with *M. tuberculosis*, TB disease will develop at some point.

Some medical conditions increase the risk that TB infection will progress to disease. Some studies suggest that the risk may be approximately 3 times greater (as with diabetes)[6,7] to more than 100 times greater (as with HIV infection) [6, 7, 8] for persons who have these conditions than for those who do not. HIV infection is the strongest known risk factor for development of TB disease in persons with LTBI. Compared with immunocompetent persons who are infected with *M. tuberculosis*, infected persons who are immunosuppressed are at considerably greater risk of developing TB disease. For example, studies suggest that the risk of developing TB is 7% to 10% each year for persons who are infected with both *M. tuberculosis* and HIV,[8,9] whereas it is 10% over a lifetime for persons infected only with *M. tuberculosis*.

Pathogenesis

- 10% of infected persons with normal immune systems develop TB at some point in life
- HIV strongest risk factor for development of TB if infected
  - Risk of developing TB disease 7% to 10% each year
- Certain medical conditions increase risk that TB infection will progress to TB disease

SLIDE 8

Conditions That Increase the Risk of Progression to TB Disease

- ➤ HIV infection
- ➤ Substance abuse
- ➤ Recent infection
- ➤ Chest radiograph findings suggestive of previous TB
- ➤ Diabetes mellitus
- ➤ Silicosis
- ➤ Prolonged corticosteriod therapy
- ➤ Other immunosuppressive therapy

SLIDE 9

Conditions That Increase the Risk of Progression to TB Disease (cont.)

- ➤ Cancer of the head and neck
- ➤ Hematologic and reticuloendothelial diseases
- ➤ End-stage renal disease
- ➤ Intestinal bypass or gastrectomy
- ➤ Chronic malabsorption syndromes
- ➤ Low body weight (10% or more below the ideal)

SLIDE 10

Common Sites of TB Disease

- ➤ Lungs
- ➤ Pleura
- ➤ Central nervous system
- ➤ Lymphatic system
- ➤ Genitourinary systems
- ➤ Bones and joints
- ➤ Disseminated (miliary TB)

SLIDE 11

Conditions that increase the risk of progression to TB disease include:

- HIV infection
- Substance abuse (especially drug injection)
- Recent infection with *M. tuberculosis* (within the past 2 years)
- Chest radiograph findings suggestive of previous TB (in a person who received inadequate or no treatment)
- Diabetes mellitus
- Silicosis
- Prolonged corticosteroid therapy
- Other immunosuppressive therapy
- Cancer of the head and neck
- Hematologic and reticuloendothelial diseases (e.g., leukemia and Hodgkin's disease)
- End-stage renal disease
- Intestinal bypass or gastrectomy
- Chronic malabsorption syndromes
- Low body weight (10% or more below the ideal)

TB disease most commonly affects the lungs; 73% of TB cases are exclusively pulmonary.[10] Patients with pulmonary TB usually have a cough and an abnormal chest radiograph, and are likely to be infectious.

However, TB is a systemic disease and may also commonly occur in the following ways: as a pleural effusion; in the central nervous, lymphatic, or genitourinary systems; in the bones and joints; or as disseminated disease (miliary TB). More rarely, TB can occur in other body sites; for example, the breast, skin, or peritoneum. Extrapulmonary TB is more common in immunosuppressed persons and in young children; lymphatic TB and miliary disease are particularly common in immunosuppressed persons. Extrapulmonary TB is often accompanied by pulmonary TB.

Drug-Resistant Tuberculosis

Drug-resistant TB is transmitted in the same way as drug-susceptible TB. The earlier outbreaks of multidrug-resistant TB support the findings that drug-resistant TB is no less infectious than drug-susceptible TB, although prolonged periods of infectiousness that often occur in patients with drug-resistant TB may facilitate transmission.

Drug resistance is divided into two types: primary resistance and secondary (or acquired) resistance. Primary resistance develops in persons who are initially infected with resistant organisms. Secondary resistance, or acquired resistance, develops during TB therapy, either because the patient was treated with an inadequate regimen or because the patient did not take the prescribed regimen appropriately.

Drug-Resistant TB

- Drug-resistant TB transmitted same way as drug-susceptible TB
- Drug resistance is divided into two types:
  - Primary resistance develops in persons initially infected with resistant organisms
  - Secondary resistance (acquired resistance) develops during TB therapy

SLIDE 12

Classification System

The current clinical classification system for TB is based on the pathogenesis of the disease (see table 1). TB disease should be ruled in or out within 3 months. Therefore, a patient should not have a class 5 classification for more than 3 months.

Health care providers should comply with state and local laws and regulations requiring the reporting of TB. All persons with class 3 or class 5 TB should be reported promptly to the state and local health department.

Table 1. Classification System for TB

Class	Type	Description
0	No TB exposure Not infected	No history of exposure Negative reaction to tuberculin skin test
1	TB exposure No evidence of infection	History of exposure Negative reaction to tuberculin skin test
2	TB infection No disease	Positive reaction to tuberculin skin test Negative bacteriologic studies (if done) No clinical, bacteriological, or radiographic evidence of active TB
3	TB, clinically active	*M. tuberculosis* cultured (if done) Clinical, bacteriological, or radiographic evidence of current disease
4	TB Not clinically active	History of episode(s) of TB **or** Abnormal but stable radiographic findings Positive reaction to the tuberculin skin test Negative bacteriologic studies (if done) **and** No clinical or radiographic evidence of current disease
5	TB suspected	Diagnosis pending

Study Questions

Answers to these questions can be found in the text.

1. How is TB spread?

2. After TB has been transmitted, how long does it take before TB infection can be detected with a tuberculin skin test?

3. What conditions increase the risk that TB infection will progress to disease?

4. Describe the classification system for TB.

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Chapter Three

Epidemiology of TB in the United States

Summary. After the introduction of anti-TB medication in the late 1940s, there was hope that TB would soon be eradicated. There was a steady decline in the incidence of TB in the United States from 1953 through 1984. However, from 1985 through 1992, the number of reported TB cases increased by 20%. Since 1993, the number of TB cases reported has again declined, and the nation has recovered from the resurgence of TB that occurred in the mid-1980s. However, the nation cannot let its guard down when the goal is TB control and prevention and eventual elimination of TB as a public health threat. Although the overall number of TB cases is decreasing, TB cases continue to be reported in every state. During 1998, a total of 18,361 new cases (rate of 6.8 per 100,000 population) of TB were reported to CDC from the 50 states and the District of Columbia. Surveillance data have shown that TB in the United States affects racial/ethnic minorities disproportionately. Resistance to anti-TB drugs among reported TB cases in the United States remains a serious public health concern. An estimated 10 to 15 million persons in this country are infected with *M. tuberculosis*. TB disease may develop in these persons at some time in the future. Efforts to control TB through the prompt identification and treatment of persons with infectious TB can reduce the number of newly infected persons who are added to this population. Some groups are at higher risk for TB than others. These groups can be divided into two categories: persons at higher risk for exposure to or infection with *M. tuberculosis*, and persons at higher risk of developing TB disease once infected with *M. tuberculosis*.

Objectives

After working through this chapter, you will be able to

- Describe how the number of TB cases reported in the United States has changed recently;
- List the racial and ethnic groups that are disproportionately affected by TB.

Trends

TB Morbidity Trends in the United States

- From 1953 to 1984, reported cases decreased by an average of 5.6% per year
- From 1985 to 1992, reported TB cases increased by 20%
- Since 1993, reported TB cases have been declining again
- 18,361 cases reported in 1998

SLIDE 15

Factors Contributing to the Increase in TB Morbidity: 1985-1992

- Deterioration of the TB public health infrastructure
- HIV/AIDS epidemic
- Immigration from countries where TB is common
- Transmission of TB in congregate settings

SLIDE 17

Factors Contributing to the Decrease in TB Morbidity Since 1993

Increased efforts to strengthen TB control programs that

- Promptly identify persons with TB
- Initiate appropriate treatment
- Ensure completion of therapy

SLIDE 18

After the introduction of anti-TB medication in the late 1940s, there was hope that TB would soon be eradicated. There was a steady decrease in the incidence of TB in the United States from 1953 through 1984 (figure 1). The number of reported cases declined by an average of 5.6% per year, from more than 84,000 cases in 1953 to 22,255 cases in 1984.[1] However, after decades of steady decline in TB, from 1985 through 1992 the number of reported TB cases increased by 20%.[2] The major factors contributing to this increase were

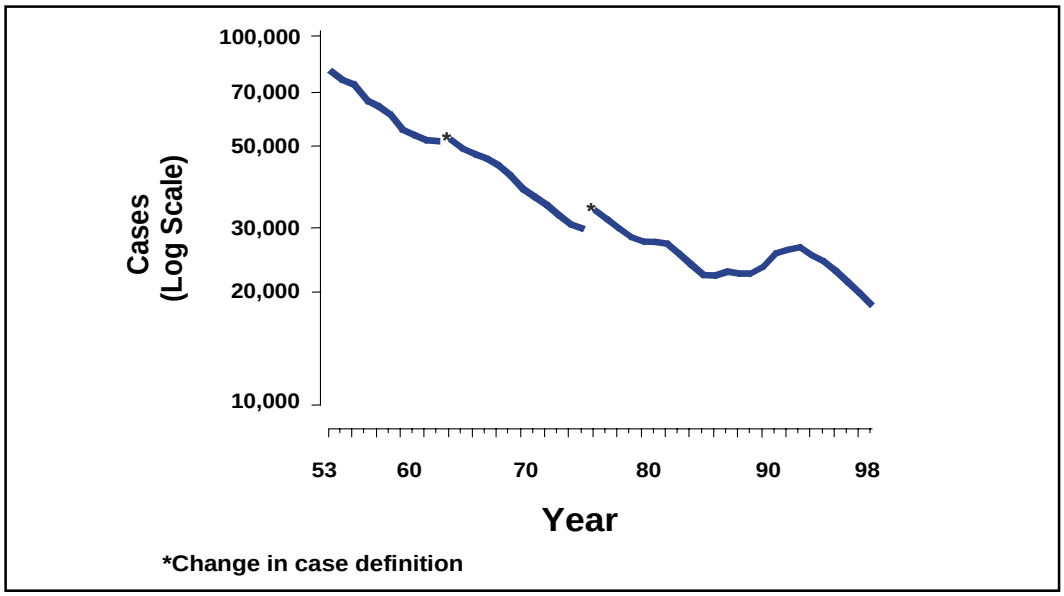
- A deterioration of the TB public health infrastructure
- The HIV/AIDS epidemic
- Immigration from countries where TB is common
- Transmission of TB in congregate settings (e.g., health care facilities, correctional facilities, homeless shelters)

Since 1993, the number of reported TB cases has again declined; the nation has recovered from the resurgence of TB that occurred in the mid-1980s, and is back on track toward TB elimination. This decline has been primarily attributed to increased efforts to strengthen TB control programs that promptly identify persons with TB, initiate appropriate treatment, and ensure the completion of therapy.[3]

During 1998, a total of 18,361 cases (rate of 6.8 per 100,000 population) of TB were reported to CDC from the 50 states and the District of Columbia, representing an 8% decrease from 1997.[1] This sixth annual consecutive decline in the number of reported TB cases also marks the lowest number and rate of reported TB cases since national reporting began in 1953.

Although the overall number of TB cases is decreasing, TB cases continue to be reported in every state. In 1998 seven states (California, Florida, Georgia, Illinois, New Jersey, New York, and Texas) reported 60% of all TB cases.[1] Cases of TB remain concentrated in urban areas: in 1998, nearly 40% of TB cases were reported from 64 major cities.[1]

Figure 1. Reported TB Cases in the United States, 1953–1998

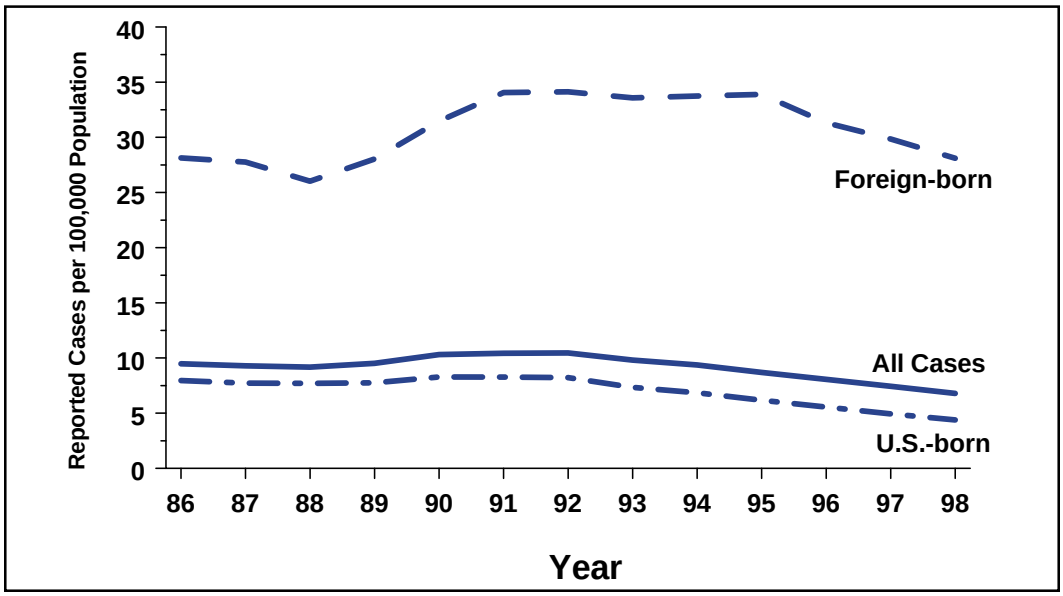


During 1992–1998, the overall decrease in TB cases reflected the substantial decline in cases among U.S.-born persons in all age groups and a small increase in the number of cases among foreign-born persons. Although the number of TB cases among foreign-born persons increased 4% during this period,[1] most of these foreign-born TB patients were probably infected before arrival in the United States.[4] The proportion of TB cases among foreign-born persons has increased steadily since the mid-1980s and increased markedly since 1992 (from 27% in 1992 to 42% in 1998) (figure 2).[1] The TB case rate for foreign-born persons has remained at least four to six times higher than that for U.S.-born persons.[1]

Surveillance data have shown that TB in the United States affects racial/ethnic minorities disproportionately. Compared with non-Hispanic whites, Asians are almost 16 times more likely to have TB; African Americans 8 times more likely; and Hispanics, Native Americans, and Alaskan Natives 5 times more likely.[1] However, it has been suggested that much of the increased risk for TB, particularly among U.S.-born persons in these racial/ethnic minorities, may be due to socioeconomic status.[5]

HIV-positive persons are at high risk for active TB disease after infection with *M. tuberculosis*. Because incomplete reporting has limited the analysis of national TB surveillance data by HIV status, state health departments have compared TB and AIDS registries to help estimate the proportion of reported TB cases with HIV coinfection. In the most recent registry comparison conducted by the 50 states and Puerto Rico, 14% of all TB cases reported during 1993–1994 had a match in the AIDS registry; 27% of cases were in persons aged 25–44 years.[6] Both this study and recent TB surveillance data indicate that the impact of the HIV/AIDS epidemic also differs by geographic location.[1]

Figure 2. Tuberculosis case rates by origin: United States, 1986–1998



Multidrug-Resistant TB (MDR TB) Remains a Serious Public Health Concern

- Resistance to INH ≥ 4% in 46 states and District of Columbia (DC) during 1993-1998
- 45 states and DC reported at least one MDR TB case during 1993-1998

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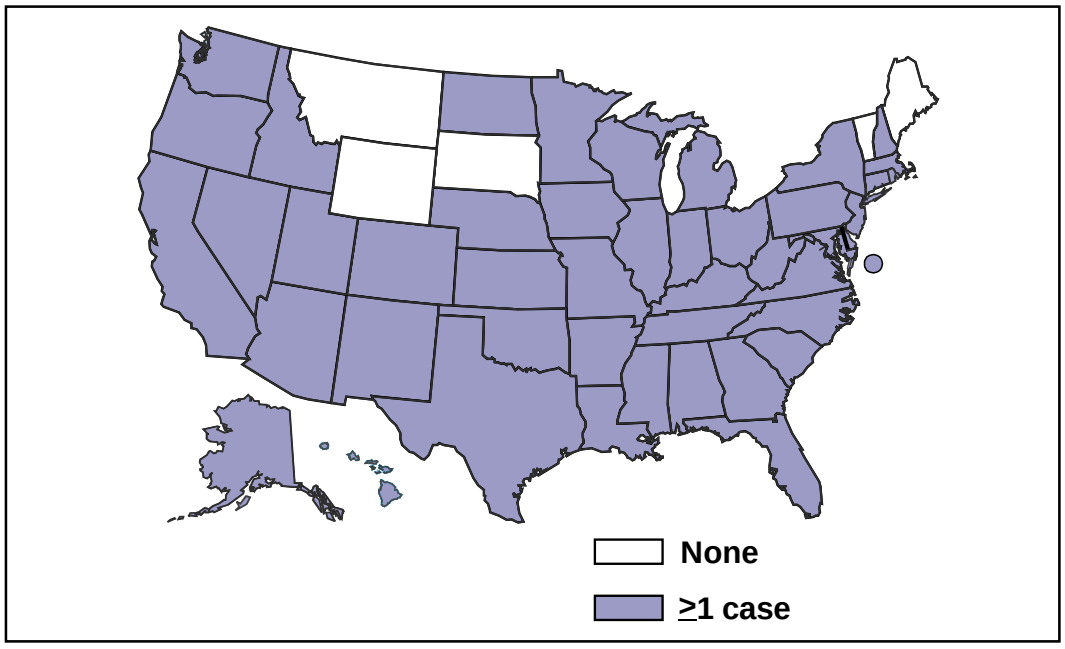
Multidrug-resistant TB (MDR TB), particularly among HIV-positive persons, contributed to the resurgence of TB in the late 1980s and early 1990s. Even now, resistance to anti-TB drugs among reported TB cases in the United States remains a serious public health concern. Since CDC began monitoring anti-TB drug resistance through the national TB surveillance system in 1993, levels of isoniazid resistance have been relatively stable.[1,7] Even among patients without a history of prior TB, resistance to isoniazid was 4% or higher in 46 states and the District of Columbia during 1993-1998.[8] Overall, the number and proportion of MDR TB cases has decreased.[1,7] Nevertheless, 45 states and the District of Columbia reported at least one MDR TB case during 1993-1998[8] (figure 3). The extent of drug resistance confirms the importance of initial treatment regimens of four first-line drugs for most TB patients and the use of drug susceptibility testing to guide optimal treatment of patients with culture-positive disease. All health departments must be prepared to deal with the challenge of MDR TB, which includes the capacity to ensure that clinicians with expertise in the management of MDR TB are always involved in the care of these patients.

Figure 3. MDR TB Cases, 1993–1998



The decrease in TB cases and MDR TB is encouraging; however, the earlier resurgence of TB taught a valuable lesson. The nation cannot let its guard down when the goal is TB control and prevention, as well as eventual elimination of TB as a public health threat. Every TB case is a potential outbreak, and maintaining strong TB control programs nationwide is essential in working toward this goal (See *Community TB Control*, p. 103). All health departments must be prepared to promptly identify persons who have active TB disease, to ensure that standards of care are met with respect to diagnosis and treatment (including prompt initiation and completion of therapy), and to identify and appropriately treat those who may have been infected through close contact with persons who have infectious TB.

Risk Groups

The following persons are at higher risk for exposure to or infection with *M. tuberculosis*:

- Close contacts of persons known or suspected to have TB (i.e., those sharing the same household or other enclosed environments)
- Foreign-born persons, including children, from areas that have a high TB incidence or prevalence (e.g., Asia, Africa, Latin America, Eastern Europe, Russia)
- Residents and employees of high-risk congregate settings (e.g., correctional institutions, nursing

Persons at Higher Risk for Exposure to or Infection with TB

- ➤ Close contacts of person known or suspected to have TB
- ➤ Foreign-born persons from areas where TB is common
- ➤ Residents and employees of high-risk congregate settings
- ➤ Health care workers (HCWs) who serve high-risk clients

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Persons at Higher Risk for Exposure to or Infection with TB (cont.)

- ➤ Medically underserved, low-income populations
- ➤ High-risk racial or ethnic minority populations
- ➤ Children exposed to adults in high-risk categories
- ➤ Persons who inject illicit drugs

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homes, mental institutions, other long-term residential facilities, and shelters for the homeless)

- Health care workers who serve high-risk clients
- Some medically underserved, low-income populations as defined locally
- High-risk racial or ethnic minority populations, defined locally as having an increased prevalence of TB (e.g., Asians and Pacific Islanders, Hispanics, African Americans, Native Americans, migrant farm workers, or homeless persons)
- Infants, children, and adolescents exposed to adults in high-risk categories
- Persons who inject illicit drugs; any other locally identified high-risk substance users (e.g., crack cocaine users)

Persons at Higher Risk of Developing TB Disease once Infected

- ➤ HIV infected
- ➤ Recently infected
- ➤ Persons with certain medical conditions
- ➤ Persons who inject illicit drugs
- ➤ History of inadequately treated TB

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Persons who are at higher risk of developing TB disease once infected with *M. tuberculosis* include

- Persons with HIV infection
- Persons who were recently infected with *M. tuberculosis* (within the past 2 years), particularly infants and very young children
- Persons who have medical conditions known to increase the risk for disease if infection occurs, e.g., diabetes, end-stage renal disease (see *Transmission and Pathogenesis*, p. 8)
- Persons who inject illicit drugs; other groups of high-risk substance users (e.g., crack cocaine users)
- Persons with a history of inadequately treated TB

An estimated 10 to 15 million persons in this country are infected with *M. tuberculosis*. TB disease may develop in these persons at some time in the future. Efforts to control TB through the prompt identification and treatment of persons with infectious TB can reduce the number of newly infected persons who are added to this population. Targeted testing of high-risk populations for TB infection and providing treatment for infection are crucial to achieving the nation's goal of eliminating TB. However, testing should not be given preference over higher priority TB prevention and control activities, such as identifying and completely treating all persons who have active TB, and conducting prompt contact investigations to identify persons who may have recently been infected and providing appropriate evaluation and treatment (see *Testing for TB Disease and Infection*, p. 25 and *Community TB Control*, p. 103).

Study Questions

Answers to these questions can be found in the text.

1. List four factors that contributed to the increase in reported TB cases from 1985 through 1992.

2. How has the number of reported TB cases changed recently?

3. Which racial and ethnic minorities are disproportionately affected by TB?

4. Why is multidrug-resistant TB a serious public health concern?

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Chapter Four

Testing for TB Disease and Infection

Summary. In most U.S. populations, targeted testing for TB is done to identify persons at high risk for TB who would benefit from treatment for latent TB infection (LTBI). Testing should be done in groups for which rates of TB are substantially higher than for the general population (targeted testing). All testing activities should be accompanied by a plan for follow-up care for persons with TB infection or disease. Clinicians should give tuberculin skin tests to high-risk persons as part of their routine evaluation. Institutional testing is recommended for the staff of health care facilities, as well as for the staff and residents of long-term care institutions where TB cases are found. The Mantoux tuberculin skin test is the preferred method of testing for TB infection.

Objectives

After working through this chapter, you will be able to

- List the 8 groups of persons who are at higher risk for exposure to or infection with *M. tuberculosis*;
- List the 6 groups of persons who are at higher risk of developing TB disease once infected with *M. tuberculosis*;
- Describe how the Mantoux tuberculin skin test is given;
- Describe the classification of the tuberculin reaction;
- Describe anergy testing and its role in tuberculin skin testing;
- Describe two-step testing.

Groups That Should Be Tested

In most U.S. populations, targeted testing for TB is done to find persons with infection and disease who would benefit from treatment. Therefore, all testing activities should be accompanied by a plan for follow-up care of persons with LTBI or disease. Healthcare agencies or other facilities should consult with the local health department before starting a skin-testing program to ensure that adequate provisions are made for the evaluation and treatment of persons whose tuberculin skin tests results are positive. Testing for TB infection should be done in well-defined groups. These high-risk groups can be divided into two categories:

- Persons at higher risk for TB exposure or infection
- Persons at higher risk for TB disease once infected

Purpose of Targeted Testing

- ➤ Find persons with LTBI who would benefit from treatment
- ➤ Find persons with TB disease who would benefit from treatment
- ➤ Groups that are not high risk for TB should not be tested routinely

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All testing activities should be accompanied by a plan for follow-up care.

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Groups That Should Be Tested for LTBI

Persons at higher risk for exposure to or infection with TB

- ➤ Close contacts of a person known or suspected to have TB
- ➤ Foreign-born persons from areas where TB is common
- ➤ Residents and employees of high-risk congregate settings
- ➤ Health care workers (HCWs) who serve high-risk clients

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Groups that are not at high risk for TB should not be tested routinely, because testing in low-risk populations diverts resources from other priority activities and because positive tests in low-risk persons may not represent TB infection. Flexibility is needed in defining high-priority groups for testing. The changing epidemiology of TB indicates that the risk for TB among groups currently considered high priority may decrease over time, and groups currently not identified as being at risk subsequently may be considered as high priority.

In general, high-risk groups that should be tested for infection include:

Persons at higher risk for TB exposure or infection

- Close contacts of persons known or suspected to have TB (i.e., those sharing the same household or other enclosed environments)
- Foreign-born persons, including children, from areas that have a high TB incidence or prevalence (e.g., Asia, Africa, Latin America, Eastern Europe, Russia)
- Residents and employees of high-risk congregate settings (e.g., correctional institutions, nursing homes, mental institutions, other long-term residential facilities, and shelters for the homeless)
- Health care workers who serve high-risk clients
- Some medically underserved, low-income populations as defined locally
- High-risk racial or ethnic minority populations, defined locally as having an increased prevalence of TB (e.g., Asians and Pacific Islanders, Hispanics, African Americans, Native Americans, migrant farm workers, or homeless persons)
- Infants, children, and adolescents exposed to adults in high-risk categories
- Persons who inject illicit drugs; any other locally identified high-risk substance users (e.g., crack cocaine users)

Persons at higher risk for TB disease once infected

- Persons with HIV infection
- Persons who were recently infected with *M. tuberculosis* (within the past 2 years), particularly infants and very young children
- Persons who have medical conditions known to increase the risk for disease if infection occurs, e.g., diabetes, end stage renal disease (see *Transmission and Pathogenesis*, p. 8)
- Persons who inject illicit drugs; other groups of high-risk substance users (e.g., crack cocaine users)
- Persons with a history of inadequately treated TB

Groups That Should Be Tested for LTBI (cont.)

Persons at higher risk for exposure to or infection with TB

- ➤ Medically underserved, low-income populations
- ➤ High-risk racial or ethnic minority populations
- ➤ Children exposed to adults in high-risk categories
- ➤ Persons who inject illicit drugs

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The preferred method of testing for TB infection in adults and children is the Mantoux tuberculin skin test. In some circumstances, testing for TB disease with chest radiographs or sputum smears may be more appropriate than testing for infection with the tuberculin skin test. For example, chest radiography is the preferred screening method when the objective is to identify persons who have current pulmonary TB and when treatment for LTBI is not the primary goal (e.g., in high-turnover jails or in some homeless shelters). Testing for TB infection or disease should always be carried out in consultation with the health department. Facilities such as drug treatment programs or long-term care facilities should test high-risk groups only when appropriate follow-up measures can be provided, either by that facility or by the health department.

Groups That Should Be Tested for LTBI (cont.)

Persons at higher risk for TB disease once infected

- ➤ Persons with HIV infection
- ➤ Persons recently infected with *M. tuberculosis*
- ➤ Persons with certain medical conditions
- ➤ Persons who inject illicit drugs
- ➤ Persons with a history of inadequately treated TB

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Clinicians should identify patients who are in a high-risk category (high risk for acquiring infection or high risk of progressing to disease once infected), and they should give tuberculin skin tests to these persons as part of their routine evaluation. In particular, persons with certain medical conditions known to increase the risk for TB disease (see *Transmission and Pathogenesis*, p. 8) should be tuberculin skin tested, and their tuberculin skin test status should be clearly noted on their medical record. Pregnant women should be targeted for tuberculin skin testing only if they have a specific risk factor for LTBI or for progression of LTBI to disease. Persons with a positive reaction should be evaluated for TB disease and, if disease is ruled out, considered for treatment for LTBI. For persons who have a positive PPD and who have had TB disease ruled out, routine follow-up skin tests and chest radiographs are unnecessary. These patients should be instructed to seek medical attention if they experience signs and symptoms suggestive of active TB disease.

Health care workers in facilities or communities where TB cases have occurred should be included in a TB testing and prevention program (see *Infection Control in Health Care Settings*, p. 87). In addition, testing is recommended for the staff of congregate living facilities who 1) may be exposed to persons with TB on the job (e.g., staff of correctional facilities) or 2) would pose a risk to large numbers of susceptible persons if they developed infectious TB (e.g., staff of AIDS hospices). Such persons should be tuberculin skin tested upon employment and thereafter at intervals determined by the risk of transmission in that facility. This testing is done for two reasons:

- To detect TB infection or disease in staff so that they may be given treatment
- To determine whether TB is being transmitted in the facility (indicated by skin test conversions among staff)

Health care workers who have a documented history of a positive tuberculin skin test, adequate treatment for disease, or adequate treatment for latent infection, should be exempt from further tuberculin skin testing. Health care workers with positive tuberculin skin test results should have a chest radiograph as part of the initial evaluation of their tuberculin skin test; if negative, repeat chest radiographs are **not** needed unless symptoms develop that could be attributed to TB. If health care workers with a documented history of a positive tuberculin skin test develop signs and symptoms suggestive of TB, they should undergo a medical evaluation including a chest radiograph. However, more frequent monitoring for symptoms of TB may be considered for recent converters and other tuberculin skin test-positive health care workers who are at increased risk for developing active TB (e.g., HIV-positive or otherwise severely immunocompromised health care workers).

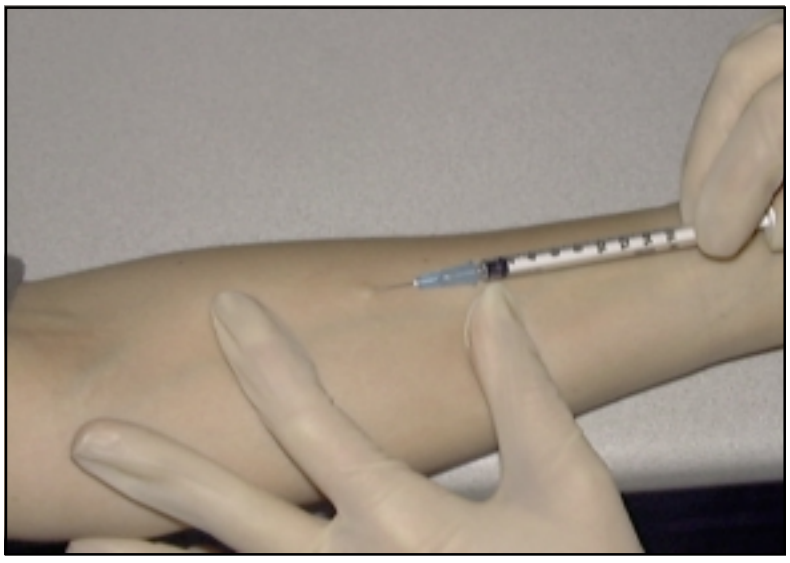

Figure 1. Administration of the tuberculin skin test using the Mantoux method.

Administration of the Tuberculin Test

The Mantoux tuberculin skin test is the standard method of identifying persons infected with *M. tuberculosis*. Multiple puncture tests (MPTs) should not be used to determine whether a person is infected. MPTs are not reliable because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy.

The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 ml of purified protein derivative (PPD) tuberculin containing 5 tuberculin units (TU) into the inner surface of the forearm (see figure 1). The injection should be made with a disposable tuberculin syringe, just beneath the surface of the skin, with the needle bevel facing upward. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter.

To prevent needle stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (e.g., the use of gloves) should be followed.

The reaction to the Mantoux test should be read by a trained health care worker 48 to 72 hours after the injection (see figure 2). Patients should never be allowed to read their own tuberculin skin test results. If a patient fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a patient who fails to return within 72 hours has a negative test, tuberculin testing should be repeated.

Administering the Tuberculin Skin Test

- Inject intradermally 0.1 ml of 5 TU PPD tuberculin
- Produce wheal 6 mm to 10 mm in diameter
- Do not recap, bend, or break needles, or remove needles from syringes
- Follow universal precautions for infection control

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Reading the Tuberculin Skin Test

- Read reaction 48-72 hours after injection
- Measure only induration
- Record reaction in millimeters

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The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis). Erythema (redness) should not be measured. All reactions should be recorded in millimeters, even those classified as negative. If no induration is found, "0 mm" should be recorded. A tuberculin skin test conversion is defined as an increase of ≥10 mm of induration within a 2-year period regardless of age.

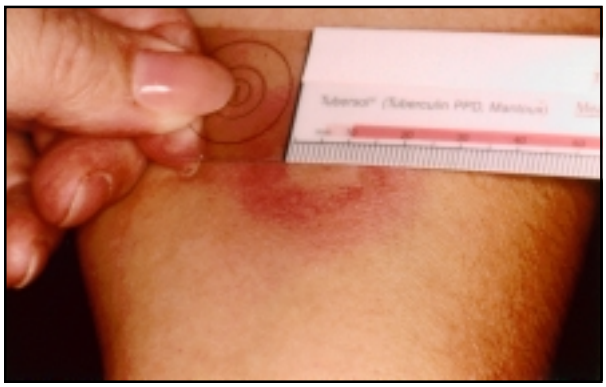

Figure 2. Correct measure of reaction to the tuberculin skin test.

Classification of the Tuberculin Reaction

A tuberculin reaction of ≥5 mm of induration is classified as positive in the following groups:

- HIV-positive persons
- Recent contacts of TB case
- Persons with fibrotic changes on chest radiograph consistent with old healed TB
- Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥ 15 mg/day of prednisone for ≥1 month)

A tuberculin reaction of ≥10 mm of induration is classified as positive in persons who do not meet the preceding criteria but who have other risk factors for TB. These include:

- Recent arrivals (< 5 years) from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health-care facilities, residential facilities for AIDS patients, and homeless shelters
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that place them at high risk (see *Transmission and Pathogenesis*, p. 8)
- Children < 4 years of age, or children and adolescents exposed to adults in high-risk categories.

A tuberculin reaction of ≥15 mm of induration is classified as positive in persons with no known risk factors for TB. However, targeted skin testing programs should only be conducted among high-risk groups.

Classifying the Tuberculin Reaction

≥5 mm is classified as positive in

- HIV-positive persons
- Recent contacts of TB case
- Persons with fibrotic changes on chest radiograph consistent with old healed TB
- Patients with organ transplants and other immunosuppressed patients

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Classifying the Tuberculin Reaction (cont.)

≥10 mm is classified as positive in

- Recent arrivals from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that place them at high risk
- Children < 4 years of age, or children and adolescents exposed to adults in high-risk categories

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In general, these guidelines for interpreting skin test reactions should also be applied to persons who may have occupational exposure to TB (e.g., health care workers or staff of nursing homes, drug treatment centers, or correctional facilities). Thus, the appropriate cutoff for defining a positive reaction depends on the employee's individual risk factors for TB, including recent TB exposure, and the prevalence of TB in the facility. In facilities where the risk of exposure is very low, ≥15 mm may be an appropriate cutoff for employees with no other risk factors. In facilities where TB patients receive care, ≥10 mm may be an appropriate cutoff for employees with no other risk factors.

The tuberculin skin test is a valuable tool, but it is not perfect. Several factors can affect the skin test reaction (see Table 1). Infection with mycobacteria other than *M. tuberculosis* (nontuberculous mycobacteria) and vaccination with bacille Calmette-Guérin (BCG) can lead to false-positive reactions (a positive skin test reaction in a person not infected with *M. tuberculosis*). See *BCG Vaccination*, p. 97, for further information on interpreting tuberculin reactions in persons with a history of BCG vaccination.

Vaccination with live viruses may also interfere with tuberculin skin test reactivity and cause false-negative reactions (a negative skin test reaction in a person infected with *M. tuberculosis)*. The Advisory Committee on Immunization Practices recommends that tuberculin skin testing be done on either the same day as vaccination with live-virus measles vaccine or 4-6 weeks after measles vaccination.[1] Other factors, such as anergy and overwhelming TB disease, can also lead to false-negative reactions.

Classifying the Tuberculin Reaction (cont.)

≥15 mm is classified as positive in

- Persons with no known risk factors for TB
- Targeted skin testing programs should only be conducted among high-risk groups

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Occupational Exposure to TB, Appropriate Cutoff Depends on

- Individual risk factors for TB
- Prevalence of TB in the facility

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Table 1
Factors that May Cause False-Positive and False-Negative Reactions to the Tuberculin Skin Test

Type of Reaction	Possible Cause
False-positive	Nontuberculous mycobacteria BCG vaccination
False-negative	Anergy Recent TB infection Very young age (< 6 months old) Live-virus vaccination Overwhelming TB disease

Anergy

- Do not rule out diagnosis based on negative skin test result
- Consider anergy in persons with no reaction if
  - HIV infected
  - Overwhelming TB disease
  - Severe or febrile illness
  - Viral infections
  - Live-virus vaccinations
  - Immunosuppressive therapy
- Anergy skin testing no longer routinely recommended

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Anergy Testing

The absence of a reaction to the tuberculin skin test does not rule out the diagnosis of TB disease or infection. In immunosuppressed persons, delayed-type hypersensitivity responses such as tuberculin reactions may decrease or disappear. This condition, known as anergy, may be caused by many factors, such as HIV infection, severe or febrile illness, measles or other viral infections, Hodgkin's disease, sarcoidosis, live-virus vaccination, or the administration of corticosteroids or immunosuppressive drugs. On average, 10% to 25% of patients with TB disease have negative reactions when tested with a tuberculin skin test at diagnosis before treatment. [2,3]

Anergy is detected by administering at least two other delayed-type hypersensitivity antigens by the Mantoux method of intradermal injection. The lack of standardization and outcome data limit the evaluation of the effectiveness of anergy testing. The use of anergy testing in conjunction with tuberculin skin testing is no longer routinely recommended for testing programs for *M. tuberculosis* infection conducted among HIV-positive persons in the United States.

Boosting

- Some people with LTBI may have negative skin test reaction when tested years after infection
- Initial skin test may stimulate (boost) ability to react to tuberculin
- Positive reactions to subsequent tests may be misinterpreted as a new infection

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Two-Step Testing

In some people who are infected with *M. tuberculosis*, delayed-type hypersensitivity to tuberculin may wane over the years. When these people are skin tested many years after infection, they may have a negative reaction. However, this skin test may stimulate (boost) their ability to react to tuberculin, causing a positive reaction to subsequent tests. This boosted reaction may be misinterpreted as a new infection. The booster phenomenon may occur at any age; its frequency increases with age and is highest among older persons. Boosted reactions may occur in persons infected with nontuberculous mycobacteria or in persons who have had a prior BCG vaccination.

Two-step testing is used to reduce the likelihood that a boosted reaction will be misinterpreted as a recent infection. If the reaction to the first test is classified as negative, a second test should be done 1 to 3 weeks later. A positive reaction to the second test probably represents a boosted reaction (past infection or prior BCG vaccination). On the basis of this second test result, the person should be classified as previously infected and cared for accordingly. This would not be considered a skin test conversion. If the second test result is also negative, the person should be classified as uninfected. In these persons, a positive reaction to any subsequent test is likely to represent new infection with *M. tuberculosis* (skin test conversion). Two-step testing should be used for the **initial** skin

testing of adults who will be retested periodically, such as health care workers.

Because of cross-reactions with other mycobacteria, the specificity of the tuberculin test is less when serial skin testing is performed than when a single test is administered. Thus, serial skin-testing programs tend to overestimate the incidence of new TB infection in the tested population. Because of this potential for overestimation of new infections, serial skin-testing programs should be targeted to populations at high risk for continued exposure to infectious persons.

Two-Step Testing

Use two-step testing for initial skin testing of adults who will be retested periodically

- ➤ If first test positive, consider the person infected
- ➤ If first test negative, give second test 1-3 weeks later
- ➤ If second test positive, consider person infected
- ➤ If second test negative, consider person uninfected

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Study Questions

Answers to these questions can be found in the text.

1. What is the purpose of testing for TB infection and disease?

2. Name eight groups who are at higher risk for exposure to or infection with *M. tuberculosis*.

3. Name six groups who are at higher risk of developing TB disease once infected with *M. tuberculosis*.

4. How is the Mantoux tuberculin skin test given? How is it read?

5. What are the cutoffs (in millimeters of induration) for different groups?

6. What can cause a false-positive reaction? What can cause a false-negative reaction?

7. What is anergy?

8. When and why should two-step testing be done?

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Chapter Five

Diagnosis of TB

Summary. The symptoms of pulmonary TB include cough, chest pain, and hemoptysis; the specific symptoms of extrapulmonary TB depend on the site of disease. Systemic symptoms consistent with TB include fever, chills, night sweats, appetite loss, weight loss, and easy fatigability. The possibility of TB should be considered in persons who have these symptoms. Persons suspected of having TB should be referred for a medical evaluation, which should include a medical history, a physical examination, a Mantoux tuberculin skin test, a chest radiograph, and any appropriate bacteriologic or histologic examinations. Positive bacteriologic cultures for *M. tuberculosis* confirm the diagnosis of TB. Clinicians should not wait for bacteriologic culture results before starting therapy. Therapy should be started when the potential risks of TB exceed the risk of therapy.

Objectives

After working through this chapter, you will be able to

- List at least five symptoms of pulmonary TB;
- Explain the purpose and significance of the acid-fast bacilli (AFB) smear;
- Explain the purpose and significance of the culture;
- List at least four groups of persons who are at an increased risk for drug resistance.

Medical Evaluation

A complete medical evaluation for TB includes a medical history, a physical examination, a Mantoux tuberculin skin test, a chest radiograph, and any appropriate bacteriologic or histologic examinations.

Medical History

The symptoms of pulmonary TB may include a productive, prolonged cough (duration of ≥ 3 weeks), chest pain, and hemoptysis. Systemic symptoms of TB include fever, chills, night sweats, appetite loss, weight loss, and easy fatigability. TB should be considered in persons who have these symptoms.

Evaluation for TB

- ➤ Medical history
- ➤ Physical examination
- ➤ Mantoux tuberculin skin test
- ➤ Chest radiograph
- ➤ Bacteriologic or histologic exam

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Symptoms of Pulmonary TB

- Productive, prolonged cough (duration of ≥3 weeks)
- Chest pain
- Hemoptysis

SLIDE 43

Systemic Symptoms of TB

- Fever
- Chills
- Night sweats
- Appetite loss
- Weight loss
- Easy fatigability

SLIDE 44

Medical History

- Symptoms of disease
- History of TB exposure, infection, or disease
- Past TB treatment
- Demographic risk factors for TB
- Medical conditions that increase risk for TB disease

SLIDE 45

Approximately 19% of TB cases are exclusively extrapulmonary.[1] The symptoms of extrapulmonary TB depend on the site affected. TB of the spine may cause pain in the back; TB of the kidney may cause blood in the urine. Extrapulmonary TB should be considered in the differential diagnosis of ill persons who have systemic symptoms and who are at high risk for TB.

It is important to ask persons suspected of having TB about their history of TB exposure, infection, or disease. Clinicians may also contact the local health department for information about whether a patient has received TB treatment in the past. If the drug regimen was inadequate or if the patient did not adhere to therapy, TB may recur and may be drug resistant. It is also important to consider demographic factors (country of origin, age, ethnic or racial group, occupation) that may increase the patient's risk for exposure to TB or to drug-resistant TB disease.

In addition, clinicians should determine whether the patient has medical conditions, especially HIV infection, that increase the risk for TB disease (see *Transmission and Pathogenesis*, p. 8). All patients who do not know their current HIV status should be referred for HIV counseling and testing.

Physical Examination

A physical examination is an essential part of the evaluation of any patient. It cannot be used to confirm or rule out TB, but it can provide valuable information about the patient's overall condition and other factors that may affect how TB is treated.

Tuberculin Skin Testing

The tuberculin skin test is useful for

- Examining a person who is not ill but may be infected with *M. tuberculosis*, such as a person who has been exposed to someone who has TB. The tuberculin skin test is the only way to diagnose TB infection before the infection has progressed to TB disease;
- Determining how many people in a group are infected with *M. tuberculosis*;
- Examining a person who has symptoms of TB.

The preferred method of testing for TB infection in adults and children is the Mantoux tuberculin skin test. The administration of tuberculin using the Mantoux method and interpretation of its results are discussed in *Testing for TB Disease and Infection*, p. 25.

As noted in *Testing for TB Disease and Infection*, p. *25*, a negative reaction to the tuberculin skin test does not exclude the diagnosis of TB, especially for patients with severe TB illness or infection with HIV. Also, some persons may not react to the tuberculin skin test if they are tested too soon after being exposed to TB. In general, it takes 2 to 10 weeks after infection for a person to develop an immune response to tuberculin. Persons who have recently been around someone with TB and who have a negative reaction to the tuberculin skin test should be retested 10 to 12 weeks after the last time they were exposed to infectious TB. Children younger than 6 months of age may not react to the tuberculin skin test because their immune systems are not yet fully developed.

Mantoux Tuberculin Skin Test

- Preferred method of testing for TB infection in adults and children
- Tuberculin skin testing useful for
  - Examining person who is not ill but may be infected
  - Determining how many people in group are infected
  - Examining person who has symptoms of TB

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Chest Radiograph

- Abnormalities often seen in apical or posterior segments of upper lobe or superior segments of lower lobe
- May have unusual appearance in HIV-positive persons
- Cannot confirm diagnosis of TB

SLIDE 47

Chest Radiograph

A posterior-anterior radiograph of the chest is the standard view used for the detection and description of chest abnormalities. In some instances, other views (e.g., lateral, lordotic) or additional studies (e.g., CT scans) may be necessary.

In pulmonary TB, radiographic abnormalities are often seen in the apical and posterior segments of the upper lobe or in the superior segments of the lower lobe (see figure 1). However, lesions may appear anywhere in the lungs and may differ in size, shape, density, and cavitation, especially in HIV-positive and other immunosuppressed persons.

In HIV-infected persons, pulmonary TB may present atypically on the chest radiograph. For example, TB may cause infiltrates without cavities in any lung zone, or it may cause mediastinal or hilar lymphadenopathy with or without accompanying infiltrates and/or cavities. In HIV-positive persons, almost any abnormality on a chest radiograph may indicate TB. In fact, the radiograph of an HIV-positive person with TB disease may even appear entirely normal.

Old healed tuberculosis usually presents a different radiographic appearance from active tuberculosis. Old healed tuberculosis can produce various radiographic findings. Dense pulmonary nodules, with or without visible calcification, may be seen in the hilar area or upper lobes. Smaller nodules, with or without fibrotic scars, are often seen in the upper lobes. Upper-lobe volume loss often accompanies these scars. Nodules and fibrotic lesions

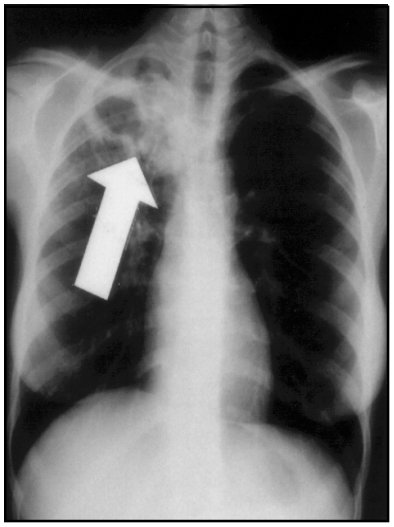

Figure 1. Arrow points to a cavity in patient's right upper lobe.

of old healed tuberculosis have well-demarcated, sharp margins and are often described as "hard." Bronchiectasis of the upper lobes is a nonspecific finding that sometimes occurs from previous pulmonary tuberculosis. Pleural scarring may be caused by old tuberculosis, but is more commonly caused by trauma or other infections.

Nodules and fibrotic scars may contain slowly multiplying tubercle bacilli with the potential for future progression to active tuberculosis. The risk of progression is significant, and persons who have nodular or fibrotic lesions consistent with findings of old tuberculosis on chest radiograph and have a positive tuberculin skin test reaction should be considered high-priority candidates for treatment of latent infection regardless of age. Conversely, calcified nodular lesions (calcified granuloma) pose a very low risk for future progression to active tuberculosis.

Abnormalities on chest radiographs may be suggestive of, but are never diagnostic of, TB. However, chest radiographs may be used to rule out the possibility of pulmonary TB in a person who has a positive reaction to the tuberculin skin test and no symptoms of disease.

Diagnostic Microbiology

Specimen Collection

- Obtain 3 sputum specimens for smear examination and culture
- Persons unable to cough up sputum, induce sputum, bronchoscopy or gastric aspiration
- Follow infection control precautions during specimen collection

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Specimen Collection

Persons suspected of having pulmonary or laryngeal TB should have at least three sputum specimens examined by smear and culture. It is best to obtain a series of early-morning specimens collected on 3 consecutive days. Specimens should be obtained in an isolated, well-ventilated area or a sputum collection booth.

A health care worker should coach and directly supervise the person at least the first time sputum is collected. Persons should be properly instructed in how to produce a good specimen. Patients should be informed that sputum is the material brought up from the lungs and that mucus from the nose or throat and saliva are not good specimens. Coaching patients individually on how to expectorate can facilitate sputum collection. Unsupervised patients are seldom successful in providing an adequate specimen, especially the first time. The amount of coaching required on later visits will depend on individual patient needs.

For patients unable to cough up sputum, deep coughing may be induced by inhalation of an aerosol of warm, hypertonic (5%-15%) saline. Patients should be given time — 15 minutes is usually sufficient — to produce sputum, which is usually brought up by a deep cough. Because induced sputum is very watery and resembles saliva, it should be labeled "induced" to ensure that the laboratory staff do not discard it.

Bronchoscopy can be done if there is suspicion of TB and the patient cannot cough up sputum. Adequate infection control precautions should be taken when performing a bronchoscopy for the purpose of diagnosing TB disease (see *Infection Control in Health Care Settings*, p. 87). Bronchial washings, brushings, and biopsy specimens may be obtained, depending on the diagnostic possibilities and findings. Sputum collected after bronchoscopy may also be useful for a diagnosis.

Gastric aspiration can also be used to obtain specimens of swallowed sputum. Although it is uncomfortable, it is more cost effective and less invasive then bronchoscopy. It is the best way to obtain specimens from infants and some young children who cannot produce sputum even with aerosol inhalation. When using gastric aspiration to obtain specimens from children, it should be done in the morning before the patient gets out of bed or eats.

During specimen collection, patients produce an aerosol that may be hazardous to health care workers or other patients in close proximity. For this reason, precautionary measures for infection control must be followed during sputum induction, bronchoscopy, and other common diagnostic procedures (see *Infection Control in Health Care Settings*, p.87).

Because TB can occur in almost any anatomical site, a variety of clinical specimens other than sputum (e.g., urine, cerebrospinal fluid, pleural fluid, pus, or biopsy specimens) may be submitted for examination when extrapulmonary TB disease is suspected. Tissue specimens for the culture of *M. tuberculosis* should be placed in a transport medium (e.g., Dubos) or a normal saline solution. Formalin or other preservatives should not be used because these solutions kill or inhibit the growth of *M. tuberculosis.* Tissue specimens should be delivered to the laboratory promptly.

Laboratory Examination

Detection of acid-fast bacilli (AFB) in stained smears examined microscopically may provide the first bacteriologic clue of TB (see figure 2). Fluorochrome staining with auramine-rhodamine is the preferred staining method because it is faster than the traditional methods in which Ziehl-Neelsen or Kinyoun (basic fuchsin dye) stains are used. Smear examination is an easy and quick procedure; results should be available within 24 hours of specimen collection. However, smear examination permits only the presumptive diagnosis of TB because the AFB in a smear may be mycobacteria other than *M. tuberculosis*. Furthermore, many TB patients have negative AFB smears.

Smear Examination

- ➤ Strongly consider TB in patients with smears containing acid-fast bacilli (AFB)
- ➤ Results should be available within 24 hours of specimen collection
- ➤ Presumptive diagnosis of TB

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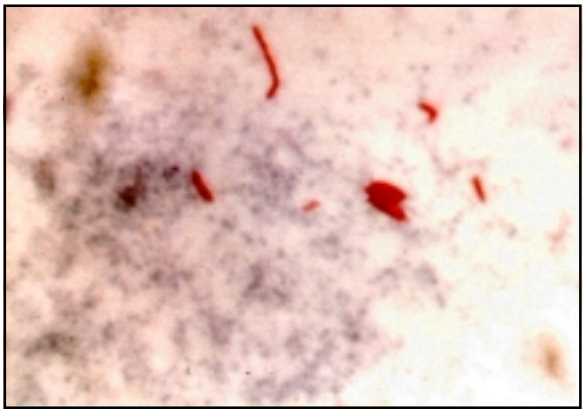

Figure 2. AFB (shown in red) are tubercle bacilli.

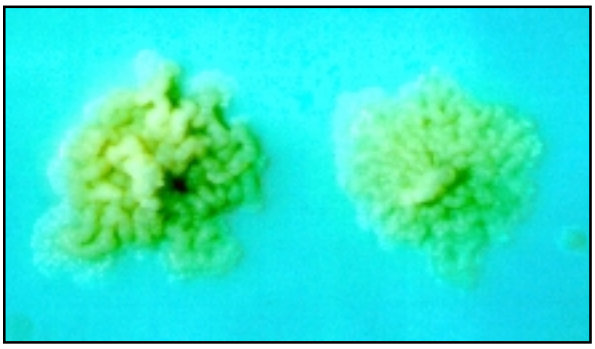

Figure 3. Colonies of *M. tuberculosis* growing on media.

Positive cultures for M. tuberculosis confirm the diagnosis of TB; however, TB may also be diagnosed on the basis of clinical signs and symptoms in the absence of a positive culture. Culture examinations should be done on all specimens, regardless of AFB smear results (figure 3). The BACTEC Radiometric System or other recently developed liquid medium systems allow detection of mycobacterial growth in 4 to 14 days. [2, 3]

Once the mycobacteria have been grown in culture, nucleic acid probes can identify the species in 2 to 4 hours.[4] Nucleic acid probes specific for the *M. tuberculosis* complex, for *M. avium*, and for *M. intracellulare* provide a rapid method of species identification. High-performance liquid chromatography (HPLC), which detects differences in the spectrum of mycolic acids in the cell wall, is equally rapid and can identify most pathogenic mycobacterial species.[5] A test for inhibition by ρ-nitro-α-acetylamino-β-hydroxypropio-phenone (NAP or NAP test) can identify *M. tuberculosis* in 3 to 4 days.[4] If a solid medium and conventional biochemical tests are used, the isolation and identification of the organism can take 6 to 12 weeks.[3]

Cultures

- Use to confirm diagnosis of TB
- Culture all specimens, even if smear negative
- Results in 4 to 14 days when liquid medium systems used

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Nucleic acid amplification (NAA) tests, such as polymerase chain reaction (PCR) and other methods for amplifying DNA and RNA, may facilitate rapid detection of microorganisms. Commercial NAA kits for the identification of *M. tuberculosis* complex have been approved by the Food and Drug Administration (FDA) for use on processed clinical specimens. These tests perform worst where needed most. Specificity is inadequate when applied to smear-negative specimens and sensitivity is inadequate when applied to smear-positive specimens. The test is approved for use in conjunction with culture for respiratory specimens that are positive for AFB on microscopy and were obtained from untreated patients. When used as approved, a positive NAA test result indicates a high likelihood of TB, but a negative result does not exclude TB. However, a reformulated

AMPLIFIED Mycobacterium Tuberculosis Direct (MTD) Test for the detection of *M. tuberculosis* in both smear-positive and smear-negative clinical specimens has recently been approved. This is the first NAA test approved for this indication. Decisions about when and how to use NAA tests for TB diagnosis should be individualized. NAA tests cannot replace clinical judgment or be relied on as the only guide for therapy or isolation practices. The tests may enhance diagnostic certainty, but should be interpreted in a clinical context and on the basis of local laboratory performance.

Follow-up bacteriologic examinations are important for assessing the patient's infectiousness and response to therapy. At a minimum, specimens should be obtained at monthly intervals until the culture results convert to negative. Culture conversion is the most important *objective* measure of response to treatment. Conversion is documented by the first negative culture in a series of cultures (i.e., all subsequent culture results must remain negative).

Laboratories should report positive smears and positive cultures within 24 hours by telephone or fax to the primary health care provider. Out-of-state laboratories must contact the health care provider in the patient's state of origin. Follow-up results may be reported by mail. It is the responsibility of the primary health care provider to promptly report all suspected or confirmed cases of TB to the health department so that a contact investigation can be initiated as quickly as possible (see *Community TB Control*, p. 103).

For all patients, the initial *M. tuberculosis* isolate should be tested for drug resistance. It is crucial to identify drug resistance as early as possible in order to ensure appropriate treatment. Susceptibility results from laboratories should be promptly forwarded to the health department. Drug susceptibility patterns should be repeated for patients who do not respond adequately or who have positive culture results despite 2 months of therapy.

The BACTEC radiometric method, which uses a liquid medium, is faster than conventional methods for determining susceptibility to first-line TB medications. Usually, susceptibility results can be obtained within 7-14 days of BACTEC inoculation; conventional methods, which use solid media for growth, can take as long as 21 days after inoculation.[2, 3]

Groups at an increased risk for drug resistance include

- Persons who have a history of treatment with TB drugs;
- Contacts of persons known to have drug-resistant TB;

Drug Susceptibility Testing

- ➤ Drug susceptibility testing on initial *M. tuberculosis* isolate
- ➤ Repeat for patients who
  - ➤ Do not respond to therapy
  - ➤ Have positive cultures despite 2 months of therapy
- ➤ Promptly forward results to the health department

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Persons at Increased Risk for Drug Resistance

- ➤ History of treatment with TB drugs
- ➤ Contacts of persons with drug-resistant TB
- ➤ Foreign-born persons from high prevalent drug resistant areas
- ➤ Smears or cultures remain positive despite 2 months of TB treatment
- ➤ Received inadequate treatment regimens for > 2 weeks

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- Foreign-born persons from areas where the prevalence of drug-resistant TB is high;
- Persons whose smears or cultures remain positive despite 2 months of therapy with TB drugs;
- Persons receiving inadequate treatment regimens for > 2 weeks.

Restriction fragment length polymorphism (RFLP), a method of DNA fingerprinting, can be used to identify specific strains of *M. tuberculosis* and thus track TB transmission during outbreaks. The restriction enzymes used in this technique cut DNA at certain sites to produce fragments of various lengths. These fragments are separated by size to produce a pattern, or "fingerprint," that is specific for each strain. Related isolates show the same pattern. In addition, DNA fingerprinting can be used to detect lab contamination by determining if the isolates from the contaminating source culture and the suspect culture are related. If the isolates have differing DNA fingerprint patterns, cross-contamination is very unlikely to have taken place.

Study Questions

Answers to these questions can be found in the text.

1. What are the components of a complete medical evaluation for TB?

2. List the symptoms of pulmonary TB.

3. What is the tuberculin skin test useful for?

4. What are the purposes of the chest radiograph?

5. What is the purpose of an acid-fast bacilli smear?

6. What is the purpose of the culture?

7. Why are drug susceptibility tests done? How often should they be done?

8. What groups of persons are at an increased risk for drug resistance?

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Chapter Six

Treatment of Latent TB Infection

Summary. Treatment of latent TB infection (LTBI) is essential to controlling and eliminating TB in the United States. Treatment of LTBI substantially reduces the risk that TB infection will progress to disease. Certain groups are at very high risk of developing TB disease once infected. Targeted testing programs should be designed to identify persons who are at high risk for TB and who would benefit from treatment of LTBI. There are several treatment regimens available for the treatment of LTBI, and providers should discuss treatment options with their patients. Baseline laboratory testing is not routinely indicated for all patients at the start of treatment for LTBI. Baseline hepatic measurements of serum AST (SGOT) or ALT (SGPT) and bilirubin are indicated for patients whose initial evaluation suggests an increased risk for liver disease.

Objectives

After working through this chapter, you will be able to

- List the high-risk groups who should be given high priority for treatment of latent TB infection;
- Describe the treatment-of-latent-TB-infection regimens for HIV-positive and HIV-negative persons;
- Describe how patients should be monitored.

Treatment of latent TB infection (LTBI) is essential to controlling and eliminating TB in the United States. Treatment of LTBI substantially reduces the risk that TB infection will progress to disease. Certain groups are at very high risk of developing TB disease once infected, and every effort should be made to begin appropriate treatment and to ensure those persons complete the entire course of treatment for LTBI.

Candidates for Treatment of Latent TB Infection

Targeted testing programs should be designed to identify persons who are at high risk for TB and who would benefit from treatment of LTBI. **Careful assessment to rule out the possibility of TB disease is necessary before treatment for LTBI is started.**

Persons in the following high-risk groups should be given treatment for LTBI if they have positive skin test results (≥5 mm):

- HIV-positive persons;
- Recent contacts of a TB case;
- Persons with fibrotic changes on chest radiograph consistent with old TB;

Candidates for Treatment of LTBI

Positive skin test result ≥5 mm

- HIV-positive persons
- Recent contacts of a TB case
- Persons with fibrotic changes on chest radiograph consistent with old TB
- Patients with organ transplants and other immunosuppressed patients

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Candidates for Treatment of LTBI (cont.)

Positive skin test result ≥10 mm

- Recent arrivals from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that make them high-risk
- Children < 4 years of age, or children and adolescents exposed to adults in high-risk categories

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Candidates for Treatment of LTBI (cont.)

Positive skin test result ≥15 mm

- Persons with no known risk factors for TB may be considered
- Targeted skin testing programs should only be conducted among high-risk groups

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- Patients with organ transplants, and other immunosuppressed patients (receiving the equivalent of ≥15 mg/day of prednisone for ≥1 month).

In addition, persons in the following high-risk groups should be considered for treatment of LTBI if their reaction to the tuberculin skin test is ≥10 mm:

- Recent arrivals (< 5 years) from high-prevalence countries;
- Injection drug users;
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities);
- Mycobacteriology laboratory personnel;
- Persons with clinical conditions that make them high-risk (see *Transmission and Pathogenesis*, p 8);
- Children < 4 years of age, or children and adolescents exposed to adults in high-risk categories.

No Known Risk Factors

Persons with no known risk factors for TB may be considered for treatment of LTBI if their reaction to the tuberculin test is ≥15 mm. This group should be given a lower priority for prevention efforts than the groups listed above.

Close Contacts

Some contacts who have a negative tuberculin skin test reaction (less than 5 mm of induration) should be evaluated for treatment of LTBI, after TB disease has been ruled out. These contacts include children under 4 years of age, immunosuppressed people, and others who may develop TB disease quickly after infection. Close contacts who have a negative reaction to an initial skin test should be retested 10 to 12 weeks after they were last exposed to TB. Treatment of latent infection may be discontinued if the skin test result is again negative and if the person is no longer exposed to TB. However, persons known to have or suspected of having HIV infection and other immunocompromised persons should be given treatment for LTBI regardless of their skin test reaction.

Children and Adolescents

Because or their age, infants and young children with LTBI are known to have been infected recently, and thus are at a high risk of their infection progressing to disease. Infants and young children are also more likely than older children and adults to develop life-threatening forms of TB. Children < 4 years of age who are close contacts should receive treatment for LTBI even if the tuberculin skin test result and chest radiograph do not suggest TB, because infected infants may be anergic as late as 6 months of age. A second tuberculin test should be placed 10-12 weeks after the last exposure to infectious TB. Treatment of LTBI can be discontinued if **all** of the following conditions are met:

- The infant is at least 6 months of age;
- The second tuberculin test is also negative;
- The second test was performed at least 10 weeks after the child was last exposed to infectious TB.

Regimens

(See tables 1 [pp. 112-113] and 2 [pp. 114-115])

There are several treatment regimens available for the treatment of LTBI, and providers should discuss options with their patients. For persons who are at especially high risk for TB and are either suspected of nonadherence or are on an intermittent dosing regimen, directly observed therapy (DOT) of LTBI should be considered. This method of treatment is especially appropriate when a household member is on DOT for active disease, or in institutions and facilities where treatment for infection can be observed by a staff member.

Isoniazid

In clinical trials, daily isoniazid treatment for latent infection for 12 months reduced the risk for TB disease by more than 90% in patients who completed a full course of therapy.[1] There is evidence that 6 months of treatment for LTBI with isoniazid can also confer a high degree of protection (approximately 70% in patients who complete the regimen) against the progression of TB infection to TB disease.[1] The protection conferred by taking at least 9 months of isoniazid is greater than that conferred by taking 6 months.

Treatment of LTBI with Isoniazid (INH)

- ➤ 9-month regimen considered optimal
- ➤ Children should receive 9 months of therapy
- ➤ Can be given twice-weekly if directly observed

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Isoniazid is normally used alone for treatment of LTBI in a single daily dose of 300 mg in adults and 10-15 mg/kg body weight in children, not to exceed 300 mg per dose. Isoniazid can be given two times a week at a dosage of 15 mg/kg as DOT of LTBI.[2,3] When isoniazid is given alone to persons with active TB disease, resistance to isoniazid is likely to develop. For this reason, persons suspected of having TB disease should receive the recommended multidrug regimen for treatment of disease until the diagnosis is confirmed or ruled out.

A 9-month regimen (minimum of 270 doses administered within 12 months) is considered optimal treatment for both HIV-positive and HIV-negative adults. A 6-month regimen (minimum of 180 doses administered within 9 months) may also provide sufficient protection. HIV-positive and HIV-negative children should receive 9 months of isoniazid treatment for infection. Twice-weekly regimens should consist of at least 76 doses administered within 12 months for the 9-month regimen and 52 doses within 9 months for the 6-month regimen. Treatment for LTBI for 6 months rather than 9 months may be more cost-effective and result in greater adherence by patients, therefore, local programs may prefer to implement the 6-month regimen rather then the 9-month regimen. Every effort should be made to ensure that patients adhere to treatment for infection for at least 6 months.

Peripheral neuropathy is associated with the use of isoniazid but is uncommon at doses of 5 mg/kg. Persons with conditions in which neuropathy is common (e.g., diabetes, uremia, alcoholism, malnutrition, HIV-infection), as well as pregnant women and persons with a seizure disorder, may be given pyridoxine (vitamin B_6) (10-50 mg/day) with isoniazid.

Treatment of LTBI with a Rifamycin and Pyrazinamide (PZA)

HIV-Positive Persons

- A rifamycin and PZA daily for 2 months
- May be given twice weekly
- Administration of rifampin (RIF) contraindicated with some protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs).

HIV-Negative Persons

Clinical trials have not been conducted

- Daily RIF and PZA for 2 months
- May be given twice weekly

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Rifampin/Pyrazinamide

Two- and three-month regimens with daily rifampin in combination with pyrazinamide and/or isoniazid have recently been evaluated in HIV-positive adult patients and appear to be as effective as longer courses of isoniazid.[2,3] Clinical trials of rifampin and pyrazinamide have not been conducted in HIV-negative persons. Therefore, the strength of the recommendation for use of this regimen is less for this population than for those who are HIV-positive. Regimens consisting of 2 months of rifampin and pyrazinamide are not recommended for pregnant women. Pyrazinamide's effect on the fetus is unknown.

HIV-Negative Persons

The recommended 2-month treatment-of-latent-infection regimen (60 doses to be administered within 3 months) includes daily rifampin and pyrazinamide. Rifampin is given in a daily dose of 10 mg/kg (maximum dose 600 mg) and pyrazinamide is given in a daily dose of 15-20 mg/kg (maximum dose 2 g). Rifampin and pyrazinamide may also be given two times a week (16 doses to be administered for 2 months or 24 doses to be administered for 3 months). However, this regimen has not been studied in this population and should be used only when other effective regimens cannot be given. Like all intermittent regimens, this regimen must always be administered under DOT.

HIV-Positive Persons

Two-month regimens for treatment of LTBI that include rifampin or rifabutin are appropriate for HIV-positive adults who are likely to be infected with TB organisms susceptible to rifamycins.

The administration of rifampin is contraindicated with some protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) used for HIV therapy. For these

patients, a substitution of rifabutin for rifampin is generally recommended. Clinicians are advised to consider potential drug interactions when prescribing rifamycins to patients receiving HIV therapy with PIs and NNRTIs. Daily regimens of a rifamycin (rifampin or rifabutin) and pyrazinamide should consist of at least 60 doses to be administered for 2 months or up to 3 months. This regimen may also be given two times a week (16 doses to be administered for 2 months or 24 doses to be administered for 3 months).

For HIV-positive patients receiving PIs or NNRTIs, an alternative 2-month regimen includes **rifabutin** and pyrazinamide administered daily. However, the concurrent administration of **rifabutin** is contraindicated with hard-gel saquinavir and delavirdine. An alternative is the use of **rifabutin** with indinavir, nelfinavir, amprenavir, ritonavir, efavirenz, and possibly soft-gel saquinavir and nevirapine. Caution is advised when using **rifabutin** with soft-gel saquinavir and nevirapine, because data regarding the use of **rifabutin** with soft-gel saquinavir and nevirapine are limited. **Rifabutin** is given in a daily dose of 5 mg/kg (maximum dose 300 mg) and pyrazinamide is given in a daily dose of 15-20 mg/kg (maximum dose 2 g). The dosage of **rifabutin** may need to be adjusted when given with certain PIs and NNRTIs (see table 5, pp. 120-121).

For HIV-positive patients **not** receiving PIs or NNRTIs, the recommended 2-month treatment-of-latent-infection regimen includes daily **rifampin** and pyrazinamide. **Rifampin** is given in a daily dose of 10-20 mg/kg (maximum dose 600 mg) and pyrazinamide is given in a daily dose of 15-20 mg/kg (maximum dose 2 g).

Rifampin

For both HIV-negative and HIV-positive patients who cannot tolerate isoniazid or pyrazinamide, an alternative treatment regimen is 4-months (minimum of 120 doses administered within 6 months) of rifampin.

Regimens for Specific Situations

Contacts of Isoniazid-Resistant TB

For persons who are known to be contacts of patients with isoniazid-resistant, rifampin-susceptible TB, a 2-month regimen of rifampin and pyrazinamide is recommended. For patients who are unable to tolerate pyrazinamide, a 4-month regimen of daily rifampin alone is recommended. In situations where rifampin cannot be used, rifabutin may be substituted. For HIV-positive persons, a 2-month regimen with a rifamycin and pyrazinamide is recommended.

Contacts of Multidrug-Resistant TB

For persons likely to have been infected with a strain of *M. tuberculosis* resistant to both isoniazid and rifampin, alternative regimens should be considered. Alternative

Contacts of INH-Resistant TB

- Treatment with a rifamycin and PZA
- If unable to tolerate PZA, 4-month regimen of daily RIF
- HIV-positive persons: 2 month regimen with a rifamycin and PZA

Contacts of Multidrug-Resistant TB

- Use 2 drugs to which the infecting organism has demonstrated susceptibility
- Treat for 6 months or observe without treatment (HIV-negative)
- Treat HIV-positive persons for 12 months
- Follow for 2 years regardless of treatment

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regimens should consist of two drugs to which the infecting organism has demonstrated susceptibility. Potential alternative regimens include either 6-12 months of daily ethambutol and pyrazinamide or 6-12 months of pyrazinamide and a quinolone (i.e, levofloxacin, ofloxacin, or ciprofloxacin). Immunocompetent contacts may be treated for 6 months or observed without treatment. Immunocompromised contacts (e.g., HIV-positive persons) should be treated for 12 months. Persons receiving pyrazinamide and a quinolone antibiotic should be monitored closely for adverse effects. Some evidence suggests that the combination of pyrazinamide and ofloxacin may be poorly tolerated.[4] All persons with suspected multidrug-resistant LTBI should be followed for 2 years regardless of the treatment regimen.

Ethambutol at the usual dose is safe for children. The regimen of pyrazinamide and ethambutol for 9-12 months is recommended for children if the infecting organism has demonstrated susceptibility. When pyrazinamide and/or ethambutol cannot be used, a combination of two other drugs to which the infecting organism is likely susceptible is recommended.

Persons with Fibrotic Lesions

Patients who have a chest radiograph suggestive of old fibrotic lesions thought to represent previous TB, a positive tuberculin skin test (≥5 mm), no evidence of active disease, and no history of treatment for TB should be treated for LTBI. Acceptable regimen options include

- 9 months of isoniazid
- 2 months of rifampin plus pyrazinamide **or**
- 4 months of rifampin (with or without isoniazid)

Fibrotic Lesions

Acceptable regimens include

- ➤ 9 months of INH
- ➤ 2 months RIF plus PZA
- ➤ 4 months of RIF (with or without INH)

Pregnancy and Breast-feeding

- ➤ INH daily or twice weekly
- ➤ Pyridoxine supplementation
- ➤ Breast-feeding not contraindicated

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Patients who have a positive tuberculin skin test and radiographic findings suggestive of healed, primary TB (calcified solitary pulmonary nodules, calcified hilar lymph nodes, and apical pleural capping) are not at significantly increased risk of TB. Their risk for progression to TB disease and the need for treatment of LTBI should be determined by other risk factors and the size of the tuberculin reaction.

Pregnancy and Breast-feeding

Isoniazid administered either daily or twice-weekly are the preferred regimens for the treatment of LTBI in pregnant women. Such women taking isoniazid should also take pyridoxine (vitamin B_6) supplementation. Although rifampin may be safe, there are no efficacy data supporting its use in this population.

For women who are at high risk for the progression of LTBI to active disease, especially those who are HIV-positive or who have been recently infected, initiation of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. For these women, careful clinical monitoring and/or lab monitoring should be conducted.

Breast-feeding is not contraindicated when a mother is being treated for LTBI. Likewise, the amount of isoniazid provided by breast milk is inadequate for the treatment of an infant. Infants whose breast-feeding mothers are taking isoniazid should receive supplemental pyridoxine.

Monitoring

Before treatment for LTBI is started, clinicians should conduct a medical history to

- Rule out the possibility of TB disease;
- Determine the history of treatment for LTBI or disease;
- Determine if there are any preexisting medical conditions that are a contraindication to treatment or are associated with an increased risk of adverse effects of treatment;
- Obtain information about current and previous drug therapy, including any previous adverse reactions to drugs considered for treatment of LTBI and to current drugs which have known interactions with drugs used for the treatment of LTBI;
- Recommend HIV testing if risk factors are present.

Monitoring Patients

Before treatment for LTBI is started, clinicians should

- ➤ Rule out possibility of TB disease
- ➤ Determine history of treatment for LTBI or disease
- ➤ Determine contraindications to treatment
- ➤ Obtain information about current and previous drug therapy
- ➤ Recommend HIV testing if risk factors are present

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In addition, conducting a medical history provides an opportunity to establish rapport with the patient and to highlight important aspects of treatment, such as

- Benefits of treatment
- Importance of adherence to the treatment regimen
- Possible adverse side effects of the regimen
- Establishment of an optimal follow-up plan

Monitoring Patients (cont.)

Establish rapport with patient and emphasize

- ➤ Benefits of treatment
- ➤ Importance of adherence to treatment regimen
- ➤ Possible adverse side effects of regimen
- ➤ Establishment of optimal follow-up plan

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Baseline laboratory testing is not routinely indicated for all patients at the start of treatment for LTBI. Baseline hepatic measurements of serum AST (SGOT) or ALT (SGPT) and bilirubin are indicated for patients whose initial evaluation suggests a liver disorder. Baseline testing is also indicated for patients with HIV infection, women who are pregnant or in the immediate postpartum period (within 3 months of delivery), and persons with a history of chronic liver disease (e.g., hepatitis B or C, alcoholic hepatitis or cirrhosis, persons who use alcohol regularly, and others who are at risk of chronic liver disease). Baseline laboratory testing is not routinely indicated in older persons. However, testing may be considered on an individual basis, particularly for patients who are taking other

Monitoring Patients (cont.)

Baseline laboratory testing

- Not routinely indicated
- Baseline hepatic measurements for
  - Patients whose initial evaluation suggests a liver disorder
  - Patients with HIV infection
  - Pregnant women and those in immediate postpartum period
  - Patients with history of chronic liver disorder

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Monitoring Patients (cont.)

At least monthly, evaluate for

- Adherence to prescribed regimen
- Signs and symptoms of active TB disease
- Signs and symptoms of hepatitis (if receiving isoniazid alone, and at 2, 4, and 8 weeks if receiving RIF and PZA)

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medications for chronic medical conditions. Active hepatitis and end-stage liver disease are relative contraindications to the use of isoniazid or pyrazinamide for treatment of LTBI. Use of these drugs in such patients must be undertaken with caution.

At least once a month, clinicians should evaluate patients receiving treatment of LTBI for

- Adherence to the prescribed regimen
- Signs and symptoms of active TB disease
- Signs and symptoms of hepatitis (if receiving isoniazid alone, and at 2, 4, and 8 weeks if receiving rifampin and pyrazinamide)

Routine laboratory monitoring during treatment of LTBI is indicated only for those whose baseline liver function tests are abnormal and for other persons with a risk of hepatic disease. There should be laboratory testing, such as liver function studies for patients with symptoms compatible with hepatotoxicity or a uric acid measurement to evaluate patients who develop acute arthritis, to evaluate possible adverse reactions that occur during the treatment regimen.

Some evidence suggests that women, particularly black and Hispanic women, are at increased risk for fatal hepatitis associated with isoniazid.[5] This risk may also be increased during the postpartum period. These persons should be closely monitored for adverse reactions throughout the course of treatment.

About 10% to 20% of persons taking isoniazid will have some mild, asymptomatic elevation of liver enzymes. These abnormalities tend to resolve even if isoniazid is continued. If any of the measurements exceed three to five times the upper limit of normal or if the patient reports symptoms of adverse reactions, the discontinuation of isoniazid should be strongly considered.

Study Questions

Answers to these questions can be found in the text.

1. Which groups of persons should receive high priority for treatment of LTBI?

2. What are the recommended regimens for treatment of LTBI for HIV-positive patients?

3. What are the recommended regimens for treatment of LTBI for HIV-negative patients?

4. Which patients should receive baseline laboratory testing?

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Chapter Seven

Treatment of TB Disease

Summary. For most patients, the preferred regimen for treating TB disease consists of an initial 2-month phase of four drugs: isoniazid, rifampin, pyrazinamide, and ethambutol followed by a 4-month continuation phase of isoniazid and rifampin. Streptomycin may be substituted for ethambutol, but must be given by injection. Ethambutol (or streptomycin) can be discontinued when drug susceptibility results show the infecting organism to be fully drug-susceptible. In areas where the rate of isoniazid resistance is documented to be less than 4% and the patient has had no previous treatment with TB drugs, is not from a country with a high prevalence of drug resistance, and has no known exposure to a patient with drug-resistant disease, three drugs (isoniazid, rifampin, and pyrazinamide) may be adequate for the initial regimen. TB treatment regimens may need to be altered for HIV-positive patients taking HIV protease inhibitors. Whenever possible, the care for HIV-related TB should be provided by or in consultation with experts in the management of both TB and HIV disease. The major determinant of the outcome of treatment is patient adherence to the drug regimen. Thus, careful attention should be paid to measures designed to foster adherence, and treating all patients with directly observed therapy (DOT) is strongly recommended. Multidrug-resistant TB (i.e., TB resistant to both isoniazid and rifampin) presents difficult treatment problems and requires expert consultation.

Objectives

After working through this chapter, you will be able to

- Describe the recommended regimen for the initial treatment of TB in HIV-negative persons;
- Describe the recommended TB treatment regimens for HIV-positive persons;
- Explain why case management and directly observed therapy are important;
- List the common adverse reactions to the drugs used to treat TB;
- Describe how patients should be evaluated for their response to treatment.

Basic Principles of Treatment

- ➤ Provide safest, most effective therapy in shortest time
- ➤ Multiple drugs to which the organisms are susceptible
- ➤ Never add single drug to failing regimen
- ➤ Ensure adherence to therapy

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TB must be treated for a long time (at least 6 months for most patients) compared with many other infectious diseases. If treatment is not continued for a sufficient length of time, some tubercle bacilli may survive and the patient may become ill and infectious again. Regimens for the treatment of TB must contain multiple drugs to which the organisms are susceptible. Treatment with a single drug can lead to the development of a bacterial population resistant to that drug. Likewise, the addition of a single drug to a failing anti-TB regimen can lead to resistance to that drug. When two or more drugs to which there is susceptibility are used simultaneously, each helps prevent the emergence of tubercle bacilli resistant to the others.

The initial phase of treatment is crucial for preventing the emergence of drug resistance and determining the ultimate outcome of the regimen. Four drugs — isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin — should be included in the initial treatment regimen until the results of drug susceptibility tests are available. Each of the drugs in the initial regimen plays an important role. Isoniazid and rifampin allow for short-course regimens with high cure rates. Pyrazinamide has potent sterilizing activity which allows further shortening of the regimen from 9 to 6 months. Ethambutol (or streptomycin) is added to prevent the emergence of drug resistance when primary isoniazid resistance is possible. In the rare circumstance where the disease-causing strain is known to be drug-sensitive or where the likelihood of drug resistance is low (i.e., less than 4% primary resistance to isoniazid in the community and the patient has had no previous treatment with TB drugs, is not from a country with a high prevalence of drug resistance, and has no known exposure to a patient with drug-resistant disease), three drugs (isoniazid, rifampin, and pyrazinamide) may be adequate for the initial regimen.

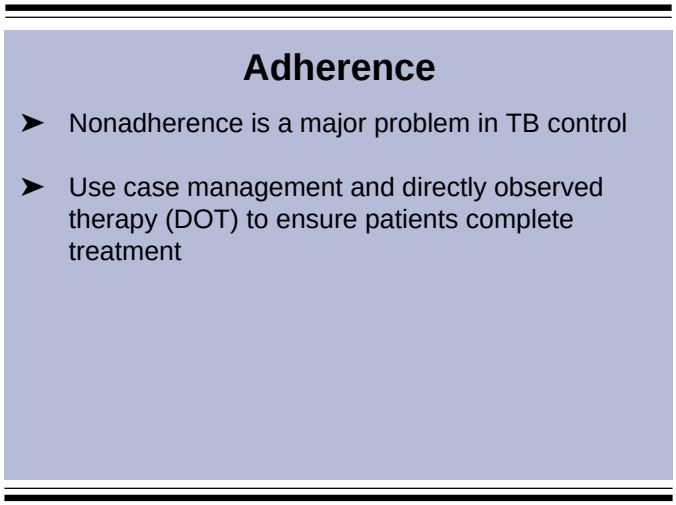
There are several options for daily and intermittent therapy, but the aim of treatment should be to provide the safest and most effective therapy in the shortest period of time. Given adequate treatment, almost all patients will become bacteriologically negative, recover, and remain well.

For each patient with newly diagnosed TB, a specific treatment and monitoring plan should be developed in collaboration with the local health department within 1 week of the presumptive diagnosis. This plan should include a description of the treatment regimen, the methods of assessing and ensuring adherence to the anti-TB regimen, and the methods of monitoring for adverse reactions.

Adherence

Nonadherence to TB treatment is a major problem in TB control. Of cases reported in the United States for 1994, 14% of patients who were started on treatment had not completed a full course by 1998.[1] Inadequate treatment can lead to relapse, continued transmission, and the development of drug resistance.

Most health departments have public health nurses or community outreach workers who can work with patients and clinicians to help patients adhere to a prescribed regimen. Whenever possible, a worker who has the same cultural and linguistic background as the patient should be assigned to help develop an individualized treatment adherence plan.



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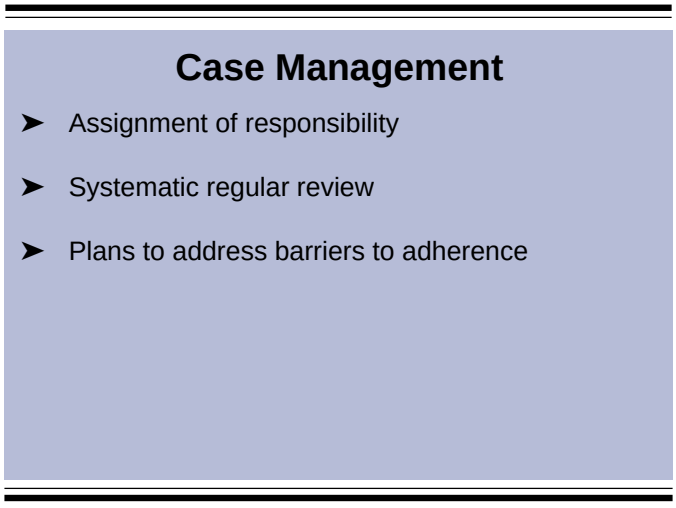
Patient Education

All patients should be educated about TB, the dosing of medications, the possible adverse reactions of the medications, and the importance of taking their medication. Health care workers must take the time to explain clearly to patients when the medication should be taken, how much, and how often, especially if the patient is not receiving directly observed therapy (DOT). Written instructions should also be provided.

Case Management

One strategy that may be used to ensure that patients complete TB treatment is case management. There are three elements of case management: assignment of responsibility, systematic regular review, and plans to address barriers to adherence. In case management, a health department employee (case manager) is assigned primary responsibility for the management of specific patients and is held accountable for ensuring that each of those patients is educated about TB and its treatment, that therapy is continuous, and that contacts are examined. Some specific responsibilities may be assigned to other persons (e.g., clinic supervisors, outreach workers, health educators, and social workers).



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Directly Observed Therapy

A component of case management that helps to ensure that patients adhere to therapy is directly observed therapy (DOT). DOT means that a health care worker or another designated person watches the patient swallow each dose of TB medication. DOT ensures an accurate account of how much medication the patient really took. DOT should be considered for all patients because clinicians are often inaccurate in predicting which patients will adhere to medication regimens on their own.[2] However, it takes good case management in concert with DOT to really make DOT programs effective.

Directly Observed Therapy (DOT)

- Health care worker watches patient swallow each dose of medication
- Consider DOT for all patients
- DOT should be used with all intermittent regimens
- DOT can lead to reductions in relapse and acquired drug resistance
- Use DOT with other measures to promote adherence

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In many areas, patients are routinely given DOT.[3] DOT has been shown to be cost-effective when intermittent regimens are used.[4,5] Furthermore, DOT can significantly reduce the frequency of the development of drug resistance and of treatment failure or relapse after the end of treatment.[6,7] Nearly all the treatment regimens for drug-susceptible TB can be given intermittently if they are directly observed; using intermittent regimens reduces the total number of doses a patient must take, as well as the total number of encounters with the health care provider or outreach worker, making these regimens more cost-effective. Multidrug-resistant TB (MDR TB) should always be treated with a daily regimen and under direct observation. There are no intermittent regimens for treatment of MDR TB.

It is important that DOT be carried out at times and in locations that are as convenient as possible for the individual patient. Therapy may be directly observed in a medical office or clinic setting, but can also be observed by an outreach worker in the field (i.e., the patient's home, place of employment, school, or other mutually agreed-upon place). In some situations, staff of correctional facilities or of drug treatment programs, home health care workers, maternal and child health staff, or designated community members may provide DOT.

Incentives and enablers should be used to enhance adherence to therapy. This may be as simple as offering a cup of coffee and talking with a patient who is waiting in the clinic or as complex as providing food and housing for a homeless patient. Establishing a relationship with the patient and addressing barriers to adherence is the core of a successful DOT program.

Health care professionals, including private practitioners, who note that a particular TB patient has demonstrated the inability or unwillingness to adhere to a prescribed treatment regimen should consult the health department. The TB control program in the health department should assist in evaluating the patient for causes of nonadherence and should provide additional services, such as the services of outreach workers, to enable the patient to complete the recommended therapy. If these efforts are unsuccessful, the health department should take appropriate action, such as seeking court-ordered DOT or, if all other measures fail, the detention of a patient who is unwilling or unable to complete treatment and who is infectious, at risk of becoming infectious, or at risk for drug-resistant TB.

Self-Administered Therapy

When therapy is self-administered, the use of fixed-dose combination capsules or tablets may enhance patient adherence and reduce the risk of inappropriate monotherapy. Therefore, it may prevent the development of acquired drug resistance. For this reason, the use of such fixed-dose combinations is strongly encouraged for adults prescribed a self-administered regimen. In the United States, the Food and Drug Administration has licensed fixed-dose combinations of isoniazid and rifampin (Rifamate) and of isoniazid, rifampin, and

pyrazinamide (Rifater). Clinicians should become familiar with the management of TB using these fixed-dose combination drugs. In addition, incentives and enablers should be used to enhance adherence to therapy.

Patients should be asked routinely about adherence at follow-up visits. Pill counts should be taken routinely, and urine tests can be used periodically to check for the presence of drug metabolites. In addition, the response to treatment (bacteriologic conversion to negative) should be monitored closely for all patients. If the patient's sputum remains positive after 2 months of treatment, the patient should be reevaluated and DOT should be considered for the remainder of treatment.

Regimens

(See tables 3 - 7, pp. 116-124)

Pulmonary TB

The duration of therapy depends on the drugs used, the drug susceptibility test results, and the patient's response to therapy. All TB drugs should be given once daily rather than in divided doses. Most patients with previously untreated pulmonary TB can be treated with either a 6-month or a 9-month regimen, although the 6-month regimen is preferred.[8] Both the 6-month and 9-month regimens are referred to as short-course regimens. All regimens of 9 months or less must contain isoniazid and rifampin; all 6-month regimens must contain isoniazid, rifampin, and, initially, pyrazinamide.

For adults with smear- or culture-positive pulmonary TB, the initial phase of a 6-month regimen should consist of a 2-month period of isoniazid, rifampin, and pyrazinamide. Ethambutol or streptomycin should also be included in the initial regimen until the results of drug susceptibility studies confirm isoniazid and rifampin susceptibility.

The initial use of a four-drug regimen is recommended to prevent the development of multidrug-resistant TB in areas where the prevalence of primary isoniazid resistance is 4% or higher. If susceptibility to isoniazid and rifampin is demonstrated, the second phase of treatment should consist of isoniazid and rifampin for an additional 4 months.

If DOT is used, medications may be dosed intermittently. Several options exist for 6-month, intermittent regimens:

- Four-drug therapy, administered daily for 8 weeks, may be followed by therapy with isoniazid and rifampin given two or three times a week for 16 weeks (if susceptibility to isoniazid and rifampin is demonstrated);[9]
- Four-drug therapy, administered daily for 2 weeks and then two times a week for 6 weeks, may be followed by therapy with isoniazid and rifampin given two times a week for 16 weeks (if susceptibility to isoniazid and rifampin is demonstrated);[9]

Treatment of TB for HIV-Negative Persons

- Include four drugs in initial regimen
  - Isoniazid (INH)
  - Rifampin (RIF)
  - Pyrazinamide (PZA)
  - Ethambutol (EMB) or streptomycin (SM)
- Adjust regimen when drug susceptibility results are known

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- Four-drug therapy may be administered three times a week throughout the 6-month treatment period. All four drugs should be continued throughout the course of treatment in this regimen.[10]

When isoniazid, pyrazinamide, and ethambutol or streptomycin are given two or three times a week instead of every day, their dosages must be increased. However, the dose of rifampin is the same whether the drug is given daily or intermittently.

Alternatively, a 9-month regimen of isoniazid and rifampin is acceptable for persons who cannot or should not take pyrazinamide (e.g., pregnant women). Again, streptomycin (except in pregnant women) or ethambutol should be included initially unless there is little possibility of drug resistance (patient has no individual risk factors for drug resistance and resides in an area where the prevalence of isoniazid-resistant TB < 4%). If susceptibility to isoniazid and rifampin is demonstrated, isoniazid and rifampin may be given twice weekly after an initial 4-8 weeks of daily treatment.[11]

For adults with smear- and culture-negative pulmonary TB (i.e., TB diagnosed only clinically), a 4-month regimen of isoniazid and rifampin combined with pyrazinamide for the first 2 months, may be used when drug resistance is unlikely.[12,13]

Treatment of TB for HIV-Positive Persons

- ➤ Management of HIV-related TB is complex
- ➤ Care for HIV-related TB should be provided by or in consultation with experts in management of both HIV and TB

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HIV-Positive Persons

(See table 4, pp. 118-119)

Management of HIV-related TB disease is complex, and the clinical and public health consequences associated with the failure of treatment are serious. Whenever possible, the care for HIV-related TB should be provided by or in consultation with experts in the management of both TB and HIV disease.

Published guidelines recommend the use of antiretroviral therapy for patients infected with HIV.[14] Widely used antiretroviral drugs available in the United States include the protease inhibitors (saquinavir, indinavir, ritonavir, and nelfinavir) and the nonnucleoside reverse transcriptase inhibitors (NNRTIs) (nevirapine, delavirdine, and efavirenz). However, these inhibitors interact with rifamycin derivatives, such as rifampin and rifabutin, which are used to treat and prevent the mycobacterial infections commonly observed in HIV-positive patients. Of the rifamycins, rifampin has the most potent interactions; rifabutin has substantially fewer interactions. Because the most recent recommendations for the use of antiretroviral therapy strongly advise against interruptions of therapy,[16] and because non–rifampin-containing alternatives for TB treatment are available, previous antituberculosis therapy options that involved stopping antiretroviral therapy to allow the use of rifampin are no longer recommended. The other class of antiretroviral agents available in the U.S., nucleoside reverse transcriptase inhibitors (NRTIs), which include zidovudine, didanosine, zalcitabine, stavudine, lamivudine, and abacavir, are not contraindicated with the use of rifamycins and do not require dose adjustments.

The use of rifampin to treat TB is not generally recommended for patients who

- Will start treatment with an antiretroviral regimen that includes a protease inhibitor or an NNRTI at the same time they begin treatment for TB, **or**
- Have established HIV infection that is being maintained on such an antiretroviral regimen when TB is newly diagnosed and needs to be treated.

Two TB treatment options are currently recommended for these patients:

1. **A rifabutin-based regimen**

   The initial phase of a **6-month** TB regimen for patients who are receiving therapy with protease inhibitors or NNRTIs consists of isoniazid, **rifabutin,** pyrazinamide, and ethambutol for the first 2 months (8 weeks). The initial phase should be followed by isoniazid and **rifabutin** to complete 6 months if sensitivity to isoniazid and rifampin has been documented. Treatment should be prolonged to 9 months or longer for patients with delayed response to therapy.

2. **An alternative nonrifamycin regimen that includes streptomycin**

   The initial phase of a **9-month** TB regimen for patients for whom the use of rifamycins is limited or contraindicated for any reason (e.g., intolerance to rifamycins, patient/clinician decision not to combine antiretroviral therapy with rifabutin), consists of a 2-month induction phase of isoniazid, ethambutol, pyrazinamide, and **streptomycin**, followed by isoniazid, pyrazinamide, and **streptomycin** administered 2-3 times per week for 7 months (30 weeks). Every effort should be made to continue the administration of **streptomycin** for the total duration of treatment. If streptomycin is not used for the recommended 9 months, **ethambutol** should be added to the continuation phase of the regimen and treatment duration should be prolonged from 9 months (38 weeks) to **12 months** (52 weeks).

Treatment of TB for HIV-Positive Persons (cont.)

RIF-based regimens generally recommended for persons

- ➤ Who have not started antiretroviral therapy
- ➤ For whom PIs or NNRTIs are not recommended

Initial treatment phase should consist of

- ➤ Isoniazid (INH)
- ➤ **Rifampin (RIF)**
- ➤ Pyrazinamide (PZA)
- ➤ Ethambutol (EMB)

RIF may be used with some PIs and NNRTIs

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Treatment of TB for HIV-Positive Persons (cont.)

- ➤ For patients receiving PIs or NNRTIs, initial treatment phase may consist of
  - ➤ Isoniazid (INH)
  - ➤ **Rifabutin (RFB)**
  - ➤ Pyrazinamide (PZA)
  - ➤ Ethambutol (EMB)
- ➤ An alternative nonrifamycin regimen includes INH, EMB, PZA, and streptomycin (SM)

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A **rifampin**-based regimen continues to be recommended for the treatment of TB in HIV-positive patients

- Who have not started antiretroviral therapy, and both the patient and the clinician agree that it would be prudent to wait before starting such therapy, **or**
- For whom antiretroviral therapy with a protease inhibitor or NNRTI is not recommended.

The following treatment option is recommended for these patients:

- The initial phase of a **6-month** regimen consists of isoniazid, **rifampin**, pyrazinamide, and ethambutol (or streptomycin) for the first 2 months (8 weeks), followed by isoniazid and **rifampin** to complete 6 months. Isoniazid, **rifampin**, pyrazinamide, and ethambutol (or streptomycin) can be administered for the entire 6-month treatment period (26 weeks). Treatment should be prolonged to **9 months** or longer for patients with delayed response to therapy.

However, new data indicate that rifampin can be used for the treatment of active TB disease for patients whose antiretroviral regimen includes

- The NNRTI efavirenz and two nucleoside reverse transcriptase inhibitors (NRTIs);
- The protease inhibitor ritonavir and one or more NRTIs; **or**
- The combination of two protease inhibitors (ritonavir and either saquinavir hard-gel capsule or saquinavir soft-gel capsule).

All patients should receive monthly clinical evaluations to monitor their response to treatment and medication side effects. During the early phase of treatment, the interval between these evaluations may be shorter (e.g., every 2 weeks).

DOT and other adherence-promoting strategies should be used for all patients with HIV-related TB. Pyridoxine (vitamin B_6) (25-50 mg daily or 50-100 mg twice weekly) should be administered to all HIV-positive patients who are undergoing TB treatment with isoniazid to reduce isoniazid-induced side effects in the central and peripheral nervous system.

Note: These recommendations are not intended to substitute for the judgment of an expert physician. As new antiretroviral agents or new data regarding existing agents result in changes in therapeutic options and preferences for antiretroviral therapy, these changes in turn may impact the recommendations for the prevention and treatment of TB for patients coinfected with HIV.

Extrapulmonary TB

➤ In most cases, treat with same regimens used for pulmonary TB

Bone and Joint TB, Miliary TB, or TB Meningitis in Children

➤ Treat for a minimum of 12 months

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Extrapulmonary TB

(See tables 3 - 7, pp. 116-124)

As a general rule, regimens that are adequate for treating pulmonary TB in adults and children are also effective for treating extrapulmonary disease. However, infants and children who have miliary TB, bone and joint TB, or TB meningitis should receive a minimum of 12 months of therapy.

The use of adjunct therapies such as surgery and corticosteroids is more commonly required for extrapulmonary TB than for pulmonary disease. Surgery may be necessary to obtain specimens for diagnosis and to treat such

processes as constrictive pericarditis and spinal cord compression from Pott's disease. Corticosteroids have been shown to be beneficial in preventing cardiac constriction from tuberculous pericarditis[15] and in decreasing the neurologic sequelae of all stages of TB meningitis,[16] especially when administered early in the course of disease.

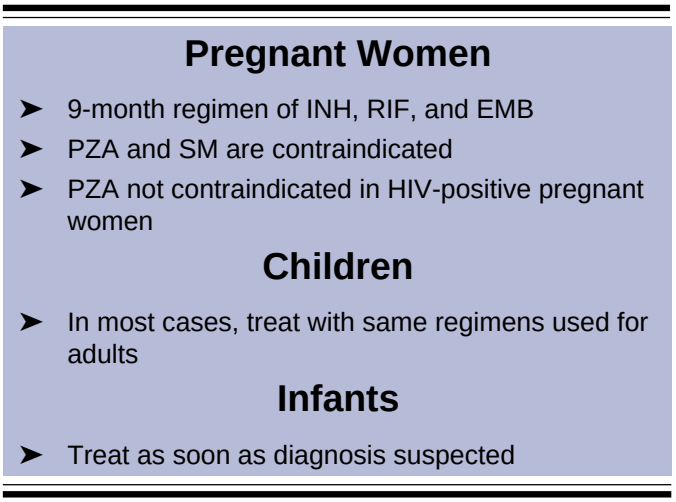
In patients with extrapulmonary TB, the type of follow-up examinations should be determined by the site of the disease. Bacteriologic evaluation may be limited by the relative inaccessibility of the site. Thus, the response to treatment must often be judged on the basis of clinical and radiologic findings.

TB Treatment for HIV-Positive Patients with Extrapulmonary TB

The basic principles that support the treatment of pulmonary TB in HIV-positive patients also apply to extrapulmonary forms of the disease. Most extrapulmonary forms of TB (including TB meningitis, tuberculous lymphadenitis, pericardial TB, pleural TB, and disseminated or miliary TB) are more common among persons with advanced-stage HIV disease than among patients with asymptomatic HIV infection. The drug regimens and treatment durations that are recommended for treating pulmonary TB in HIV-positive adults and children are also recommended for treating most patients with extrapulmonary disease. However, for certain forms of extrapulmonary disease, such as meningioma, bone TB, and joint TB, using a standard rifamycin-based regimen for at least 9 months is generally recommended.

Pregnant or Lactating Women

Pregnant women with TB must be given adequate therapy as soon as TB is suspected. The preferred initial treatment regimen is isoniazid, rifampin, and ethambutol (ethambutol may be excluded if primary isoniazid resistance is unlikely). Streptomycin should not be used because it has been shown to have harmful effects on the fetus. In addition, pyrazinamide should not be used routinely because its effect on the fetus is unknown. Because the 6-month treatment regimen cannot be used, a minimum of 9 months of therapy should be given. To prevent peripheral neuropathy, it is advisable to give pyridoxine (vitamin B_6) to pregnant women who are taking isoniazid.



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The small concentrations of TB drugs in breast milk do not have a toxic effect on nursing newborns, and breast-feeding should not be discouraged for women undergoing anti-TB therapy. Similarly, drugs in breast milk should not be considered effective treatment for disease or infection in a nursing infant.

TB Treatment for HIV-Positive Pregnant Women

HIV-positive pregnant women who have a positive *M. tuberculosis* culture or who are suspected of having TB disease should be treated without delay. Choices of TB treatment regimens for HIV-positive pregnant women are those that include a rifamycin. Although the routine use of pyrazinamide during pregnancy is not recommended in the United States

because of inadequate teratogenicity data, the benefits of a TB treatment regimen that includes pyrazinamide for HIV-positive pregnant women outweigh the potential pyrazinamide-related risks to the fetus. Aminoglycosides (e.g, streptomycin, kanamycin, amikacin), capreomycin, and fluroquinolones are contraindicated for all pregnant women because of adverse effects on the fetus.

Children and Adolescents

(See tables 3 - 7, pp. 116-124)

Infants and children with TB should be treated with one of the regimens mentioned in the section *Pulmonary TB*, pp. 69-72. In infants, TB is much more likely to disseminate; therefore, prompt and vigorous treatment should be started as soon as the diagnosis is suspected. The specific intermittent regimens have not been studied in children. Ethambutol is generally not used for young children whose visual acuity cannot be monitored. If ethambutol must be used to treat a young child (e.g., because of drug-resistant TB), the minimum dose of this drug should be used.[17]

Sputum specimens collected from children are often inadequate. In these situations, it may be necessary to rely on the results of cultures and susceptibility tests of specimens from the adult source case to confirm the diagnosis in the child and to guide the choice of drugs. When drug-resistant TB is suspected or isolates from a source case are not available, it may be necessary to perform gastric aspiration or bronchoalveolar lavage, or obtain tissue samples for diagnosis.

For children, bacteriologic examinations are also less useful for evaluating the response to treatment than for adults; thus, clinical and radiographic examinations are more important for children. Furthermore, the chest radiographs of children with hilar adenopathy may not become normal for 2 to 3 years after treatment. It is not necessary for the chest radiograph to be normal before discontinuing TB drugs once a full course of therapy is completed.

In general, extrapulmonary TB in children can be treated with the same regimens as pulmonary TB. The exceptions are bone and joint disease, disseminated (miliary) disease, and meningitis, for which a minimum for 12 months of therapy is recommended.

TB Treatment for HIV-Positive Children

In HIV-positive children, even in those who are too young to be evaluated for visual acuity and red-green perception, ethambutol at a dosage of 15 mg/kg body weight should generally be included as part of the initial regimen, unless the infecting source patient is known to have TB susceptible to isoniazid and rifampin. If drug susceptibility results are not available, a four-drug rifamycin-based regimen (e.g., isoniazid, rifamycin, pyrazinamide, and ethambutol) for 2 months, followed by isoniazid and a rifamycin for 4 months, is recommended.

Drug-Resistant TB

(See table 3, pp. 116-117)

A 6-month regimen of isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin has been demonstrated to be effective for the treatment of TB resistant only to isoniazid.[18] When resistance to isoniazid is documented during the recommended initial four-drug therapy, the regimen should be adjusted by discontinuing isoniazid and continuing the other three drugs for the entire 6 months of therapy. TB resistant only to isoniazid may also be treated with rifampin and ethambutol for 12 months.[19]

Treatment Regimens for TB Resistant Only to INH

HIV-Negative Persons

- ➤ Carefully supervise and manage treatment to avoid development of MDR TB
- ➤ Discontinue INH and continue RIF, PZA, and EMB or SM for the entire 6 months
- ➤ Or, treat with RIF and EMB for 12 months

HIV-Positive Persons

- ➤ Regimen should consist of a rifamycin, PZA, and EMB

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When isoniazid resistance is documented in the 9-month regimen without pyrazinamide, isoniazid should be discontinued. If ethambutol was included in the initial regimen, treatment with rifampin and ethambutol should be continued for a minimum of 12 months. If ethambutol was not included initially, susceptibility tests should be repeated, isoniazid should be discontinued, and two other drugs, to which the isolate is susceptible (e.g., ethambutol and streptomycin), should be added. The regimen can be adjusted when the results of the susceptibility tests become available.

Multidrug-resistant TB (i.e., TB resistant to at least isoniazid and rifampin) presents difficult treatment problems. Treatment must be individualized and based on the patient's medication history and susceptibility studies.

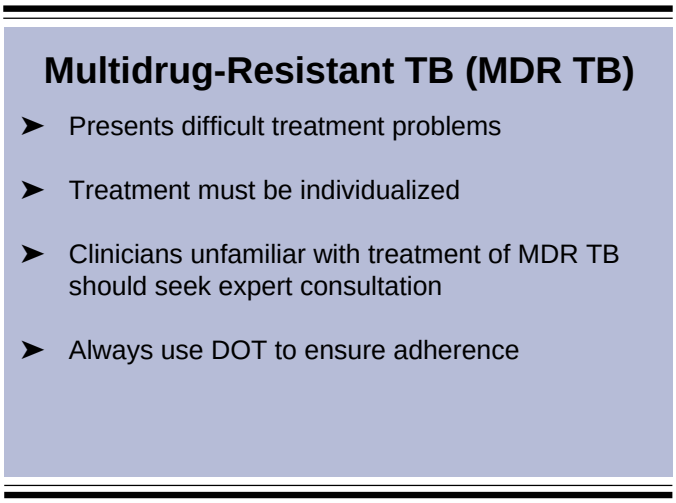
Unfortunately, adequate data are not available on the effectiveness of various regimens and the necessary duration of treatment for patients with organisms resistant to both isoniazid and rifampin. Moreover, many of these patients also have resistance to other first-line drugs (e.g., ethambutol and streptomycin) when drug resistance is discovered. Because of the poor outcome in such cases, it is preferable to give at least three new drugs to which the organism is susceptible. This regimen should be continued until culture conversion is documented, followed by at least 12 months of two-drug therapy. Often, a total of 24 months of therapy is given empirically. Some experts recommend that at least 18-24 months of three-drug therapy be given after culture conversion.[20] MDR TB should be treated using a daily regimen under direct observation (DOT). Intermittent administration of medications is not possible in treatment of MDR TB.

Clinicians who are unfamiliar with the treatment of drug-resistant TB should seek expert consultation. Because second-line drugs can cause serious adverse reactions, patients taking these drugs should be monitored closely throughout the course of treatment. The role of agents such as the quinolone derivatives and amikacin in the treatment of multidrug-resistant disease is not well characterized, although these drugs are commonly being used in such cases. Surgery may offer considerable benefit and a significantly improved cure rate for patients who have multidrug-resistant TB if the bulk of disease can be resected.[21] However, drug therapy is usually required to sterilize the remaining disease.

TB Treatment for HIV-Positive Patients with Drug-Resistant TB

TB disease resistant to isoniazid only. The treatment regimen should generally consist of a rifamycin (rifampin or rifabutin), pyrazinamide, and ethambutol for the duration of treatment. Because the development of acquired rifamycin resistance would result in MDR TB, clinicians should carefully supervise and manage TB treatment for these patients.

TB disease resistant to rifampin only. The 9-month treatment regimen should generally consist of an initial 2-month phase of isoniazid, streptomycin, pyrazinamide, and ethambutol. The second phase of treatment should consist of isoniazid, streptomycin, and pyrazinamide administered for 7 months. Because the development of acquired isoniazid resistance would result in MDR TB, clinicians should carefully supervise and manage TB treatment for these patients.



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Multidrug-resistant TB (resistant to both isoniazid and rifampin). These patients should be managed by or in consultation with physicians experienced in the management of MDR TB. Most drug regimens currently used to treat MDR TB include an aminoglycoside (e.g., streptomycin, kanamycin, amikacin) or capreomycin, and a fluoroquinolone, along with other agents to which the organism is sensitive. The recommended duration of treatment for MDR TB in HIV-positive patients is 24 months after culture conversion, and posttreatment follow-up visits to monitor for TB relapse should be conducted every 4 months for 24 months. Because of the serious personal and public health concerns associated with MDR TB, health departments should always use DOT for these patients and take whatever steps are needed to ensure their adherence to the treatment regimen.

Persons with Additional Medical Problems

A number of medical conditions may alter immune responsiveness and predispose a person to TB. Such disorders include HIV infection, immunosuppressive therapy, hematologic or reticuloendothelial malignancies, chronic renal failure, diabetes, and malnutrition. These conditions may influence the outcome of therapy. Therapeutic decisions for the impaired host must be individualized.

Patients with partial impairment of renal function should avoid streptomycin, kanamycin, and capreomycin if possible. If renal function is severely impaired, reduced doses or increased dosing intervals of other TB drugs may be necessary (see table 7, pp. 124). Measurement of drug serum levels may be helpful in adjusting the dosage.

For patients who abuse alcohol or who have neuropsychiatric disorders, close supervision — preferably using DOT — is necessary to ensure adherence and to monitor for adverse reactions to medications.

Monitoring

Adverse reactions to TB drugs are relatively rare, but in some patients they may be severe. Clinicians who treat TB should be familiar with the methods of monitoring for adverse reactions and response to treatment. In some situations (e.g., drug-resistant TB, pregnancy, HIV-positive patients), expert consultation may be required.

Monitoring for Adverse Reactions

- Baseline measurements
- Monitor patients at least monthly
- Monitoring for adverse reactions must be individualized
- Instruct patients to immediately report adverse reactions

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Adverse Reactions to First-Line TB Drugs

(See tables 5 [pp. 120-121] and 6 [pp. 122-123])

Adults treated for TB should have baseline measurements of hepatic enzymes, bilirubin, and serum creatinine or blood urea nitrogen, as well as a complete blood and platelet count (or estimate). Serum uric acid should be measured if pyrazinamide is used, and a baseline examination of visual acuity should be obtained for patients for whom ethambutol is prescribed. Audiometry should be performed at the beginning of therapy for patients for whom streptomycin is prescribed. The purpose of these baseline tests is to detect any abnormality that would complicate therapy or require a modified regimen. For children, only baseline vision tests are necessary unless a child has other medical conditions that may complicate therapy.

Monitoring for adverse reactions to TB medications must be individualized. The type and frequency of monitoring should depend on the drugs used in a given regimen and the patient's risk for adverse reactions (e.g., age, alcohol use). At minimum, patients should be seen monthly during therapy and questioned by medical personnel concerning adverse reactions, even if no problems are apparent. Patients should be specifically instructed to look for symptoms associated with the most common reactions to the medications they are taking. They should also be instructed to seek medical attention immediately should these symptoms occur. If the symptoms suggest adverse reactions, appropriate laboratory testing should be performed.

All patients receiving isoniazid, rifampin, or pyrazinamide should be instructed to stop taking the medications and to immediately report any hepatitis-suggesting symptoms (nausea, loss of appetite, vomiting, persistently dark urine, yellowish skin, malaise, unexplained elevated temperature for more than 3 days, or abdominal tenderness).

Isoniazid. Peripheral neuropathy is associated with the use of isoniazid but is uncommon at doses of 5 mg/kg. Persons with conditions in which neuropathy is common (e.g., diabetes, uremia, alcoholism, malnutrition, HIV infection), as well as pregnant women and persons with a seizure disorder, may be given pyridoxine (10–50 mg/day) with isoniazid. As little as 6 mg/day of pyridoxine has been shown to prevent isoniazid-associated neuropathy.[22,23] The interaction of isoniazid and phenytoin increases the serum concentration of both drugs.

When these drugs are given concomitantly, the serum level of phenytoin should be monitored. (See *Treatment of Latent TB Infection*, p. 53).

Rifampin. Rifampin may accelerate the clearance of drugs metabolized by the liver. These include methadone, coumarin derivatives, glucocorticoids, estrogens, oral hypoglycemic agents, digitalis, anticonvulsants, ketoconazole, fluconazole, cyclosporine, and protease inhibitors. For patients who are in a drug-treatment program, it may be necessary to increase the methadone dose by as much as 50%.[24] Rifampin may also reduce the efficacy of oral contraceptives and contraceptive implants (e.g., Norplant) by accelerating estrogen metabolism. Women using hormonal contraception and taking rifampin should supplement the contraception or use an alternative birth control method (i.e., barrier methods). Patients receiving rifampin should be monitored for possible manifestations of thrombocytopenia (bleeding tendency, easy bruising, blood in urine) or flu-like symptoms. Protease inhibitors and NNRTIs interact with rifamycin derivatives, such as rifampin and rifabutin. Of the rifamycins, rifampin has the most potent interactions; rifabutin has substantially fewer interactions.

Pyrazinamide. Hyperuricemia may occur in patients receiving pyrazinamide, but acute gout is uncommon. Asymptomatic hyperuricemia is not an indication for discontinuing the drug.

Streptomycin. Ototoxicity and neprotoxicity may occur in patients receiving streptomycin. Audiometry should be performed at periodic intervals during streptomycin therapy. If vertigo, dizziness, or ataxia occur in patients taking streptomycin, the drug should be discontinued immediately.

Ethambutol. Optic neuritis is the most frequent and serious adverse effect of ethambutol. Baseline and monthly tests of visual acuity and color vision should be conducted.

Current literature and package inserts should be consulted for other possible drug reactions.

Monitoring Response to Treatment

- Monitor patients bacteriologically monthly until cultures convert to negative
- After 3 months of therapy, if cultures are positive or symptoms do not resolve, reevaluate for
  - Potential drug-resistant disease
  - Nonadherence to drug regimen
- If cultures do not convert to negative despite 3 months of therapy, consider initiating DOT

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Response to Treatment

For patients whose sputum cultures are positive before treatment, the best way to measure the effectiveness of therapy is to obtain specimens for culture at least monthly until the cultures convert to negative. Patients whose sputum no longer contains *M. tuberculosis* after 2 months of treatment should have at least one further sputum smear and culture performed at the completion of therapy. Patients with multidrug-resistant TB should have cultures performed monthly for the entire course of treatment. Radiographic evaluations during treatment are of less importance than sputum evaluation. However, a chest film at completion of treatment provides a baseline for comparison with any future films.

Patients whose cultures have not become negative or whose symptoms do not resolve despite 3 months of therapy should be reevaluated for potential drug-resistant disease, as well as for potential failure to adhere to the regimen. If the patient is receiving self-administered therapy, the remainder of treatment should be directly observed. While the results of drug susceptibility testing are pending, the original drug regimen may be continued or may be augmented by at least two drugs not given previously. **Never add one drug at a time to a failing regimen**; this may cause further drug resistance. If drug susceptibility results show resistance to any of the first-line drugs or if the patient remains symptomatic or smear or culture positive after 3 months, a TB medical expert should be consulted.

In patients with negative sputum cultures before treatment, the major indicators of response to therapy are the chest radiograph and the clinical evaluation. The intervals at which chest radiography should be repeated depend on the clinical circumstances and the differential diagnosis that is being considered, but usually no more than every 3 months. If the radiograph does not improve after the patient has received 3 months of treatment, the abnormality may be the result of either previous (not current) TB or another process.

Routine follow-up after therapy is not necessary for patients who have had a satisfactory and prompt bacteriologic response to 6- or 9-month therapy with both isoniazid and rifampin. Patients whose organisms were fully susceptible to the drugs being used should be instructed to promptly report the development of any symptoms, particularly prolonged cough, fever, or weight loss. For patients with organisms resistant to isoniazid or rifampin or both, follow-up evaluation must be individualized.

Study Questions

Answers to these questions can be found in the text.

1. Why should at least two drugs be used to treat TB disease?

2. What factors can lead to drug resistance?

3. Which four drugs are recommended for the initial treatment of TB for HIV-negative persons?

4. Describe the treatment options for HIV-positive persons who are on an antiretroviral regimen.

5. Describe the treatment options for HIV-positive persons who are not on an antiretroviral regimen.

6. What is case management?

7. What is directly observed therapy (DOT)? Why should it be used?

8. How often should patients be monitored for adverse reactions to TB medications?

9. How can clinicians determine whether a patient is responding to therapy?

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Chapter Eight

Infection Control in Health Care Settings

Summary. The infectiousness of TB patients is directly related to the number of tubercle bacilli that they expel into the air. Infectiousness usually declines very rapidly after adequate therapy is started. The main goal of an infection control program is to detect TB disease early and to isolate and promptly treat persons who have TB. An infection control program should involve three types of controls — administrative controls, engineering controls, and personal respiratory protection — and should be based on a risk assessment of the setting (inpatient and outpatient). Administrative controls (e.g., the prompt detection of suspected cases, isolation of infectious patients, and appropriate treatment) comprise the primary strategy for infection control. Administrative controls also include training and education and TB screening for health care workers (HCWs). In addition, three types of engineering controls may be used to prevent the transmission of TB: ventilation, high-efficiency particulate air (HEPA) filtration, and ultraviolet germicidal irradiation (UVGI).

In places where administrative and engineering controls may not fully protect health care workers from infectious droplet nuclei, HCWs should use personal respirators. Precautions to prevent airborne transmission are particularly important in TB isolation rooms and during and immediately after procedures that stimulate coughing (e.g., sputum collection, bronchoscopy, and aerosolized pentamidine treatments).

Coordination with the health department is necessary in order to report all confirmed or suspected TB patients, conduct contact investigations, and plan for follow-up care for patients known to have or suspected of having TB.

Objectives

After working through this chapter, you will be able to

- Explain when a TB patient can be considered noninfectious;
- List the three types of controls in an effective infection control program;
- Explain the purpose and the characteristics of a TB isolation room;
- Describe the circumstances when personal respirators should be used.

Infectiousness

Patients should be considered infectious if they

- ➤ Are coughing
- ➤ Are undergoing cough-inducing or aerosol-generating procedures, **or**
- ➤ Have sputum smears positive for acid-fast bacilli and they
- ➤ Are not receiving therapy
- ➤ Have just started therapy, **or**
- ➤ Have poor clinical response to therapy

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Infectiousness (cont.)

Patients no longer considered infectious if they meet **all** of these criteria:

- ➤ Are on adequate therapy
- ➤ Have had a significant clinical response to therapy, **and**
- ➤ Have had 3 consecutive negative sputum smear results

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Infectiousness is directly related to the number of tubercle bacilli expelled into the air. In general, persons who have or who are suspected of having pulmonary or laryngeal TB should be considered infectious if they are

1. Coughing, are undergoing cough-inducing or aerosol-generating procedures, or have sputum smears containing acid-fast bacilli; **and**
2. Not receiving therapy, have just started therapy, or have a poor clinical or bacteriologic response to therapy.

Patients who have drug-susceptible TB are no longer considered infectious if they meet **all** the following criteria:

- They are on adequate therapy;
- They have had a significant clinical response to therapy;
- They have had three consecutive negative sputum smear results from sputum collected on different days.

Persons with extrapulmonary TB are usually not infectious. However, TB has been transmitted from a draining skin or tissue abscess containing *M. tuberculosis*.[1]

Patients with TB disease should be closely monitored for response to therapy. Smear examinations should be done regularly (e.g., initially every 1 or 2 weeks). Persistent infectiousness is usually due to the patient's failure to take medications as prescribed or to drug resistance. These possibilities should be considered for any patient who does not clinically respond to therapy within 2 to 3 weeks.

In patients with drug-resistant TB, infectiousness may last several weeks or even months. In these patients, the response to treatment should be closely monitored, and for those in institutional settings, TB isolation should be maintained until infectiousness is ruled out. Continued isolation throughout hospitalization should be considered for patients with multidrug-resistant TB because these patients are more likely to experience treatment failure or relapse, which may prolong infectiousness.

Developing an Infection Control Program

An effective TB infection control program requires the early detection, isolation, and treatment of persons with infectious TB. TB infection control measures should be based on a careful assessment of risk for transmission of TB in the facility or setting. The primary emphasis of the infection control plan should be on achieving these three goals through a hierarchy of control measures, including

- The use of ***administrative controls*** to reduce the risk of exposure to persons with infectious TB;
- The use of ***engineering controls*** to prevent the spread and reduce the concentration of infectious droplet nuclei in the air;
- The use of ***personal respiratory protection*** in areas where there is an increased risk of exposure to *M. tuberculosis*, such as in TB isolation rooms.

Infection Control Measures

- **Administrative controls** to reduce risk of exposure
- **Engineering controls** to prevent spread and reduce concentration of droplet nuclei
- **Personal respiratory protection** in areas where increased risk of exposure

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Administrative Controls

The first level of the hierarchy, the use of administrative controls, is the primary strategy for infection control. Administrative controls are measures intended primarily to reduce the risk of exposing uninfected persons to persons who have infectious TB. These measures include

- Developing and implementing effective written policies and protocols to ensure the rapid identification, isolation, diagnostic evaluation, and treatment of persons likely to have TB;
- Implementing effective work practices among health care workers (HCWs);
- Educating, training, and counseling HCWs about TB;
- Screening HCWs for TB infection and disease.

Administrative Controls

Reduce risk of exposing uninfected persons to infectious disease:

- Develop and implement written policies and protocols to ensure
  - Rapid identification
  - Isolation
  - Diagnostic evaluation
  - Treatment
- Implement effective work practices among HCWs
- Educate, train, and counsel HCWs about TB
- Test HCWs for TB infection and disease

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All health care facilities or settings must have guidelines for the prompt detection of suspected TB cases. These guidelines should include assigning supervisory responsibility for TB control.

In general, clinicians should suspect TB in any patient who has a persistent cough (i.e., a cough lasting for ≥ 3 weeks), bloody sputum, night sweats, fever, weight loss, or loss of appetite. The index of suspicion should be very high in areas or among groups of patients in which the prevalence of TB is high. In ambulatory and inpatient settings, designated personnel should develop a protocol for the early detection of persons with infectious TB, basing it on the prevalence and characteristics of TB in the population served.

Risk Assessment

TB infection-control measures should be based on the assessment of the risk for transmission of TB in that particular setting. Classification of risk for a facility, for a specific area, and for a specific occupational group should be based on

- The profile of TB in the community;
- The number of infectious TB patients admitted to the area or ward, or the estimated number of infectious TB patients to whom HCWs in an occupational group may be exposed; and
- The results of analysis of HCW skin test conversions (where applicable) and possible person-to-person transmission of *M. tuberculosis*.

Administrative Controls (cont.)

Perform risk assessment and classification of facility based on

- ➤ Profile of TB in community
- ➤ Number of infectious TB patients admitted
- ➤ Analysis of HCW skin test conversions

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All TB infection-control programs should include periodic reassessments of risk. The frequency of repeat risk assessments should be based on the results of the most recent risk assessment.

Regardless of risk level, the management of patients with known or suspected infectious TB should not vary. However, the index of suspicion for infectious TB among patients, the frequency of HCW skin testing programs, the number of TB isolation rooms, and other factors will depend on whether the risk for transmission of *M. tuberculosis* in the facility, area, or occupational group is high, intermediate, low, very low, or minimal.

Inpatient Settings. The risk assessment should be conducted for the entire facility and for specific areas within the facility (e.g., medical, TB, pulmonary, or HIV wards; HIV, infectious disease, or pulmonary clinics; and emergency departments or other areas where TB patients might receive care or where cough-inducing procedures are performed). In addition, risk assessments should be conducted for groups of HCWs who work throughout the facility rather than in a specific area (e.g., respiratory therapists; bronchoscopists; environmental services, dietary, and maintenance personnel; and students, interns, residents, and fellows).

Outpatient Settings. In outpatient settings, such as medical offices, a risk assessment should be conducted periodically and TB control policies should be developed.

Managing Suspected and Confirmed Cases of TB

Inpatient Settings. In hospitals and other inpatient settings, such as hospices and emergency rooms, patients known to have TB or suspected of having TB should be placed in a TB isolation room right away. All TB isolation rooms must have negative pressure relative to other parts of the facility (air flow from the corridors into the isolation room) and must be checked daily while in use to ensure proper air flow.

Patients who are placed in isolation rooms should be educated about the transmission of TB, the reasons for isolation, and the importance of staying in their rooms. Every effort should be made to help the patient follow the isolation policy — including the use of incentives, such as providing telephones or televisions or allowing special dietary requests. As few persons as possible should enter the TB isolation room, and anyone entering the room should wear respiratory protection (see *Personal Respiratory Protection*, p. 93).

If patients who may have infectious TB must be transported outside their isolation rooms for medically essential procedures that cannot be performed in the isolation rooms, they should wear surgical masks that cover the mouth and nose during transport. Persons transporting the patients do not need to wear respiratory protection outside TB isolation rooms. Procedures for these patients should be scheduled at times when they can be performed rapidly and when waiting areas are less crowded.

Because TB is transmitted through the air rather than by fomites or direct contact, the sterilization of personal items or eating utensils and the cleaning of walls are unnecessary.

Outpatient Settings. In an outpatient setting (e.g, medical offices, clinics), patients who have signs or symptoms of TB should be moved to an area away from other patients (preferably into a TB isolation room) and promptly given a diagnostic evaluation. These patients should be given a surgical mask and instructed to keep it on. They should also be given tissues and asked to cover the nose and mouth when coughing or sneezing to contain droplet nuclei before they are expelled into the air.

When EMS personnel must transport patients who are suspected or confirmed cases of TB, a surgical mask should be placed over the patient's nose and mouth.

After a thorough and timely diagnostic evaluation (see *Diagnosis of TB*, p. 39), patients in whom TB has been confirmed or is suspected should start appropriate therapy at once. TB should be considered in HIV-positive patients with undiagnosed pulmonary disease. If TB is suspected, appropriate precautions to prevent airborne transmission should be taken unless infectious TB is ruled out.

TB Skin Testing and Prevention Program for Health Care Workers

The risk assessment should identify which HCWs have the potential for exposure to TB and the frequency with which the exposure may occur. This information can then be used to determine which HCWs to include in the skin-testing program and the frequency with which they should be tested. Health care workers, including home health nurses and emergency medical technicians, should be included in a TB testing and prevention program if the risk assessment indicates that they are at risk for exposure. This means tuberculin skin testing for HCWS upon employment and at repeated intervals determined by their risk of exposure thereafter. Any worker who develops symptoms of TB disease or whose tuberculin skin test result converts to positive should be evaluated promptly. In addition, all health care workers should be educated about the basic concepts of TB transmission and pathogenesis, including information concerning the difference between latent TB infection and active TB disease, infection control practices, the signs and symptoms of TB, and the importance of participating in the employee skin testing program.

Discharge Planning

Health care facilities should work closely with the health department to report all confirmed or suspected cases of TB, to ensure that contact investigations are carried out for all cases, and to develop an appropriate discharge plan, including arrangements for DOT and follow-up care, for TB patients or persons suspected of having TB. Patients who are suspected of having infectious TB may be discharged to their home after starting TB therapy, even though they may still be infectious. It is important to note that after treatment has started, persons who have TB are less likely to transmit the disease to members of their household. However, before the patient is discharged to home, clinicians and discharge planners should consider whether any household members were previously exposed or are at very high risk for TB disease if infected (e.g., HIV-positive or otherwise severely immunocompromised persons or children ≤4 years of age). If the household does include such persons, arrangements should be made to prevent them from being exposed to the TB patient until a determination has been made that the patient is noninfectious.

Engineering Controls

To prevent spread and reduce concentration of infectious droplet nuclei

- Use ventilation systems in TB isolation rooms
- Use HEPA filtration and ultraviolet irradiation with other infection control measures

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Engineering Controls

The second level of the hierarchy is the use of engineering controls to prevent the spread and reduce the concentration of infectious droplet nuclei. Engineering controls are based primarily on the use of adequate ventilation systems; these may be supplemented with high-efficiency particulate air (HEPA) filtration and ultraviolet germicidal irradiation (UVGI) in high-risk areas. These strategies are designed to reduce the concentration of infectious droplet nuclei in the air, prevent the dissemination of droplet nuclei throughout the facility, or render droplet nuclei noninfectious by killing the tubercle bacilli they contain.

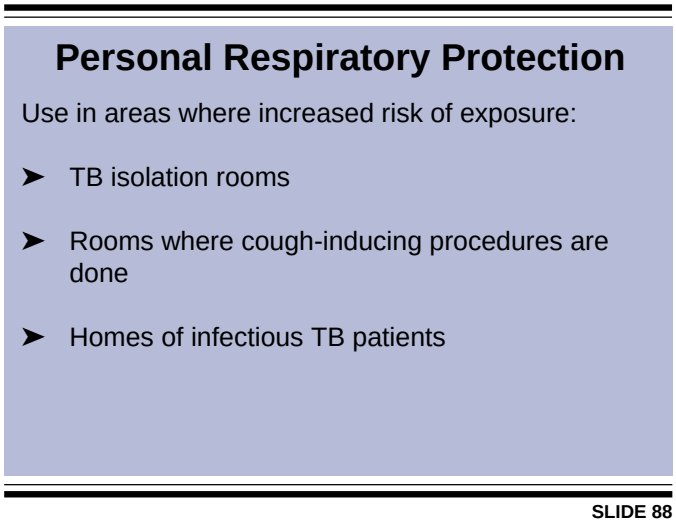
Inpatient Settings. In isolation rooms, ventilation systems are necessary to maintain negative pressure and to exhaust the air properly. Isolation rooms should be monitored daily when in use to ensure the negative pressure is maintained. Isolation room doors should be kept closed, except when patients or personnel must enter or exit the room, in order to maintain negative pressure. Ventilation systems can also be designed to minimize the spread of TB in other areas of the health care facility.

HEPA filters can be used in ventilation systems to remove droplet nuclei from the air. These filters can be installed in ventilation ducts to filter air for recirculation into the same room or recirculation to other areas of a facility. The effectiveness of portable HEPA filtration units has not been adequately evaluated. All HEPA filters must be carefully installed and meticulously maintained to ensure adequate function.

UVGI, or ultraviolet lighting, may kill *M. tuberculosis* contained in droplet nuclei. Because exposure to ultraviolet light can be harmful to the skin and eyes, the lamps must be installed in the upper part of rooms or corridors or placed in exhaust vents.

Outpatients settings. In outpatient settings, such as medical offices, that provide care to populations at high risk for TB, the use of engineering controls may be appropriate.

Personal Respiratory Protection



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The third level of the hierarchy is the use of personal respiratory protection. In some settings — for example, TB isolation rooms and rooms where cough-inducing procedures are done — administrative and engineering controls may not fully protect health care workers from infectious droplet nuclei. Health care workers should use personal (particulate) respirators in these settings. The Occupational Safety and Health Administration (OSHA) requires the use of certified respirators when respiratory protection is needed. Only particulate respirators that have been certified by the National Institute for Occupational Safety and Health (NOSH) should be worn for TB protection. A respiratory protection program that teaches health care workers how and when to use personal respirators should be included in all infection control programs.

Some people confuse surgical masks and personal (particulate) respirators. Surgical masks are designed to prevent the respiratory secretions of the person wearing the mask from entering the air. Particulate respirators are designed to filter the air before it is inhaled by the person wearing the respirator. Patients suspected of having or known to have TB should never wear a respirator that has an exhalation valve, because this type of respirator does not prevent expulsion of droplet nuclei into the air.

Inpatient Settings. Precautions to prevent the airborne transmission of tubercle bacilli are particularly important during and immediately after procedures that stimulate coughing (e.g., sputum collection, sputum induction, bronchoscopy, and aerosolized pentamidine treatments) by persons at risk for TB. Persons who carry out these procedures should wear personal respirators, and the procedures should be done in rooms or booths with negative air pressure in relation to adjacent rooms or hallways. The air from these rooms should be exhausted directly to the outside and away from intake sources.

Outpatient Settings. HCWs who work in outpatient settings, such as medical and dental offices, should use personal respiratory protection when working with patients who have, or who are strongly suspected of having, infectious TB. This includes using personal respirators when visiting the home of an infectious TB patient.

EMS personnel should wear respiratory protection when transporting patients suspected or confirmed to have TB. If feasible, the windows of the vehicle should be kept open. The heating and air-conditioning system should be set on a nonrecirculating cycle.

Study Questions

Answers to these questions can be found in the text.

1. When can a TB patient be considered noninfectious?

2. What is the main goal of an infection control program?

3. What are the three types of controls in an effective infection control program?

4. What are the important characteristics of a TB isolation room?

5. What are the three types of engineering controls?

6. When should personal respirators be used?

Endnotes

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Chapter Nine

BCG Vaccination

Summary. BCG vaccination is not generally recommended in the United States because of the low risk of infection with *M. tuberculosis*, the variable effectiveness of the BCG vaccine against pulmonary TB, and the vaccine's interference with the ability to determine tuberculin reactivity. In the United States, the use of BCG vaccination as a TB prevention strategy is reserved for selected persons who meet specific criteria. BCG vaccination should be considered for infants and children who reside in settings in which the likelihood of *M. tuberculosis* transmission and subsequent infection is high, provided no other measures can be implemented (e.g., removing the child from the source of infection). In addition, BCG vaccination may be considered for health care workers who are employed in settings in which the likelihood of transmission and subsequent infection with *M. tuberculosis* strains resistant to isoniazid and rifampin is high, provided comprehensive TB infection-control precautions have been implemented in the workplace and have not been successful. BCG vaccination is not recommended for children and adults who are infected with HIV because of the potential adverse reactions associated with the use of the vaccine in these persons. A diagnosis of *M. tuberculosis* infection and the use of treatment for infection should be considered for any BCG-vaccinated person who has a positive tuberculin skin test, especially if there is a likelihood of prior exposure to *M. tuberculosis.*

Objectives

After working through this chapter, you will be able to

- Explain how reactions to the tuberculin skin test are interpreted for BCG-vaccinated persons;
- Explain when BCG vaccination should be considered for an infant or child;
- Explain when BCG vaccination should be considered for health care workers.

Recommendations for the Use of BCG Vaccine

The use of BCG vaccination as a TB prevention strategy in the United States is limited because its effectiveness in preventing infectious forms of TB is uncertain. In 1993 and 1994, two meta-analyses of the published results of BCG vaccine clinical trials and case-control studies confirmed that the protective efficacy of BCG for preventing serious forms of TB in children is high (i.e., >80%).[1, 2] These analyses, however, did not clarify the protective efficacy of BCG for preventing pulmonary TB in adolescents and adults; this protective

efficacy is variable, from 0% to 80%.[3] Furthermore, BCG immunization may cause a positive reaction to the tuberculin skin test. Thus, it may complicate decisions about prescribing treatment for infection for BCG-vaccinated persons who have a positive skin-test result.

Recommendations for BCG Vaccination

- Not recommended in immunization programs or TB control programs in the U.S.
- BCG vaccination undertaken after consultation with health department

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Recommendations for BCG Vaccination (cont.)

Considered for an infant or child with negative skin-test result who

- Is continually exposed to untreated or ineffectively treated patient
- Will be continually exposed to multidrug-resistant TB

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CDC guidelines do not recommend including BCG vaccination in immunization programs or TB control programs. BCG vaccine should be considered only for selected persons who meet specific criteria. These criteria are seldom met and therefore the use of the BCG vaccination should be undertaken only after consultation with local health authorities and experts in the management of TB. First, BCG vaccine should be considered for an infant or child who has a negative tuberculin skin-test result if the following circumstances are present:

- The child is exposed continually to an untreated or ineffectively treated patient who has infectious pulmonary TB, and the child cannot be separated from the presence of the infectious patient or given long-term primary treatment for infection;

  or

- The child is exposed continually to a patient who has infectious pulmonary TB caused by *M. tuberculosis* strains resistant to isoniazid and rifampin, and the child cannot be separated from the presence of the infectious patient.

Second, BCG vaccination of health care workers should be considered on an individual basis in settings in which

- A high percentage of TB patients are infected with *M. tuberculosis* strains resistant to both isoniazid and rifampin;
- Transmission of such drug-resistant *M. tuberculosis* strains to health care workers and subsequent infection are likely; and
- Comprehensive TB infection-control precautions have been implemented and have not been successful.

Vaccination with BCG should not be required for employment or for assignment of health care workers in specific work areas. Health care workers considered for BCG vaccination should be counseled regarding the risks and benefits associated with both BCG vaccination and TB preventive therapy.

BCG is contraindicated in persons who have an impaired immune response (e.g., persons who have HIV infection, congenital immunodeficiency, leukemia, lymphoma, or generalized malignancy) or who are immunosuppressed because of high-dose steroid therapy, alkylating agents, antimetabolites, or radiation therapy. HIV infection should be ruled out before BCG vaccine is administered to persons in groups at high risk for HIV infection. It is also prudent to avoid giving BCG vaccination to pregnant women, although no harmful effects of BCG on the fetus have been observed.

Recommendations for BCG Vaccination (cont.)

HCWs considered on individual basis in settings in which

- High percentage of MDR TB patients has been found
- Transmission of drug-resistant TB strains and subsequent infection are likely, and
- Comprehensive TB infection-control precautions implemented and not successful

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BCG Contraindications

Contraindicated in persons with impaired immune response from

- HIV infection
- Congenital immunodeficiency
- Leukemia
- Lymphoma
- Generalized malignancy
- Receiving high-dose steroid therapy
- Receiving alkylating agents
- Receiving antimetabolites
- Receiving radiation therapy

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Interpretation of Tuberculin Reactions in Persons with a History of BCG Vaccination

Many foreign countries still use BCG as part of their TB control programs, especially for infants. In persons vaccinated with BCG, sensitivity to tuberculin is highly variable, depending upon the strain of BCG used and the group vaccinated. The presence or size of a postvaccination tuberculin skin-test reaction does not predict whether BCG will provide any protection against TB disease. Furthermore, the size of a tuberculin skin-test reaction in a BCG-vaccinated person is not a factor in determining whether the reaction is caused by *M. tuberculosis* infection or by the prior BCG vaccination.

Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG, and the skin-test results of such persons are used to support or exclude the diagnosis of *M. tuberculosis* infection. The booster phenomenon may occur among persons who have had a prior BCG vaccination (see *Two-Step Testing*, p 32). A diagnosis of *M. tuberculosis* infection and the use of treatment for infection should be considered for any BCG-vaccinated person who has a tuberculin skin-test reaction of ≥10 mm of induration, especially if any of the following circumstances are present:

- The vaccinated person is a contact of another person who has infectious TB, particularly if the infectious person has transmitted *M. tuberculosis* to others;
- The vaccinated person was born or has resided in a country in which the prevalence of TB is high; or

BCG Vaccination and Tuberculin Skin Testing

- Tuberculin skin testing not contraindicated for BCG-vaccinated persons
- LTBI diagnosis and treatment for LTBI considered for any BCG-vaccinated person whose skin test reaction is ≥10 mm, if any of these circumstances are present:
  - Was contact of another person with infectious TB
  - Was born or has resided in a high TB prevalence country
  - Is continually exposed to populations where TB prevalence is high

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- The vaccinated person is exposed continually to populations in which the prevalence of TB is high (e.g., some health care workers, employees and volunteers at homeless shelters, and workers at drug-treatment centers).

Treatment for infection should be considered for BCG-vaccinated persons who are infected with HIV and who are at risk for *M. tuberculosis* infection if they have a tuberculin skin-test reaction of ≥5 mm induration. Because HIV-infected persons may be anergic (i.e., may not react to tuberculin because of immunosuppression), isoniazid treatment for infection should be considered for these persons if they have a history of contact with another person who has infectious TB, regardless of the fact that they may be nonreactive to tuberculin.

Study Questions

Answers to these questions can be found in the text.

1. What is the current recommendation concerning BCG vaccination for most persons in the United States?

2. Under what circumstances should BCG vaccination be considered in the United States?

3. When is BCG vaccination contraindicated?

4. When should a diagnosis of TB infection be considered in a BCG-vaccinated person?

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Chapter Ten

Community TB Control

Summary. State and local health departments have the primary responsibility for preventing and controlling TB. However, other health care providers who provide TB services also have responsibility for preventing and controlling TB in their communities. Prevention and control efforts should include three priority strategies: (1) identifying and treating all persons who have TB disease, (2) finding and evaluating persons who have been in contact with TB patients to determine whether they have TB infection or disease, and treating them appropriately, and (3) testing high-risk groups for TB infection to identify candidates for treatment of latent infection and to ensure the completion of treatment.

Objectives

After working through this chapter, you will be able to

- Describe the three priority strategies for preventing and controlling TB in communities;
- Describe the activities health care providers offering direct services for TB patients should conduct.

Preventing and Controlling TB

State and local health departments have the primary responsibility for preventing and controlling TB. However, other health care providers who provide TB services in settings such as private clinics, managed care organizations, HIV clinics, correctional facilities, and hospitals also have responsibility for preventing and controlling TB in communities.

Preventing and Controlling TB

Three priority strategies:

- ➤ Identify and treat all persons with TB disease
- ➤ Identify contacts to persons with infectious TB; evaluate and offer therapy
- ➤ Test high-risk groups for LTBI; offer therapy as appropriate

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Prevention and control efforts should be conducted through the coordination of health care providers in a variety of settings to ensure the provision of direct services for TB patients. Prevention and control efforts should include three priority strategies:

1. Identifying and treating all persons who have TB disease. This means finding cases of TB and ensuring that patients complete appropriate therapy;
2. Finding and evaluating persons who have been in contact with TB patients to determine whether they have TB infection or disease, and treating them appropriately;

3. Testing high-risk groups for TB infection to identify candidates for treatment of latent infection and to ensure the completion of treatment.

Health care providers should work with health department in the following areas:

- ➤ Overall planning and policy development
- ➤ Identification of persons with clinically active TB
- ➤ Management of persons with disease or TB suspects
- ➤ Identification and management of persons with LTBI
- ➤ Laboratory and diagnostic services
- ➤ Data collection and analysis
- ➤ Training and education

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Health care providers offering direct services for TB patients should achieve the three priority strategies by working in cooperation with the local health department in the following areas:

- Overall planning and policy development
- Identification of persons who have clinically active TB
- Management of persons who have disease or who are suspected of having disease
- Identification and management of persons infected with *M. tuberculosis*
- Laboratory and diagnostic services
- Data collection and analysis
- Training and education

Overall Planning and Policy

- ➤ Develop overall TB control strategy
- ➤ Review local laws, regulations, and policies
- ➤ Guide and oversee TB control efforts of local institutions and practitioners
- ➤ Provide consultations in TB treatment, contact investigations, and infection control practices
- ➤ Seek out necessary funding and resources
- ➤ Educate policymakers

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Overall Planning and Policy Development

TB control programs should develop an overall TB control strategy in collaboration with local clinicians, professional societies, and volunteer organizations. Ideally, the plan should be developed by the state or local TB advisory council, in conjunction with community TB coalition representatives. This process includes periodic review of applicable local laws, regulations, and policies that aim to protect the public from TB to ensure that they are consistent with currently recommended medical and public health practices.

TB control programs should guide and oversee the TB control efforts of local institutions and practitioners (and local health departments where appropriate) to ensure that these efforts reflect the current standards of care and public health practice.

Health department staff or other experts may provide consultation on patient care such as treatment of drug-resistant TB, assessment of response to therapy, detection and management of adverse drug reactions, methods of ensuring adherence to therapy such as the use of directly observed therapy (DOT), laboratory methods, infection control practices, contact or outbreak investigations, and access to available resources.

TB control programs should seek the funding necessary for carrying out TB control activities, and they should educate policymakers about the local TB problem and local program priorities, needs, and objectives. Programs should have adequate and appropriate staff to meet their objectives.

Identification of Persons Who Have Clinically Active TB

Although TB care and treatment are often provided by other medical care providers, the health department has the ultimate responsibility for ensuring that TB patients do not transmit *M. tuberculosis* to others. Health departments must ensure that medical services are available, accessible, and acceptable for TB patients, suspects, contacts, and others at high risk, without regard to the patients' ability to pay for such services.

Identification of Persons Who Have Clinically Active TB

- Health department has ultimate responsibility for ensuring TB patients do not transmit TB

Contact Investigation

Purpose of a contact investigation is to find persons who

- Have TB disease so treatment can be given, and further transmission stopped
- Have LTBI so treatment can be given
- Are at high risk of developing TB disease and require treatment until LTBI excluded

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Contact Investigation

Prompt and thorough contact investigation is essential for the control of TB. The purpose of the investigation is to find contacts who (1) have TB disease so that they can be given treatment, and further transmission can be stopped, (2) have latent TB infection (LTBI) so they can be given treatment, and (3) are at high risk of developing TB disease and therefore require treatment until LTBI can be excluded.

The health department is legally responsible for ensuring that a complete and timely contact investigation is done for the TB cases reported in its area. Therefore, health departments should work closely with other agencies (e.g., managed care organizations, private providers) to ensure the prompt reporting of suspected TB cases. The health department should work closely with other agencies to plan the contact investigation and receive a report of the results. Occasionally, a contact investigation may be conducted by people outside of the health department, but under the supervision of the health department.

Management of Persons Who Have Disease or Who Are Suspected of Having Disease

TB programs should ensure that the services needed to evaluate, treat, and monitor TB patients are readily available in each community. In some areas, the state health department provides these services. In other areas, the local health department or other medical providers (e.g., managed care organizations, private physicians) provide treatment services to patients under the supervision of the state TB control program. The management of persons who have disease or who are suspected of having disease involves a range of services which include

- Developing a treatment plan

Management of Persons Who Have TB Disease or TB Suspects

Management involves range of services, which include

- Developing a treatment plan
- Promoting and ensuring adherence
- Providing a referral system for other medical problems
- Providing clinical consultation services
- Providing inpatient care when necessary
- Providing appropriate facilities to isolate and treat patients with infectious TB
- Maintaining an infection control program

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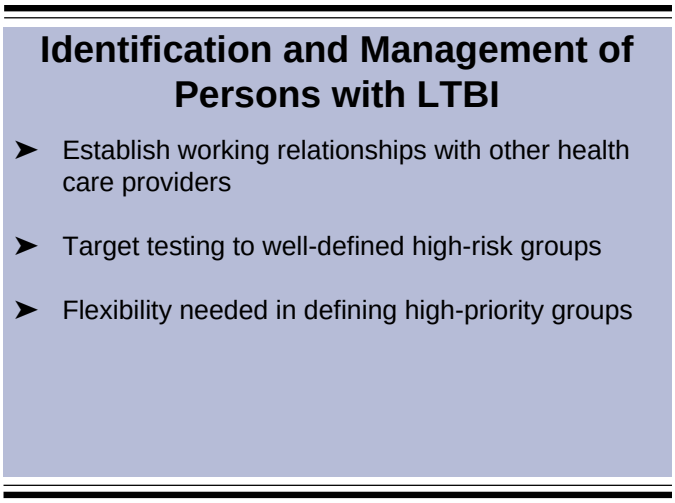
- Promoting and ensuring adherence
- Providing a referral system for other medical problems
- Providing clinical consultation services
- Providing inpatient care when necessary
- Providing appropriate facilities to isolate and treat patients with infectious TB
- Maintaining an infection control program

Coordinating care with other health care providers and facilities is crucial to the prevention and control of TB. TB patients often receive care in a variety of settings including HIV clinics, managed care organizations, hospitals, correctional facilities, and nursing homes. As patients move among these settings, continuity of care may be compromised unless a system is in place to provide coordination of care.



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Identification and Management of Persons Infected with *M. tuberculosis*

TB control programs should establish working relationships with other health care providers and agencies who provide health care services to high-risk populations and should assist them in developing and implementing testing programs.

Testing for TB infection should be done in well-defined groups. Groups that are not at high risk for TB should not be tested routinely, because testing in low-risk populations diverts resources from other priority activities and because positive tests in low-risk persons may not represent TB infection. Flexibility is needed in defining high-priority groups for testing. The changing epidemiology of TB indicates that the risk for TB among groups currently considered high priority may decrease over time, and groups currently not identified as being at risk subsequently may be considered as high priority.

Laboratory and Diagnostic Services

Both outpatient and inpatient facilities that offer services for TB patients should have ready access to laboratory and diagnostic services. Access to radiological services includes radiography equipment, trained radiography technicians, and radiograph interpretation by a qualified person. Radiograph findings and reports should be available within 24 hours.

Laboratory services should be readily accessible to provide results of acid-fast bacilli smear examinations within 24 hours of specimen collection. TB prevention and control programs should work closely with laboratories to ensure the rapid delivery of specimens to the laboratory and prompt reporting of acid-fast bacilli smear results, culture results, and results of drug susceptibility tests to the clinician and health department. Laboratory services should also be available to provide monitoring of bacteriologic response to therapy.

Data Collection and Analysis

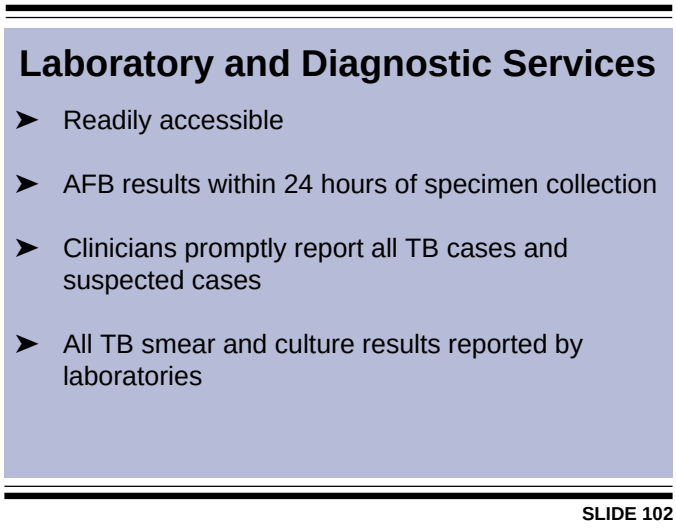
TB reporting is required by law in every state. All new TB cases and suspected cases should be reported promptly to the health department by the clinician. Cases may also be reported by infection control nurses or by pharmacies when TB drugs are dispensed. In addition, all positive TB smears and cultures should be reported promptly by laboratories.

Early reporting is important for the control of TB, and it gives clinicians access to the resources of the health department for assistance in case management and contact investigation. State and local health departments have different procedures for reporting TB and other infectious diseases. Health care providers should become familiar with the system used in their area.

All drug susceptibility results should be forwarded to the health department. These results are important for the evaluation and treatment of infected contacts. In addition, health departments use this information to determine drug resistance rates and patterns in their area.

Training and Education

TB control programs should provide training for all program staff and should provide leadership in TB education to the community. TB control programs should form networks and coalitions with community-based organizations that work in communities with a high prevalence of TB to ensure that community leaders, clinicians, and policymakers are knowledgeable about TB; to educate the public about TB; and in some instances, to help provide testing and prevention services.



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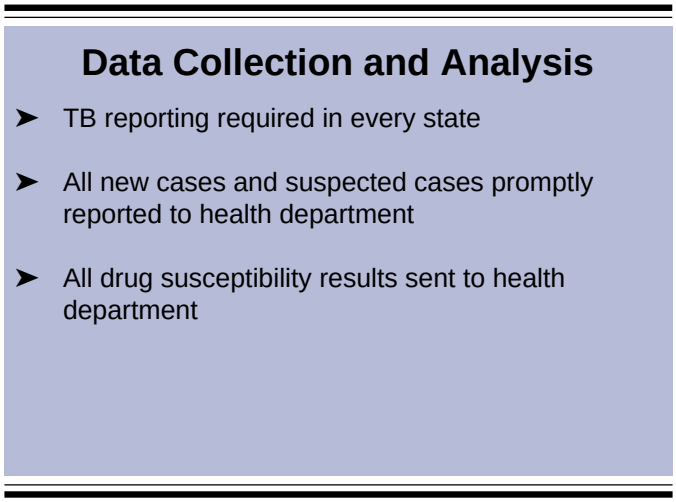

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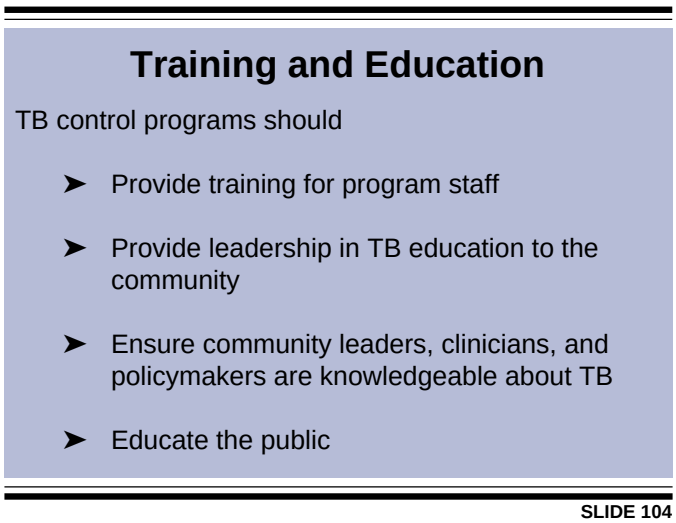

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Study Questions

Answers to these questions can be found in the text.

1. What are the three priority strategies for TB prevention and control efforts?

2. What activities should be conducted in TB prevention and control efforts?

3. What is a contact investigation, and why is it important in TB control efforts?

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Tables

Table 1. Regimen Options for Treatment of Latent TB Infection in HIV-Negative Persons

Drug	Regimens			
	Daily		Twice Weekly[†]	
	Children	Adults	Children	Adults
	Duration	Duration	Duration	Duration
Isoniazid	9 months	9 months	9 months	9 months
Isoniazid	_____	6 months	_____	6 months
Rifampin *and* Pyrazinamide	Not recommended	2 months	Not recommended	2 or 3 months
Rifampin	4 months	4 months	Not recommended	

INH - isoniazid, RIF - rifampin, RFB - rifabutin, PZA - pyrazinamide, EMB - ethambutol

[†] Directly observed treatment of LTBI should be used.

Comments
Minimum of 270 doses administered within 12 months Twice-weekly regimens should consist of at least 76 doses administered within 12 months. Recommended regimen for pregnant women Contraindicated for persons who have active hepatitis and end-stage liver disease
Minimum of 180 doses administered within 9 months Twice-weekly regimens should consist of at least 52 doses within 9 months. Recommended regimen for pregnant women 6-month regimen not recommended for those with fibrotic lesions on chest radiographs or children Contraindicated for persons who have active hepatitis and end-stage liver disease
Minimum of 60 doses to be administered within 3 months Twice-weekly regimens should consist of at least 16 doses to be administered for 2 months or 24 doses to be administered for 3 months. May be used for isoniazid-intolerant patients Avoid PZA for pregnant women because of the risk of adverse effects to the fetus. This regimen has not been evaluated in HIV- negative persons. Contraindicated for persons who have active hepatitis and end-stage liver disease
Minimum of 120 doses administered within 6 months For persons who are contacts of patients with INH-resistant, RIF-susceptible TB May be used for patients who cannot tolerate INH or PZA

Table 2. Regimen Options for Treatment of Latent TB Infection for Persons with HIV Infection

Drug	Regimens			
	Daily		Twice Weekly†	
	Children	Adults	Children	Adults
	Duration	Duration	Duration	Duration
INH	9 months	9 months	9 months	9 months
RIF and PZA*	Not recommended	2 months	Not recommended	2-3 months
RFB and PZA*	Not recommended	2 months	Not recommended	2-3 months

INH - isoniazid; PZA - pyrazinamide; RFB - rifabutin; RIF- rifampin; DOPT- directly observed preventive therapy; PIs - protease inhibitors; NNRTIs - nonnucleoside reverse transcriptase inhibitors;
NRTIs - nucleoside reverse transcriptase inhibitors

*For patients with intolerance to PZA, some experts recommend the use of a rifamycin (RIF or RFB) alone for preventive treatment. Most experts agree that available data support the recommendation that this treatment can be administered for as short a duration as 4 months, although some experts would treat for 6 months.

Comments	Contraindications
Minimum of 270 doses administered within 12 months Twice-weekly regimens should consist of at least 76 doses administered within 12 months. INH can be administered concurrently with NRTIs, PIs, or NNRTIs Directly observed treatment of latent TB infection should be used when twice-weekly dosing is used	History of an INH-induced reaction, including hepatic, skin or other allergic reactions, or neuropathy Known exposure to person who has INH-resistant TB Chronic severe liver disease
Minimum of 60 doses to be administered within 3 months Twice-weekly regimens should consist of at least 16 doses to be administered for 2 months or 24 doses to be administered for 3 months. If RFB is administered, patient should be monitored carefully for potential RFB drug toxicity and potential decreased antiretroviral drug activity. Dose adjustments, alternative therapies, or other precautions might be needed when rifamycins are used (e.g., patients using hormonal contraceptives must be advised to use barrier methods, and patients using methodone require dose adjustments). PIs or NNRTIs should generally not be administered concurrently with RIF; in this situation, an alternative is the use of RFB[†] and PZA.	History of a rifamycin-induced reaction, including hepatic, skin or other allergic reactions, or thrombocytopenia Pregnancy Chronic severe hyperuricemia Chronic severe liver disease

[†]The concurrent administration of rifabutin is contraindicated with hard-gel saquinavir and delavirdine. An alternative is the use of rifabutin with indinavir, nelfinavir, amprenavir, ritonavir, efavirenz, and possibly soft-gel saquinavir and nevirapine. Caution is advised when using rifabutin with soft-gel saquinavir and nevirapine, because data regarding the use of rifabutin with soft-gel saquinavir and nevirapine are limited.

Note: For patients whose organisms are resistant to 1 or more drugs, administer at least 2 drugs to which there is demonstrated susceptibility and consult a TB medical expert. Clinicians should review the drug-susceptibility pattern of the *M. tuberculosis* strain isolated from the infecting source-patient before choosing a preventive therapy regimen.

Table 3. Regimen Options for Treatment of TB Disease

Option	Indication	Total Duration (weeks)	Induction Phase	
			Drugs	Interval and Duration
1	Pulmonary and extrapulmonary TB in adults and children	24	INH RIF PZA[4] EMB or SM[4]	Daily for 8 weeks
2	Pulmonary and extrapulmonary TB in adults and children	24	INH RIF PZA[4] EMB or SM[4]	Daily for 2 weeks and then 2 times/week[1] for 6 weeks
3	Pulmonary and extrapulmonary TB in adults and children	24	INH RIF PZA[4] EMB or SM[4]	3 times/week[1] for 24 weeks[2]
4	Smear- and culture-negative pulmonary TB in adults	16	INH RIF PZA[4] EMB or SM[4]	Follow option 1, 2, or 3 for 8 weeks
5	Pulmonary and extrapulmonary TB in adults and children when PZA is contraindicated	36	INH RIF EMB or SM[4]	Daily for 4-8 weeks

INH – isoniazid, RIF – rifampin, PZA – pyrazinamide, EMB – ethambutol, SM – streptomycin

Note: For all patients, if susceptibility results show resistance to any of the first-line drugs or if the patient remains symptomatic or smear or culture positive after 3 months, consult a TB medical expert.

Continuation Phase		Comments
Drugs	**Interval and Duration**	
INH RIF	Daily or 2 or 3 times/week[1] for 16 weeks[2]	EMB or SM should be continued until susceptibility to INH and RIF is demonstrated. In areas where primary INH resistance <4%, EMB or SM may not be necessary for patients with no individual risk factors for drug resistance. Intermittent regimen should be directly observed.
INH RIF	2 times/week[1] for 16 weeks[2]	Regimen should be directly observed. After the 8 week induction phase, continue EMB or SM until susceptibility to INH and RIF is demonstrated, unless drug resistance is unlikely.
		Regimen should be directly observed. Continue all four drugs for 6 months.[3] This regimen has been shown to be effective for INH-resistant TB.
INH RIF PZA[4] EMB or SM[4]	Daily or 2 or 3 times/week[1] for 8 weeks	Continue all four drugs for 4 months. If drug resistance is unlikely (primary INH resistance <4% and patient has no individual risk factors for drug resistance), EMB or SM may not be necessary and PZA may be discontinued after 2 months.
INH RIF	Daily or 2 times/ week[1] for 28-32 weeks[2]	EMB or SM should be continued until susceptibility to INH and RIF is demonstrated. In areas where primary INH resistance <4%, EMB or SM may not be necessary for patients with no individual risk factors for drug resistance.

[1] All intermittent dosing should be used with directly observed therapy
[2] For infants and children with miliary TB, bone and joint TB, or TB meningitis, treatment should last at least 12 months. For adults with these forms of extrapulmonary TB, response to therapy should be monitored closely. If response is slow or suboptimal, treatment may be prolonged as judged on a case-by-case basis.
[3] There is some evidence that SM may be discontinued after 4 months if the isolate is susceptible to all drugs.
[4] Avoid SM and PZA for pregnant women because of the risk of adverse effects to the fetus.

Table 4. Regimen Options for Treatment of HIV-Related TB Disease

Total Duration (months)	Induction Phase		Continuation Phase	
	Drugs	Interval/ Duration	Drugs	Interval/ Duration
6*	INH RFB PZA† EMB† INH RFB PZA† EMB†	Daily for 2 months (8 weeks) **or** Daily for 2 weeks and then 2 times/ week for 6 weeks	INH RFB INH RFB	Daily or 2 times/ week for 4 months (18 weeks) **or** 2 times/week for 4 months (18 weeks)
9*	INH SM PZA EMB INH SM PZA EMB	Daily for 2 months (8 weeks) **or** Daily for 2 weeks and then 2* times/ week for 6 weeks	INH SM PZA INH SM PZA	2–3 times/week for 7 months (30 weeks) **or** 2–3 times/week for 7 months (30 weeks)
6*	INH RIF PZA§ EMB§ or SM INH RIF PZA§ EMB§ or SM INH RIF PZA EMB or SM	Daily for 2 months (8 weeks) **or** Daily for 2 weeks and then 2–3 times/ week for 6 weeks **or** 3 times/week for 2 months (8 weeks)	INH RIF INH RIF INH RIF PZA EMB or SM	Daily or 2–3 times/ week for 4 months (18 weeks) **or** Daily or 2–3 times/ week for 4 months (18 weeks) **or** 3 times/week for 4 months (18 weeks)

EMB – ethambutol, INH – isoniazid, PZA – pyrazinamide, RFB – rifabutin, RIF – rifampin, SM – streptomycin
PIs – protease inhibitors, NNRTIs – nonnucleoside reverse transcriptase inhibitors,
NRTIs – nucleoside reverse transcriptase inhibitors

Considerations for HIV Therapy	Comments
Concurrent administration of rifabutin is contraindicated with hard-gel saquinavir and delavirdine. 20%–25% increase in the dose of PIs or NNRTIs might be necessary Patient should be monitored carefully for RFB drug toxicity (arthralgia, uveitis, leukopenia) if RFB is used concurrently with PIs or NNRTIs. Evidence of decreased antiretroviral drug activity should be assessed periodically with HIV RNA levels. No contraindication exists for the use of RFB with NRTIs.	If the patient is also taking nelfinavir, indinavir, amprenavir, or ritonavir, the daily dose of RFB is decreased from 300 mg to 150 mg, and to 150 mg two or three times a week when used with ritonaivr. The twice-weekly dose of RFB (300 mg) remains unchanged if the patient is also taking these PIs. If the patient is also taking efavirenz, the daily dose of RFB is increased from 300 mg to 450 mg or 600 mg. Thrice-weekly dosing for RFB has not been studied and cannot be currently recommended.
Can be used concurrently with antiretroviral regimens that include PIs, NRTIs, and NNRTIs.	SM is contraindicated for pregnant women. Every effort should be made to continue administering SM for the total duration of treatment. When SM is not used for the recommended 9 months, EMB should be added to the regimen and the treatment duration should be prolonged from 9 months (38 weeks) to 12 months (52 weeks).
Rifampin can be used for the treatment of active TB disease for patients whose antiretroviral regimen includes • The NNRTI efavirenz and two nucleoside reverse transcriptase inhibitors (NRTIs); • The protease inhibitor ritonavir and one or more NRTIs; or • The combination of two protease inhibitors (ritonavir and either saquinavir hard-gel capsule of saquinavir soft-gel capsule). NTRIs may be administered concurrently with RIF. If appropriate, patients should be assessed every 3 months to evaluate the decision to initiate antiretroviral therapy. A 2–week “P-450 induction wash-out” period may be necessary between the last dose of RIF and the first dose of protease inhibitors or NNRTIs.	SM is contraindicated for pregnant women.

* Duration of therapy should be prolonged for patients with delayed response to therapy. Criteria for delayed response should be assessed at the end of the 2-month induction phase and include a) lack of conversion of the *Mycobacterium tuberculosis* culture from positive to negative or b) lack of resolution or progression of signs or symptoms of TB.

† Continue PZA and EMB for the total duration of the induction phase (8 weeks).

§ Continue PZA for the total duration of the induction phase (8 weeks). EMB can be stopped after susceptibility test results indicate *Mycobacterium tuberculosis* susceptibility to INH and RIF.

Note: Directly observed therapy (DOT) is recommended for all TB treatment regimens.

Table 5. First-Line Anti-TB Medications

Drug	Route	Dose in mg/kg (Maximum Dose)					
		Daily		2 Times/Week*		3 Times/Week*	
		Children	Adults	Children	Adults	Children	Adults
INH	PO or IM	10–20 (300 mg)	5 (300 mg)	20–40 (900 mg)	15 (900 mg)	20–40 (900 mg)	15 (900 mg)
RIF	PO or IV	10–20 (600 mg)	10 (600 mg)	10–20 (600 mg)	10 (600 mg)	10–20 (600 mg)	10 (600 mg)
RFB[†]	PO or IV	10–20 (300 mg) or *(150 mg)*[§] or *(450 mg)*[¶]	5 (300 mg) or *(150 mg)*[§] or *(450 mg)*[¶]	10–20 (300 mg) or 10–20 (300 mg) or *(450 mg)*[¶]	5 (300 mg) or 5[§] (300 mg) or *(450 mg)*[¶]	Not Known Not Known Not Known	Not Known Not Known Not Known
PZA	PO	15–20 (2 g)	15–30 (2 g)	50–70 (4 g)	50–70 (4 g)	50–70 (3 g)	50–70 (3 g)
EMB[#]	PO	15–25	15–25	50	50	25–30	25–30
SM	IM or IV	20–40 (1 g)	15 (1 g)	25–30 (1.5 g)	25–30 (1.5 g)	25–30 (1.5 g)	25–30 (1.5 g)

INH – isoniazid, RIF – rifampin, RFB – rifabutin, PZA – pyrazinamide, EMB – ethambutol,
SM – streptomycin, PIs – Protease Inhibitors, NNRTIs – nonnucleoside reverse transcriptase inhibitors
PO – by mouth, IM – intramuscular, IV – intravenous, CNS – central nervous system

Notes: Consult product insert for detailed information.
Children ≤12 years old.
Adjust weight-based dosages as weight changes.

Adverse Reactions	Monitoring	Comments
Rash Hepatic enzyme elevation Hepatitis Peripheral neuropathy Mild CNS effects Drug interactions resulting in increased phenytoin (Dilantin) or disulfiram (Antabuse) levels	Baseline measurements of hepatic enzymes for adults Repeat measurements if • baseline results are abnormal • patient is at high risk for adverse reactions • patient has symptoms of adverse reactions	Hepatitis risk increases with age and alcohol consumption Pyridoxine (Vitamin B_6) may prevent peripheral neuropathy and CNS effects 10–15 mg/kg should be used for children when treating for latent TB infection
GI upset Drug interactions Hepatitis Bleeding problems Flu-like symptoms Rash Renal failure Fever	Baseline measurements of CBC, platelets, and hepatic enzymes Repeat measurements if • baseline results are abnormal • patient has symptoms of adverse reactions	Significant interactions with methadone, birth control hormones, PIs, NNRTIs, and many other drugs Contraindicated or should be used with caution when administered with PIs and NNRTIs Colors body fluids orange May permanently discolor soft contact lenses
Rash Hepatitis Fever Thrombocytopenia With increased levels of RFB: • Severe arthralgias • Uveitis • Leukopenia	Baseline measurements of CBC, platelets, and hepatic enzymes Repeat measurements if • baseline results are abnormal • patient has symptoms of adverse reactions Use adjusted daily dose of RFB[§], and monitor for decreased antiretroviral activity and for RFB toxicity if RFB taken concurrently with PIs or NNRTIs	RFB is contraindicated in patients taking ritonavir or delavirdine Reduces levels of many drugs (e.g., PIs, NNRTIs, methadone, dapsone, ketoconazole, hormonal contraceptives, etc.) Colors body fluids orange May permanently discolor soft contact lenses
Hepatitis Rash GI upset Joint aches Hyperuricemia Gout (rare)	Baseline measurements of uric acid and hepatic enzymes Repeat measurements if • baseline results are abnormal • patient has symptoms of adverse reactions	Treat hyperuricemia only if patient has symptoms May make glucose control more difficult in diabetics
Optic neuritis Rash	Baseline and monthly tests of visual acuity and color vision	Not recommended for children too young to be monitored for changes in vision unless TB is drug resistant Optic neuritis may be unilateral, check each eye separately
Ototoxicity (hearing loss or vestibular dysfunction) Renal toxicity	Baseline and repeat as needed of hearing and renal function tests	Ultrasound and warm compresses to injection site may reduce pain Avoid or reduce dose in adults ≥60 years old

*All intermittent dosing should be used with directly observed therapy.
[†]The concurrent administration of rifabutin is contraindicated with hard-gel saquinavir and delavirdine. An alternative is the use of rifabutin with indinavir, nelfinavir, amprenavir, ritonavir, efavirenz, and possibly soft-gel saquinavir and nevirapine. Caution is advised when using rifabutin with soft-gel saquinavir and nevirapine, because data regarding the use of rifabutin with soft-gel saquinavir and nevirapine are limited.
[§]If nelfinavir, indinavir, amprenavir, or ritonavir is administered with RFB, blood concentrations of the PIs decrease. Thus, when RFB is used concurrently with any of these drugs, the daily dose of RFB is reduced from 300 mg to 150 mg when used with nelfinavir, indiavir, or amprenavir, and to 150 mg two or three times a week when used with ritonaivr.
[¶]If efavirenz is administered with RFB, blood concentrations of RFB decrease. Thus, when RFB is used with efavirenz, the daily dose of RFB should be increased from 300 mg to 450 mg or 600 mg.
[#]No maximum dosages for EMB but in obese patients dosage should be calculated on lean body weight.

Table 6. Second-Line Anti-TB Medications

Drug	Route	Daily Dose** (Maximum Dose)	Adverse reactions
Capreomycin	IM or IV	15–30 mg/kg (1 g)	Toxicity • auditory • vestibular • renal
Kanamycin	IM or IV	15–30 mg/kg (1 g)	Toxicity • auditory • vestibular • renal
Amikacin	IM or IV	15–30 mg/kg (1 g)	Toxicity • auditory • vestibular • renal Chemical imbalance Dizziness
Ethionamide	PO	15–20 mg/kg (1 g)	GI upset Hepatotoxicity Hypersensitivity Metallic taste
Para-aminosalicylic acid (PAS)	PO	150 mg/kg (16 g)	GI upset Hypersensitivity Hepatotoxicity Sodium load
Cycloserine	PO	15–20 mg/kg (1 g)	Psychosis Convulsions Depression Headaches Rash Drug interactions
Ciprofloxacin	PO	750–1500 mg/day	GI upset Dizziness Hypersensitivity Drug interactions Headaches Restlessness
Ofloxacin	PO	600–800 mg/day	GI upset Dizziness Hypersensitivity Drug interactions Headaches Restlessness
Levofloxacin	PO	500 mg/day	GI upset Dizziness Hypersensitivity Drug interactions Headaches Restlessness
Clofazimine	PO	100–300 mg/day	GI upset Discoloration of skin Severe abdominal pain and organ damage due to crystal deposition

PO–by mouth, IM–intramuscular, IV–intravenous

Monitoring	Comments
Assess vestibular function and hearing function prior to initiation of therapy and at regular intervals during treatment Measure blood urea nitrogen and creatinine throughout treatment	After bacteriologic conversion, dosage may be reduced to 2–3 times per week Safety and effectiveness in children have not been established
Assess vestibular function and hearing function prior to initiation of therapy and at regular intervals during treatment Measure blood urea nitrogen and creatinine throughout treatment	After bacteriologic conversion, dosage may be reduced to 2–3 times per week Not approved by FDA for TB treatment
Assess vestibular function and hearing function prior to initiation of therapy and at regular intervals during treatment Measure renal function and serum drug levels	After bacteriologic conversion, dosage may be reduced to 2–3 times per week Not approved by FDA for TB treatment
Measure hepatic enzymes	Start with low dosage and increase as tolerated May cause hypothyroid condition, especially if used with PAS
Measure hepatic enzymes Assess volume status	Start with low dosage and increase as tolerated Monitor cardiac patients for sodium load May cause hypothyroid condition, especially if used with ethionamide
Assess mental status Measure serum drug levels	Start with low dosage and increase as tolerated Pyridoxine may decrease CNS effects
Drug interactions	Not approved by the FDA for TB treatment Should not be used in children Avoid coadministration within 2 hours of: • antacids • iron • zinc • sucralfate
Drug interactions	Not approved by the FDA for TB treatment Should not be used in children Avoid coadministration within 2 hours of: • antacids • iron • zinc • sucralfate
Drug interactions	Not approved by the FDA for TB treatment Should not be used in children Avoid coadministration within 2 hours of: • antacids • iron • zinc • sucralfate
Drug interactions	Not approved by FDA for TB treatment Avoid sunlight Consider dosing at mealtime Efficacy unproven

* Consult product insert for detailed information
**Adjust weight-based dosages as weight changes.

Notes: Doses for children the same as for adults. Use these drugs only in consultation with a clinician experienced in the management of drug-resistant TB.

Table 7. First-Line TB Drugs in Special Situations*

Drug	CNS TB Disease	Renal Insufficiency
Isoniazid	Good penetration	Normal clearance
Rifampin	Fair penetration of inflamed meninges (10%–20%)	Normal clearance
Pyrazinamide	Good penetration	Clearance reduced Decrease dose or prolong interval
Ethambutol	Penetrates inflamed meninges (4%–64%)	Clearance reduced Decrease dose or prolong interval
Streptomycin	Fair penetration of inflamed meninges (20%)	Clearance reduced Avoid in end-stage renal disease

CNS–central nervous system

*Consult product insert for detailed information.

Continuing Education

Core Curriculum on Tuberculosis
Course #SS3043

Goal

The goal of this *Core Curriculum on Tuberculosis: What the Clinician Should Know* is to provide the reader with basic information about TB. Upon completion of this educational activity, the reader should possess a clear working knowledge of the diagnosis, treatment, and prevention of TB infection and disease.

Accreditation

Continuing Medical Education (CME) Credit: The Centers for Disease Control and Prevention (CDC) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The CDC designates this educational activity for a maximum of **5** hours in category 1 credit towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Continuing Nursing Education (CNE) Credit: This activity for **6** contact hours is provided by CDC, which is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's (ANCC) Commission on Accreditation.

Continuing Education Units (CEU): The CDC awards **.5** Continuing Education Units (CEUs). The CDC is an Authorized CEU Sponsor of the International Association for Continuing Education and Training.

Instructions

1. Read the *Core Curriculum on Tuberculosis: What the Clinician Should Know*, 4th ed.

2. Complete the posttest and evaluation. There are two options for completing the posttest and evaluation to receive credit:

    a. **Mail:** A continuing education packet (instructions, scan forms, and a postage-paid return envelope) are included with the booklet. Complete the posttest and evaluation and mail the packet to the CDC Continuing Education Program in the postage-paid return envelope provided. You should receive certification of continuing education credit in 4 to 6 weeks.

    b. **Internet:** Go to **www.cdc.gov/nchstp/tb/pubs/corecurr/** and follow the instructions for completing the posttest and evaluation on-line. You will receive immediate feedback and certification of continuing education credit.

3. If you need additional continuing education packets, you may contact the CDC Continuing Education Program to request additional packets in one of the following ways:

    a. **Email:** Send an email to **CE@cdc.gov** and provide your name, address, and daytime phone number, and specify that you would like materials for the course entitled *Core Curriculum on Tuberculosis,* course number SS3043.

    b. **Fax:** Place a toll-free call from a touch tone phone to 888-CDC-FAXX (888-232-3299). When prompted, enter document number **564007**, then enter your 10-digit fax number. Fax the completed continuing education request form to 404-639-0800.

    c. **Phone:** Call 1-800-41-TRAIN, follow the prompts, and state your request for a continuing education packet for the course entitled *Core Curriculum on Tuberculosis*, course number SS3043.

You should receive your continuing education packet in 2 to 3 weeks.

Continuing Education Posttest and Evaluation

True or False

Answer A = True or B = False

1. TB is spread from person to person through the air.

   A. True
   B. False

2. Secondary drug resistance develops during TB therapy.

   A. True
   B. False

3. Surveillance data indicate that TB in the United States affects racial/ethnic minorities disproportionately.

   A. True
   B. False

4. The Mantoux tuberculin skin test is given by using a needle and syringe to inject 0.1 ml of 5 tuberculin units of liquid tuberculin intradermally into the inner surface of the forearm.

   A. True
   B. False

5. The use of anergy testing in conjunction with tuberculin skin testing is routinely recommended for screening programs for *M. tuberculosis* infection conducted among HIV-positive persons in the United States.

   A. True
   B. False

6. Culture examinations should be done on all specimens regardless of AFB smear results.

   A. True
   B. False

7. A rifampin-based TB treatment regimen is recommended for HIV-positive patients who have started on antiretroviral therapy.

   A. True
   B. False

8. The best way to measure the effectiveness of treatment is to obtain specimens for culture at least monthly.

   A. True
   B. False

9. In isolation rooms, ventilation systems are necessary to maintain positive pressure and exhaust the air properly.

   A. True
   B. False

10. Personal respirators should be used in settings where administrative and engineering controls may not fully protect health care workers from infectious droplet nuclei.

    A. True
    B. False

11. CDC guidelines recommend BCG vaccination in U.S. immunization programs and TB control programs.

    A. True
    B. False

12. Tuberculin skin testing is contraindicated in persons who have been vaccinated with BCG.

    A. True
    B. False

For questions 13 - 20, answer ***true*** or ***false*** for the conditions that can increase the risk that TB infection will progress to TB disease.

13. High blood pressure

14. Injection of illicit drugs

15. HIV infection

16. Normal chest x-ray

17. Diabetes mellitus

18. Silicosis

19. High body weight (20% or more above the ideal)

20. Recent TB infection (within the past 2 years)

Multiple Choice

Choose the one best answer.

21. Which of the following statements is true?

    A. During 1992-1998, the overall decrease in TB cases reflected the substantial decline in cases among U.S.-born persons in all age groups and a small increase in the number of cases among foreign-born persons

    B. During 1992-1998, the overall decrease in TB cases reflected the substantial increase in cases among U.S.-born persons in all age groups and a small decrease in the number of cases among foreign-born persons

    C. During 1992-1998, the overall decrease in TB cases reflected the substantial decline in cases among U.S.-born persons in all age groups and a small decrease in the number of cases among foreign-born persons

    D. During 1992-1998, the overall decrease in TB cases reflected the substantial increase in cases among U.S.-born persons in all age groups and a small increase in the number of cases among foreign-born persons

22. Generally, what percentage of people in the United States who have TB infection and normal immune systems develop TB disease at some point in their lives?

    A. 2%

    B. 10%

    C. 50%

    D. 90%

23. For the following groups, what induration size is considered a positive reaction? (Choose only one answer for all 3 groups)

    - Recent contacts of a TB case
    - HIV-positive persons
    - People who have chest x-ray findings consistent with old healed TB

    A. 5 millimeters or greater

    B. 10 millimeters or greater

    C. 15 millimeters or greater

24. Which of the following groups should be given high priority for treatment of latent TB?

    A. Patients with organ transplants and other immunosuppressed patients

    B. HIV-positive persons

    C. Recent contacts of a TB case

    D. Persons with fibrotic changes consistent with old healed TB

    E. All of the above

25. Which of the following regimens is an alternative to isoniazid for treatment of LTBI in HIV-positive persons?

    A. Streptomycin and ethambutol

    B. Rifampin and pyrazinamide

    C. Ethambutol and pyrazinamide

    D. Rifampin and ethambutol

26. Which of the following treatment-of-latent-TB-infection regimens is an alternative to isoniazid for HIV-positive persons who are receiving protease inhibitors or nonnucleoside reverse transcriptase inhibitors?

    A. Streptomycin and ethambutol

    B. Rifampin and pyrazinamide

    C. Ethambutol and pyrazinamide

    D. Rifabutin and pyrazinamide

27. How often should patients be evaluated for signs and symptoms of active TB disease during treatment of LTBI?

    A. Weekly

    B. At least monthly

    C. Only if symptoms of adverse reactions occur

    D. Every 3 months

28. The recommended regimen for the initial phase of a 6-month regimen for TB in HIV-negative individuals is

    A. Isoniazid and rifampin

    B. Isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin

    C. Isoniazid, rifabutin, ethambutol

    D. Isoniazid, rifabutin, streptomycin, ethionamide

29. Which of the following is recommended as the initial phase of a 6-month TB regimen for HIV-positive patients who are on or will begin an antiretroviral regimen including protease inhibitors or nonnucleoside reverse transcriptase inhibitors?

    A. Isoniazid, rifampin, pyrazinamide, ethambutol

    B. Isoniazid, ethambutol, pyrazinamide, streptomycin

    C. Isoniazid, rifabutin, pyrazinamide, ethambutol

    D. Isoniazid, rifampin, pyrazinamide, ethionamide

30. Which of the following describes directly observed therapy (DOT)?

    A. A public health worker gives the patient a bottle of pills monthly.

    B. A designated individual watches the patient swallow every dose of the prescribed medication.

    C. A public health worker counts the remaining pills in the medication bottles.

    D. All of the above

31. Peripheral neuropathy is associated with the use of

    A. Pyrazinamide

    B. Isoniazid

    C. Rifampin

    D. Ethambutol

32. When can a TB patient be considered noninfectious?

    A. When they are on adequate therapy

    B. When they have had a significant clinical response to therapy

    C. When they have had 3 consecutive negative sputum smear results from specimens collected on different days

    D. When all of the above are true

33. What are the three types of controls in an infection control program?

    A. Administrative, isolation, personal respiratory protection

    B. Administrative, engineering, personal respiratory protection

    C. Isolation, ventilation systems, HEPA filtration

    D. Ventilation systems, personal respiratory protection, HEPA filters

34. A diagnosis of *M. tuberculosis* infection and the use of treatment for infection should be considered for a BCG-vaccinated person with a reaction of ≥10 mm of induration if

    A. The vaccinated person is a contact of another person who has infectious TB

    B. The vaccinated person was born or has resided in a country in which the prevalence of TB is high

    C. The vaccinated person is exposed continually to populations in which the prevalence of TB is high

    D. All of the above

35. BCG vaccination should be considered in which of the following circumstances:

    A. A child who is continually exposed to a patient who had noninfectious pulmonary TB caused by *M. tuberculosis* strains resistant to isoniazid and rifampin and the child can be separated from the presence of the noninfectious patient

    B. A child who is continually exposed to an untreated or ineffectively treated patient who has infectious pulmonary TB and the child cannot be separated from the presence of the infectious patient

    C. Health care workers who work in settings where there is a high percentage of TB patients infected with *M. tuberculosis*

    D. All of the above

Multiple - Multiples

For each question there are 4 choices listed (1, 2, 3, and 4). Choose the best answer (A, B, C, D, or E) which consists of multiple combinations of correct answers.

A = 1, 2, and 3 are correct
B = 1 and 3 are correct
C = 2 and 4 are correct
D = Only 4 is correct
E = All are correct

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36. Which of the following statements is correct?

    1. All persons with class 3 or class 5 TB should be reported promptly to the health department.

    2. A patient should not have a class 5 classification for more than 3 months.

    3. The current clinical classification system for TB is based on the pathogenesis of the disease.

    4. Health care providers should comply with state and local laws and regulations requiring the reporting of TB.

37. Which of the following is true about two-step testing?

    1. Two-step testing should be used for the initial skin testing of adults who will be retested periodically.

    2. Two-step testing is used to reduce the likelihood that a boosted reaction will be misinterpreted as a recent infection.

    3. Delayed-type hypersensitivity to tuberculin may wane over the years and a skin test may boost the ability to react to tuberculin, causing a positive reaction to subsequent tests.

    4. Two-step testing should be used for all adults.

38. Which of the following may be a symptom of TB disease?

    1. Fever

    2. Weight loss

    3. Fatigue

    4. Runny nose

A = 1, 2, and 3 are correct
B = 1 and 3 are correct
C = 2 and 4 are correct
D = Only 4 is correct
E = All are correct

39. Which of the following confirms the diagnosis of TB?

    1. Chest x-ray
    2. Detection of acid-fast bacilli in smear examination
    3. Positive tuberculin skin test
    4. Positive culture of *M. tuberculosis*

40. Which of the following persons are at an increased risk for drug resistance?

    1. Contacts of persons known to have drug-resistant TB
    2. Persons receiving inadequate TB treatment regimens for >2 weeks
    3. Persons whose smears or cultures remain positive despite 2 months of therapy with TB drugs
    4. Persons who have a history of treatment with TB drugs

41. Which of the following are priorities for state and local health departments?

    1. Identifying and treating all persons who have TB disease
    2. Finding and evaluating persons who have been in contact with TB patients to determine whether they have TB infection or disease and treating them appropriately
    3. Testing high-risk groups for TB infection to identify candidates for treatment of latent infection and to ensure the completion of therapy
    4. Testing all groups for TB infection to identify candidates for treatment of latent infection and to ensure the completion of therapy

42. Which of the following are roles of the health department?

    1. Conducting contact investigations
    2. Ensuring that TB patients do not transmit *M. tuberculosis* to others
    3. Periodically reviewing applicable local laws, regulations, and policies that aim to protect the public from TB
    4. Conducting surveillance of all new cases and suspected cases

Evaluation Questions

Multiple Choice

43. I am applying for (choose only one):

    A. Continuing medical education (CME) credit

    B. Continuing nursing education (CNE) credit

    C. Continuing education units (CEU)

44. Indicate your primary occupation:

    A. Physician

    B. Nurse

    C. Health Educator

    D. Respiratory Care Practitioner

    E. Student

    F. Other

45. Please indicate the setting where you work:

    A. City/county/state health department

    B. Other public health agency (e.g., drug treatment facility, Federal agency, nursing home, correctional institution, community based organization)

    C. Hospital

    D. Other health care agency (e.g., managed care organization, private physician's office, clinic)

    E. Academic institution

    F. Other

46. Indicate the approximate percentage of time that you spend on your job working on TB activities:

    A. 75% - 100%

    B. 50% - 74%

    C. 25% - 49%

    D. 10% - 24%

    E. 1% - 9%

    F. 0%

47. Approximately how long did it take you to read the publication and complete the exam?

    A. Less than 5 hours

    B. 5-7 hours

    C. 8-9 hours

    D. Greater than 9 hours

48. How did you learn about this continuing education activity?

    A. Internet (World Wide Web)

    B. Advertisement (flyer, publication cover, newsletter, journal)

    C. Co-worker/Supervisor

    D. Conference/Presentation

    E. Other

The following questions will assess your perceptions of the readability and applicability of the material.

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
49. The objectives of this course were clearly stated and achieved.	A	B	C	D	E
50. The presentation of course material enhanced my ability to understand the material.	A	B	C	D	E
51. The course materials were organized, clear, and helpful.	A	B	C	D	E
52. I will use this publication as a teaching tool.	A	B	C	D	E
53. Overall, the objectives met the stated goals of this publication.	A	B	C	D	E