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Tuberculosis

2.00 Contact Hours

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Outcomes

≥ 92% of participants will understand the transmission of tuberculosis, who is at risk, the signs and symptoms, the different types, and how tuberculosis is diagnosed and treated.

Objectives

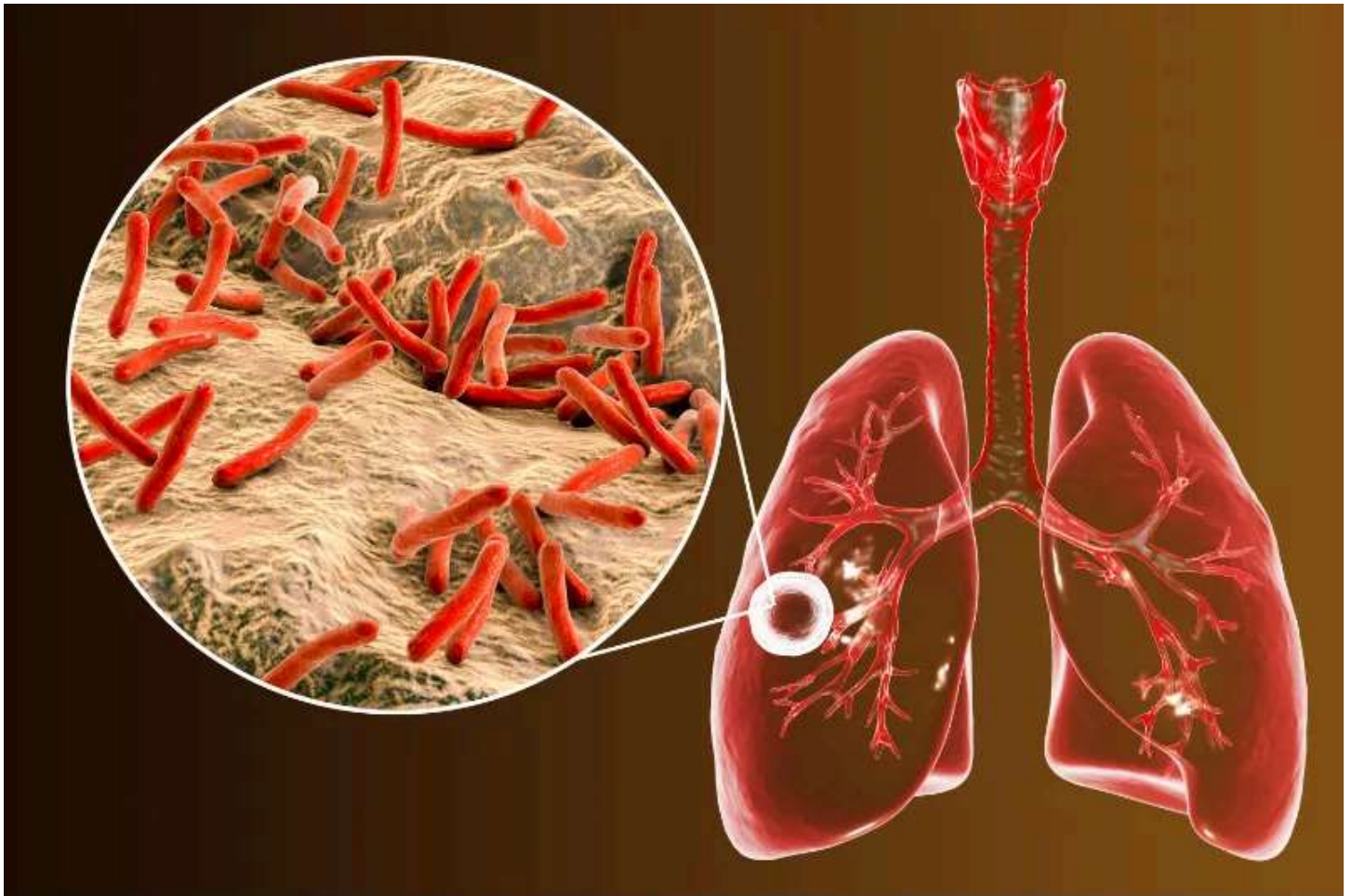
After completing this course, the learner will be able to:

1. Describe the transmission of tuberculosis.
2. Summarize the signs and symptoms of tuberculosis.
3. Identify diagnostic tests for the presence of tuberculosis.
4. List risk factors for tuberculosis.
5. Outline treatment options for tuberculosis.
6. Characterize patient monitoring for patients being treated for tuberculosis.

Introduction

Tuberculosis (TB) is an infectious disease caused by a bacterium of the *Mycobacterium* (*M. tuberculosis*) complex (Raviglione & Gori, 2022). TB is primarily a respiratory disease that is transmitted by inhalation of airborne infected droplets. However, other organ systems can also be affected (Raviglione & Gori, 2022); these conditions are called extrapulmonary TB and miliary TB.

A TB infection is easily cured with prompt recognition and proper care (Raviglione & Gori, 2022). In the United States (US), TB infections and death from TB are uncommon for most of the population (CDC, 2023a; CDC, 2022a). However, the risk is increased for some US residents, *e.g.*, people who are living with human immunodeficiency virus (HIV) or who are immunocompromised (Goletti et al., 2023; Lumu et al., 2023). A TB infection can be a very serious condition, and in some parts of the world, medical care and drug therapy are unavailable, or there is limited availability. In 2021, there were 6.4 million new cases of TB (World Health Organization [WHO], 2022) and 1.4 million deaths from TB, and most of these cases occurred in low-income countries (WHO, 2022). TB is the leading cause of death by infectious disease (Naidoo & Perumal, 2023; Nardell, 2022b).



Tuberculosis Infection

Epidemiology of Tuberculosis

In the US, in 2022, 8,300 cases of TB were reported (CDC, 2023a); this is an incidence rate of 2.5 cases per 100,000 persons (CDC, 2023a) and is an increase from 2021 (CDC, 2022a). An estimated 13 million Americans have latent TB (CDC, 2023a). Knowing the true number of latent TB cases is difficult because latent TB is not a reportable disease (Mirzazadeh et al., 2021). In some population groups, like non-native Americans, the prevalence of latent TB cases has been estimated to be as high as 31% (Collins et al., 2021). (Note: Latent TB will be explained later in the module).

In the US, there are few TB-associated deaths. "The National Vital Statistics System collects information on reported TB disease-related deaths. Data are released after a 1-year lag. There were 600 TB-related deaths (0.2 deaths per 100,000 persons) reported in 2020, the most recent year for which data are available" (CDC, 2022a).

Transmission of Tuberculosis

M. tuberculosis is primarily transmitted by inhalation of airborne, infected droplets (Nardell, 2022a; Raviglione & Gori, 2022). The droplets are expelled by an infected person when they cough, speak, or sneeze or by any forceful respiratory effort, and after they are expelled, they become airborne (Nardell, 2022b; Raviglione & Gori, 2022). Inhaled droplets are usually expelled, but around 10% will reach the alveoli (Raviglione & Gori, 2022).

Other transmission routes, *e.g.*, dermal transmission (Chatterjee et al., 2021), are uncommon (Raviglione & Gori, 2022). Vertical transmission of TB can happen with hematogenous (carried by the blood) transmission of the bacterium through the placenta or by aspiration of infected vaginal secretions during birth (Raviglione & Gori, 2022).

The risk of transmission and infection is primarily determined by environmental/social variables (Raviglione & Gori, 2022) like the duration of contact with an infected person, proximity to an infected person, how infectious the contacts are, and the frequency of contact with an infected person (CDC, 2016c; Nardell, 2022b; Raviglione & Gori, 2022). The risk of developing the disease after infection – a situation called primary TB – depends on patient variables like the status of their immune system (Raviglione & Gori, 2022).

Approximately 5% to 10% of all persons infected with TB will eventually develop active TB at some point in their lives (Nardell, 2022b; Raviglione & Gori, 2022), but the risk for any individual varies significantly (Nardell, 2022b). Factors that increase the risk of developing active TB are listed in Table 1. The common theme in these risk factors is compromised immune system function (Ali et al., 2022; Awad et al., 2019; Nardell, 2022b; Vikrant, 2019). Infection with HIV is the most important risk factor for developing active TB (Raviglione & Gori, 2022).

Table 1: Risk Factors for Developing Active Tuberculosis

Chronic Renal Failure/Hemodialysis
Diabetes Mellitus
HIV Infection
IV Drug Use
Recent Infection
(Ali et al., 2022; Awad et al., 2019; Nardell, 2022b; Vikrant, 2019)

Infection with Tuberculosis: Pathophysiology and Natural History

Once the TB bacteria reach the alveoli, one of five situations can occur:

1. The bacteria is completely cleared, and infection does not develop.
2. Primary TB: Primary TB occurs soon after the TB bacteria reach the alveoli (Raviglione & Gori, 2022). The TB bacteria establish an infection, but in most cases, the bacteria is contained. Patients with primary TB are usually asymptomatic and have no radiographic evidence of infection (Fitzpatrick et al., 2023).
3. Primary progressive TB: The patient develops an active infection called primary progressive TB soon after exposure. Primary progressive TB occurs in 5% of those infected with the pathogen (Fitzpatrick et al., 2023) and is more common in children and immunocompromised people (Raviglione & Gori, 2022). Patients are usually considered immunocompromised because of a comorbidity (See Table 1), they have an acute infection like COVID-19 (Friedman & DeGeorge, 2022; Leonso et al., 2022), or because of treatment for an infection (Friedman & DeGeorge, 2022; Leonso et al., 2022).

4. Latent TB: The definition of latent TB is "a state of persistent immune response to stimulation by *M. tuberculosis* antigens without evidence of clinically manifested active TB and with bacillary replication absent or below some undefined threshold as a result of immunologic control" (Shah & Dorman, 2021).
 - In latent TB, macrophages surround and contain TB bacteria through phagocytosis. Phagocytosis of TB bacteria produces a barrier around them, such as a granuloma shell (Raviglione & Gori, 2022). Typically, when macrophages engulf bacteria or other xenobiotics, the foreign particles are destroyed by enzymes inside the macrophage. However, because of the physical nature of the granuloma and certain characteristics of the TB bacteria that protect it from macrophagic enzymes, TB can live inside a granuloma for many years, even decades (Fitzpatrick et al., 2023). Latent TB is not contagious (Fitzpatrick et al., 2023).
 - Note: Part of the definition of latent TB is a persistent immune response to stimulation by *M. tuberculosis* antigens. However, TB tests are neither 100% sensitive nor specific, and some people can be immunoreactive to TB antigen tests – which could be interpreted as indicating the presence of TB – but they have cleared the bacterium (Behr et al., 2021). These issues make determining the incidence of latent TB a significant challenge.
5. Reactivation: A patient who has latent TB develops active TB. Approximately 5–15% of patients with latent TB who are not treated will develop active TB (Fitzpatrick et al., 2023; Shah & Dorman, 2021). Approximately 90% of all cases of TB in adults are a reactivation of latent infection (Fitzpatrick et al., 2023). Reactivation typically occurs several years after the infection (Fitzpatrick et al., 2023; Raviglione & Gori, 2022). The clinical presentation of primary progressive TB and reactivation of latent TB are indistinguishable (Fitzpatrick et al., 2023).
 - Note: The terminology of TB infections can be confusing. Primary progressive TB and reactivation of latent TB are sometimes referred to as active TB or active disease. In the treatment section of the module, primary progressive TB will be referred to as active TB, but in most circumstances, reactivation of latent TB is called active TB or active disease, as well. Treatment of latent TB will refer to patients who have latent TB.

Signs and Symptoms

Primary Tuberculosis

People who have primary TB may be asymptomatic, and there are no signs seen on an X-ray of a TB infection (Fitzpatrick et al., 2023), or they may have non-specific signs and symptoms like cough, fever, and pleuritic chest pain (Raviglione & Gori, 2022). As previously mentioned, primary TB can develop into active TB, and the clinical presentation does not definitively distinguish the primary disease from the reactivation of latent TB infection (Fitzpatrick et al., 2023). See the next section for a discussion of the signs and symptoms of an active TB infection.

Latent Tuberculosis Reactivation

Latent TB reactivation is characterized by non-specific signs and symptoms, including (but not limited to) anorexia, cough, dyspnea, fever, malaise, night sweats, weakness, and weight loss (Fitzpatrick et al., 2023; Raviglione & Gori, 2022). Cough is very common (90%). Initially, the cough is non-productive, but most patients eventually have a productive cough with purulent sputum (Fitzpatrick et al., 2023; Raviglione & Gori, 2022). Hemoptysis can occur (Fitzpatrick et

al., 2023; Raviglione & Gori, 2022), and massive hemoptysis – > 100 mL of blood expectorated within 24 hours – can be life-threatening (Iqbal et al., 2022). The lung sounds may be normal, or rales may be present (Fitzpatrick et al., 2023).

Diagnosis of Primary Tuberculosis

This section will discuss the diagnosis of primary pulmonary TB infection. Diagnosing latent TB and other forms of TB will be discussed in separate sections.

Primary TB active infection is diagnosed using the following four criteria (Fitzpatrick et al., 2023; Raviglione & Gori, 2022).

1. A high index of suspicion: Consider a diagnosis of primary active TB if a patient has the characteristic signs and symptoms of TB and the patient:
 - is infected with HIV
 - has a positive TB screening test
 - has been exposed to someone who is known to have active disease
 - has been treated for TB
 - has traveled to an area where TB is endemic
 - is homeless or incarcerated
 - uses IV drugs
 - is very young
 - has other medical conditions that increase the susceptibility to the development of TB
 - Because the signs and symptoms of TB are non-specific and laboratory confirmation of TB takes time, the index of suspicion is the most important part of a provisional diagnosis of TB.
2. Signs and symptoms: The signs and symptoms of active TB include (but are not limited to) cough, fatigue, malaise, productive cough, night sweats, weakness, and weight loss.
3. X-ray findings: A chest x-ray (CXR) is an important part of the diagnostic workup for TB. However, a CXR is highly sensitive but poorly specific. A CXR cannot distinguish between active and inactive TB, and the "classic" findings of upper lobe infiltrate and cavitation may be absent (Raviglione & Gori, 2022).
4. Laboratory testing: The definitive diagnosis of TB requires isolation and identification of *M. tuberculosis* from a sputum sample or another clinical sample (Raviglione & Gori, 2022) or identification of TB by nucleic acid amplification (NAA) testing in the context of a high likelihood of TB infection (Fitzpatrick et al., 2023).

Laboratory Testing

Three laboratory tests are used to detect and diagnose TB (Fitzpatrick et al., 2023; Lewinsohn et al., 2017; Raviglione & Gori, 2022). They include the following:

1. Acid-fast bacillus (AFB) smear test: An AFB smear test is done by microscopic examination of a sputum sample to identify a TB bacterium. AFB testing is relatively inexpensive and simple to do. However, it has low sensitivity and a low negative predictive value, and the sensitivity of an AFB smear test is especially low in patients who are infected with HIV (Fitzpatrick et al., 2023). A positive AFB test cannot be used to make a diagnosis of *M. tuberculosis* infection "... since nontuberculous mycobacteria may colonize the airways and are increasingly recognized to cause clinical illness in patients with underlying structural lung disease" (Fitzpatrick et al., 2023). In addition, it is ...

"sufficiently common that a positive AFB smear result does not confirm pulmonary TB" (Lewinsohn et al., 2017). Despite these limitations, the Clinical Practice Guidelines of the American Thoracic Society (ATS), Infectious Diseases Society of America (ISDA), and the CDC recommend that an AFB smear test should be done in all patients suspected of having TB (Lewinsohn et al., 2017).

- The sputum sample for an AFB smear test should be at least 3 mL in volume, but preferably 5 to 10 mL (Lewinsohn et al., 2017). Three samples should be collected; they should be collected in the morning and should be at least eight hours apart (Fitzpatrick et al., 2023). If a patient cannot produce enough sputum, sputum induction using 3% hypertonic saline should be done (Fitzpatrick et al., 2023). If this isn't successful, use flexible bronchoscopy to obtain a sample (Lewinsohn et al., 2017). If possible, the sputum sample should be collected while the patient is in an airborne isolation room, a sputum collection booth, or a well-ventilated area (CDC, 2021a).

2. Nucleic acid amplification (NAA): A NAA test detects TB deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) in a respiratory secretion sample (CDC, 2021a; Lewinsohn et al., 2017). The Clinical Practice Guidelines of the ATS, ISDA, and CDC recommend that an NAA test be done in all patients suspected of having TB (Lewinsohn et al., 2017).

- The NAA test that is commonly used, the Xpert *M. tuberculosis* complex and resistance to rifampin (MTB/RIF) assay, has an overall sensitivity of 85%; 98% if the AFB smear is positive and 70% if the AFB smear is negative (Raviglione & Gori, 2022): The specificity is 98%. The results are available in < 2 hours (CDC, 2021a; Fitzpatrick et al., 2023; Raviglione & Gori, 2022).
- If the AFB smear is positive, a negative NAA test indicates that it's unlikely the patient has a TB infection (Lewinsohn et al., 2017).
- Suppose the AFB smear is negative; there is an intermediate to high suspicion that the patient has a TB infection. A positive NAA test can be considered presumptive evidence of TB infection (Lewinsohn et al., 2017).
- A negative NAA test cannot exclude the possibility that a patient has TB (Lewinsohn et al., 2017).
 - Rapid detection of TB is beneficial in many ways, such as earlier initiation of treatment, improved outcome, earlier detection of drug-resistant TB, interruption/reduction of transmission by way of early identification of infected persons, earlier use of infection control techniques like respiratory isolation, and better contact tracing (CDC, 2021a).

3. Culturing: The definitive diagnosis of TB depends on the identification of *M. tuberculosis* by culturing (Fitzpatrick et al., 2023; Raviglione & Gori, 2022). The drawback to culturing is that it takes four to eight weeks until there is sufficient growth of the bacterium to detect/identify it (Raviglione & Gori, 2022). (Note: Newer methods that provide results much faster are available, but these tests are unavailable in the US).

Diagnosis of Latent Tuberculosis

Routine Evaluation for Risk

As a part of routine primary care, all patients, adults, and children should be evaluated for the presence of risk factors for *M. tuberculosis* exposure or for the risk of latent TB reactivation (National Society of Tuberculosis Clinicians [NSTC], 2021; Shah & Dorman, 2021).

Screening Healthcare Personnel

In the US, the incidence of TB in healthcare personnel is similar to the incidence of TB in the general population (Sosa et al., 2019). The CDC's and the National Tuberculosis Controllers Association's (NCTA) recommendations for TB testing in healthcare personnel are listed in Table 2.

Table 2: Recommendations for Tuberculosis Screening of US Healthcare Personnel

TB screening with an individual risk assessment and symptom evaluation at baseline (preplacement)
Interferon-gamma release assay (IRGA) test or tuberculin skin test (TST) if there is no documentation of prior TB disease or latent TB infection
Routine, serial TB testing after baseline testing is not recommended if there is no known exposure to or ongoing transmission of TB
Personnel who have latent TB should be encouraged to receive treatment
Annual screening for personnel who have untreated latent TB
Annual TB education for all healthcare personnel
(Sosa et al., 2019)

Testing for Latent Tuberculosis: Who Should Be Tested?

Testing for latent TB should be done if the patient has a medical condition and a social situation that significantly increases the risk of developing TB infection or latent TB reactivation (NSTC, 2021; Shah & Dorman, 2021). These medical conditions and social factors are listed in Table 3.

Table 3: High-Risk Factors for Tuberculosis Infection and Latent Tuberculosis Reactivation

Birth or residence in a country with a medium to high incidence of TB
Close contact with someone who has TB
Immunosuppression: A medical condition like HIV or immunosuppression from medical treatment, <i>e.g.</i>, drugs that suppress immune system function, immunosuppressive drugs given to an organ transplant patient, or chemotherapy drugs
Recent TB infection
(NSTC, 2021; Shah & Dorman, 2021)

Other medical conditions increase the risk of TB infection or the risk of latent TB reactivation (NSTC, 2021; Shah & Dorman, 2021). These are considered moderate risk factors (NSTC, 2021; Shah & Dorman, 2021), and testing should be considered if one or more of these factors is present (NSTC, 2021; Shah & Dorman, 2021).

"Having one or more of these conditions without a history suggestive of TB exposure is not an independent reason for being tested.... However, testing may be indicated for other reasons—for example, infection control at a hemodialysis center or local epidemiology showing an association between a condition and TB disease" (NSTC, 2021).

Table 4: Moderate Risk Factors for Tuberculosis Infection and Latent Tuberculosis Reactivation

Cancer of the head or neck
Chronic kidney disease
Diabetes mellitus
End-stage renal disease
Intestinal bypass or gastrectomy
Leukemia or lymphoma
Silicosis
Smoking, current or former
(NSTC, 2021)

People who have been homeless, incarcerated, and who have been employed in a correctional facility may have an increased risk of exposure to TB (NSTC, 2021). The U.S. Preventive Services Task Force (USPSTF) recommends screening at-risk populations for latent TB, including persons who live in or have lived in high-risk congregate settings such as homeless shelters and correctional facilities (USPSTF, 2016). The USPSTF recommends that clinicians check with local or state health departments to see if they (the clinicians) may be caring for at-risk populations (USPSTF, 2016).

Testing Methods for Latent Tuberculosis

The IRGA assay and the TST are used to test for latent TB (Lewinsohn et al., 2017; NSTC, 2021; Shah & Dorman, 2021), but these tests cannot provide direct microbiologic evidence of a TB infection (Shah & Dorman, 2021). The IRGA assay and the TST detect an immune response to antigens. The TST uses an intradermal injection of purified protein derivatives (PPD) of the bacterium that acts as an antigen, and the IRGA uses synthetic peptides that resemble the *M. tuberculosis* protein and act as antigens. The peptides are added to a blood sample, and an immune response does or does not occur (Mazurek et al., 2010).

The IRGA assay is the preferred test, but the TST can be used (Lewinsohn et al., 2017; NSTC, 2021). There are differences between the two in terms of cost, convenience, and interpretation of the results; clinicians should know and understand them. One of the most important differences involves the TST and Bacillus Calmette–Guérin (BCG) vaccination. The BCG vaccine is a live vaccine that can prevent TB infection and is widely used in other parts of the world. A BCG vaccination can cause a false-positive TST, but this does not happen with the IRGA assay (NSTC, 2021; Shah & Dorman, 2021).

Neither the IRGA assay nor the TST can distinguish between latent TB and active infection (Shah & Dorman, 2021), and in addition:

1. The IRGA assay and the TST cannot be used to monitor the effectiveness of treatment (NSTC, 2021; Shah & Dorman, 2021).
2. A positive IRGA assay and the TST cannot predict the development of active infection (NSTC, 2021).
3. A negative IRGA assay or a TST cannot be used to exclude the presence of active TB in a patient with signs and symptoms of the disease (NSTC, 2021).
4. False negatives and false positives of the IRGA and TST occur (NSTC, 2021).

HIV Infection and Testing for Latent Tuberculosis

For patients living with HIV, the risk of latent TB reactivation is 30–50% (Keramat et al., 2020). Identifying HIV-infected patients who have TB is critically important, but using the IRGA assay or the TST is problematic in this situation. The IRGA assay and the TST depend on the patient's immune response to provide a result, and in immunosuppressed patients – like a patient living with HIV – immunosuppression may result in a false negative (NSTC, 2021). Behr et al. (2021) note that the IRGA and the TST are neither 100% sensitive nor specific and ". . . a negative TST/IGRA test is observed in 10–40% of HIV-negative individuals with culture-confirmed pulmonary TB . . ." (Behr et al., 2021). In addition, the accuracy of these tests decreases as the cluster of differentiation (CD) cell count decreases (Mthembu et al., 2023; NSTC, 2021).

Every patient who is living with HIV should be tested for latent TB (NSTC, 2021). If a patient's test is negative and their CD cell count is < 200 cells/mm³, and they have a significant risk for progression, *e.g.*, close contact with someone who has TB infection, the test should be repeated when the CD cell count is > 400 cells/mm³ (NSTC, 2021).

Simultaneous testing with an IRGA assay and TST increases the sensitivity of detecting infection (NSTC, 2021). With dual testing, ". . . a positive result from either test is taken as evidence of *M. tuberculosis* infection" (NSTC, 2021).

If a patient has no signs and symptoms of TB, the CXR is normal, and if the IRGA or the TST is positive, the patient does not have active TB; they have latent TB (NSTC, 2021).

Drug-Resistant Tuberculosis

Drug-resistant TB is caused by *M. tuberculosis* organisms that anti-tubercular drugs cannot eliminate. Drug-resistant TB is transmitted like drug-susceptible TB and is not more infectious than drug-susceptible TB (CDC, 2021a). Drug-resistant TB is uncommon in the US population (CDC, 2021b). In 2020, there were 56 cases of multidrug-resistant (MDR) TB at the initial diagnosis of TB, most being in non-US-born persons (CDC, 2021b). One extensively drug-resistant (XDR) TB case was reported in the US in 2020 (CDC, 2021b).

There are two types of drug-resistant TB, MDR-TB, and XDR-TB (CDC, 2021a). MDR-TB is caused by *M. tuberculosis* that is resistant to Isoniazid (INH) and rifampin (CDC, 2021a). XDR-TB is caused by *M. tuberculosis* that is resistant to INH, rifampin, all the fluoroquinolones, and at least one of the three second-line injectable drugs that include amikacin, capreomycin, and kanamycin (CDC, 2021a).

Drug-resistant TB occurs in primary and secondary ways (CDC, 2021a).

Primary drug-resistant TB is caused by person-to-person transmission of the drug-resistant bacterium (CDC, 2021a).

Secondary drug-resistant TB occurs during the treatment of drug-resistant TB, and there are multiple reasons why this can happen (CDC, 2021a). The reasons include the following:

- The patient did not receive the correct drug regimen.
- The patient did not take the anti-tubercular drugs correctly.
- Drug-drug interactions negatively impacted the effectiveness of the anti-tubercular drugs, *e.g.*, decreased serum drug levels.
- Malabsorption of the anti-tubercular drugs.

The risk of developing drug-resistant TB increases if the following situations occur (CDC, 2021a):

- Exposure to someone who has drug-resistant TB
- Exposure to someone who has TB, who has previously been treated and had a treatment failure or relapse, and the results of their drug-susceptibility test are unknown
- Exposure to someone from an area in which drug-resistant TB is common
- Exposure to someone with positive smear and cultures after two months of treatment

Patients with risk factors for drug-resistant TB and a positive AFB smear or a positive NAA test should be tested for drug-resistant TB (CDC, 2021a).

If the initial susceptibility test of a sputum sample confirms that the patient has a strain of *M. tuberculosis* that is resistant to rifampin, molecular drug-resistant testing should be done (CDC, 2021a). Molecular drug-resistant testing uses DNA sequencing to detect TB mutations resistant to the first-line and second-line anti-tuberculars and drugs repurposed to treat TB (CDC, 2022b).

Treatment of Active Tuberculosis

Basic Issues: Public Health, Location of Treatment, Infection Control

- All suspected and confirmed TB cases should be promptly reported to local and state public health authorities (Fitzpatrick et al., 2023).
- Patients who are being treated for active TB do not need to be hospitalized unless:
 1. they may expose new, susceptible people,
 2. they cannot do self-care,
 3. they have a serious ongoing illness, or
 4. they need a diagnostic procedure (Fitzpatrick et al., 2023; Nardell, 2022a).
- Infection control in the home: A patient who has or is presumed to have TB should:
 1. sleep alone and should not sleep in the same room with another person,
 2. cover their mouth when they cough and sneeze, and
 3. not have visitors until they (the patient) are non-infectious (CDC, 2021a). Healthcare professionals who visit the patient should wear an N95 respirator or its equivalent. If they are collecting a specimen, this process should be done away from other people and in a well-ventilated area (CDC, 2021a).
- Infection control in a hospital or other healthcare setting: Preventing TB transmission in hospitals and other healthcare settings is complex, and a full discussion is not provided here. The primary issues of infection control and TB that clinicians must know are:

1. TB is transmitted by the respiratory route,
 2. patients who have TB must be in an airborne infection isolation room, and
 3. healthcare personnel and anyone having close contact with an infected patient must use standard precautions, airborne precautions, respiratory precautions, and use personal protective equipment (PPE) as directed (CDC, 2021a; Jensen et al., 2005).
- Treating a patient who has TB and is living with HIV is complicated, and experts in TB and HIV should be consulted (Fitzpatrick et al., 2023).

Drug Therapy

Multiple treatment regimens are used to treat active TB (CDC, 2023b; CDC, 2021a; CDC, 2016b; Fitzpatrick et al., 2023; Nardell, 2022b). The regimens are of different durations, use specific drug combinations, and differ in dosing amounts and frequency (CDC, 2023b). The appropriate regimen for a patient depends on multiple factors, such as:

- Coexisting medical conditions
- Drug-drug interactions
- Drug-susceptibility (CDC, 2023b; CDC, 2016b)

The drugs that are typically considered first-line medications for the treatment of TB and are part of many of the commonly used drug regimens are ethambutol, INH, Pyrazinamide, and rifampin (Nardell, 2022b). These drugs and other commonly used drugs are listed below.

- Ethambutol is an oral anti-tubercular drug; its primary mechanism of action is inhibiting the synthesis of the *M. tuberculosis* cell wall (Drew, 2022a).
- INH is an oral antitubercular drug. It has a bactericidal action and inhibits the synthesis of the *M. tuberculosis* cell wall (Drew, 2021a).
- Moxifloxacin is a fluoroquinolone antibiotic. It can be given IV or orally, has bactericidal activity, and inhibits DNA replication and transposition (Hooper, 2023).
- Pyrazinamide is an oral antitubercular drug (Drew, 2021b). The mechanism of action by which it functions as an anti-tubercular is unknown (Drew, 2021b).
- Rifampin is an anti-tubercular drug that can be given IV or orally. Rifampin inhibits *M. tuberculosis* RNA synthesis (Drew, 2022b).
- Rifapentine is an oral antitubercular drug. Rifapentine has a bactericidal action, inhibiting DNA-dependent RNA polymerase in *M. tuberculosis* (Drew, 2022b).
- Bedaquiline is an oral anti-tubercular drug that disrupts the activity of adenosine triphosphate (ATP) synthase, specifically in *M. tuberculosis* bacilli (Deshkar & Shirure, 2022).
- Pretomanid is an oral antibacterial and anti-tubercular drug. Pretomanid inhibits the synthesis of the *M. tuberculosis* cell wall (Occhinieri et al., 2022).
- Linezolid is an oxazolidinone antibiotic, and it is given orally as a treatment for drug-resistant TB (Hashemian et al., 2018).

Administering Anti-tuberculars: General Considerations

Drug regimens for TB treatment can be complex; memorizing them would be impractical and unnecessary: There are many easily accessed sources for this information, like the CDC. However, in the next section, as an example, a drug-susceptible TB drug regimen is explained.

What is practical and needed is knowing how the anti-tubercular drugs should be administered to achieve maximum effectiveness.

- Pre-treatment testing: Before beginning drug therapy for a patient with active TB, these tests should be done (CDC, 2021a).
 1. Alkaline phosphatase, bilirubin, serum creatinine, serum transaminases, HIV serology testing, and glycated hemoglobin (HbA1c). Hepatic and renal function should be assessed because some anti-tubercular drugs are cleared by the kidneys, so dosing adjustments may be needed if the patient has compromised/impaired renal function. Baseline hepatic function is assessed because TB can cause abnormal liver function tests, and some anti-tubercular drugs can cause drug-induced hepatitis and other forms of liver injury (LiverTox, 2018a; LiverTox, 2018b).
 2. Do serology testing for patients at risk of being infected with hepatitis B or C.
 3. Patients who will be taking ethambutol: Test their visual acuity by using a Snellen chart and test for the presence of color blindness by using the Ishihara test.
 4. If the patient lives with HIV, measure a CD4+ lymphocyte count.
- Drug Susceptibility Testing (DST): Testing for drug susceptibility of the *M. tuberculosis* bacterium is done by molecular and or phenotype testing of a respiratory sample (CDC, 2023b; Zhu et al., 2021). The CDC recommends that molecular and phenotype testing of a respiratory sample should be done at baseline (CDC, 2023b). This topic will be discussed further in the section on drug-resistant TB.
- Directly observed therapy (DOT): DOT for TB patients is the direct observation by a healthcare worker of the patient ingesting anti-tubercular drugs (Fitzpatrick et al., 2023). Nonadherence to an anti-TB drug regimen is a major cause of treatment failure (Fitzpatrick et al., 2023). Nonadherence can cause a relapse of TB, drug resistance, and transmission of TB (CDC, 2021a). DOT can significantly increase adherence (Nardell, 2022b), and the CDC recommends in-person or video conference DOT (CDC, 2021a; Managan et al., 2023). In addition to ensuring patient compliance, DOT is also used to monitor for adverse drug effects and to provide social support for patients (Managan et al., 2023). DOT is particularly important for these patients and in these situations (CDC, 2016b; Fitzpatrick et al., 2023; Nardell, 2022b):
 - Children and adolescents
 - Patients living with HIV
 - Patients who have a psychiatric illness and a substance use disorder
 - Patients who are taking anti-tubercular drugs < seven days a week
 - After treatment failure, relapse, or development of drug resistance
- Therapeutic drug monitoring (TDM): "There are no prospective randomized trials that clearly define the role of TDM for anti-TB drugs. As such, opinions vary regarding the utility of TDM" (CDC, 2021a).
- Evaluation/monitoring during drug therapy: Evaluate patients at least once a month. The evaluation determines if the patient is complying with the prescribed drug regimen and identifies adverse drug reactions (CDC, 2021a). Example: Patients taking ethambutol for > 2 months or taking > 15–20 mg/kg of ethambutol should be examined for visual disturbances (CDC, 2021a).
- Treatment interruptions: Interruptions in treatment, *i.e.*, the patient stops taking the drugs, can have serious consequences such as acquired drug resistance, longer treatment times, relapse of TB, suboptimal drug concentrations, and treatment failure (Mangan et al., 2023). There are established guidelines for handling this situation during the initiation and continuation phase of TB drug treatment (CDC, 2021a).

Drug Therapy Regimens

The four basic categories of TB drug regimens for active TB are:

1. Drug-susceptible TB
2. Patients living with HIV
3. Drug-resistant TB
4. Pregnant patients

A TB drug therapy regimen has two phases, initiation and continuation (CDC, 2021a).

The initiation phase is usually several months long and is intended to kill active, growing TB microorganisms (CDC, 2021a). This phase is crucially important as it can prevent the emergence of drug-resistant *M. tuberculosis* (CDC, 2021a).

The continuation phase is typically at least two to three times as long as the initiation phase and sometimes longer. The continuation phase is intended to kill any *M. tuberculosis* bacilli that remain after the initiation phase and prevent treatment failure or relapse of the disease (CDC, 2021a). In some clinical situations, the continuation phase is continued past the standard cutoff point (CDC, 2021a).

1. Drug-susceptible TB: There are three treatment regimens for drug-susceptible active TB: four-month, six-month, and nine-month (CDC, 2023b; CDC, 2021a).
 - Four-month: The four-month regimen uses high-dose rifapentine, INH, moxifloxacin, and Pyrazinamide.
 - The initiation phase is eight weeks long, and the patient takes high-dose rifapentine, INH, moxifloxacin, and Pyrazinamide daily; the total number of doses is 56.
 - The continuation phase is nine weeks long, the patient takes high-dose rifapentine, INH, and moxifloxacin daily, and the total number of doses is 63.
 - The regimen is used for patients 12 years or older who weigh ≥ 40 kg and have drug-susceptible TB (Carr et al., 2022).
 - The four-month regimen is preferred for patients newly diagnosed with primary TB (CDC, 2023b).
 - The four-month regimen is contraindicated in these situations (Carr et al., 2022).
 - Age < 12 years.
 - Body weight < 40 kg.
 - Concurrent use of a drug/drugs that can prolong the QT interval, in addition to moxifloxacin.
 - History of prolonged QT syndrome.
 - Most types of extrapulmonary TB.
 - Patients who are infected at baseline with an *M. tuberculosis* isolate that is or is suspected to be resistant to INH, fluoroquinolones, Pyrazinamide, or rifampin.
 - Women who are pregnant or breastfeeding.
 - Six-month and nine-month: The six-month and nine-month regimens use ethambutol, INH, Pyrazinamide, and rifampin (CDC, 2023b). The initiation phase is eight weeks long. The patient takes ethambutol, INH, Pyrazinamide, and rifampin, the patient takes the drugs every day, five days a week, or three times a week, and the total number of doses is 24, 40, or 56 (CDC, 2023b). The continuation phase is four to seven months. The patient takes INH and rifampin, the dosing frequency can be twice a week, three times a week, or every day, and the total number of doses is 62 to 182 (CDC 2023b).

2. Patients living with HIV: There are two treatment regimens for patients with HIV who have drug-susceptible TB (CDC, 2023b).
 - Six months or nine months: The patient takes a rifamycin, ethambutol, INH, and Pyrazinamide in the initiation phase and INH and a rifamycin in the continuation phase (CDC, 2023b).
 - Four-month: Based on the results of a randomized, controlled trial, the CDC recommends a four-month drug regimen as a treatment for patients who are living with HIV and who have drug-susceptible TB (Carr et al., 2022). The four-month regimen was as effective as a six-month regimen and safe. The four-month regimen is an initiation phase, eight weeks of INH, moxifloxacin, Pyrazinamide, and rifapentine, orally, taken once a day, every day. The continuation phase is nine weeks, and the patient takes INH, moxifloxacin, and rifapentine, once a day every day. The regimen can be used for patients who are ≥ 12 years of age and who have drug-susceptible pulmonary TB (Carr et al., 2022).
 - The four-month regimen can be used for people living with HIV "... who have CD4 counts ≥ 100 cells/ μ L and are receiving or planning to initiate efavirenz as part of their antiretroviral therapy (ART) regimen in the absence of any other known drug-drug interactions between anti-TB and antiretroviral medications (Carr et al., 2022).
 - It is prudent to consult a clinician with expertise in TB before using this regimen (Carr et al., 2022).
3. Drug-resistant TB: These recommendations are from the ATS, the CDC, the European Respiratory Society (ERS), and the IDSA (Nahid et al., 2019).
 - If a patient has or is suspected that they have drug-resistant TB, and the potential for drug-resistant TB should always be a consideration, an expert in TB should be consulted. The CDC or a local health department can provide clinicians with contact information for CDC-supported TB Centers of Excellence, and these centers can help clinicians locate a TB expert (Nahid et al., 2019).
 - A molecular DST should be done to rapidly detect mutations that can cause drug resistance. If the *M. tuberculosis* bacilli are resistant to rifampin, additional DSTs should be done to determine if there is resistance to aminoglycosides and fluoroquinolones (Nahid et al., 2019).
 - At least five drugs should be used during the initiation phase and four drugs in the continuation phase (Nahid et al., 2019).
 - The initiation phase should be five to seven months after culture conversion (Nahid et al., 2019). Culture conversion means that the patient's sputum culture was positive before treatment, and after beginning therapy, the culture became negative (CDC, 2023c).
 - The continuation phase is eight to 16 months, and the total duration of treatment should be 15 to 21 months after culture conversion (Nahid et al., 2019). If the patient has pre-XDR-TB, the total treatment time after culture conversion should be 15 to 24 months (Nahid et al., 2019).
 - A sputum culture should be done at least once a month during treatment, and if cultures remain positive after three months of treatment, a DST should be redone (Nahid et al., 2019). Monthly evaluation for other signs of response to treatment and adverse drug effects should also be performed (Nahid et al., 2019).
4. Pregnant patients: The preferred drug regimen for a pregnant patient with TB is ethambutol, INH, and rifampin for two months, followed by INH and rifampin for seven

months (CDC, 2023b; CDC, 2021a).

- INH can cause peripheral neuropathy, and pregnancy may increase the risk of this adverse effect (Drew, 2021a). Pregnant patients should take pyridoxine (vitamin B6) supplementation (CDC, 2023b); this applies to patients who are breastfeeding, as well (CDC, 2021a).
- Amikacin, capreomycin, fluoroquinolones, kanamycin, and streptomycin are contraindicated if a patient is pregnant (CDC, 2023b), and Pyrazinamide is not recommended (CDC, 2023b; CDC, 2021a). If a pregnant patient has drug-resistant TB, a TB expert should be consulted, and the patient should be warned that the second-line TB drugs can or may be harmful to the fetus (CDC, 2023b; CDC, 2021a).
- Pregnant patients can breastfeed (CDC, 2023b; CDC, 2021a): The amounts of first-line TB drugs excreted in breast milk are very small (CDC, 2023b). Rifampin can cause breast milk to be orange (CDC, 2023b).

Treatment of Latent Tuberculosis

Basic Principles of Treatment

Basic principles of treatment for latent TB include the following (CDC, 2021a; NSTC, 2021; Shah & Dorman, 2021):

- The presence of active TB must be ruled out before starting drug therapy.
- The medical evaluation done before treatment should assess the patient for the presence of these signs and symptoms (NSTC, 2021).

Table 5: Pre-Treatment Evaluation, Signs, and Symptoms

Chest pain
Fatigue
Fever or chills
Hemoptysis
Loss of appetite
Night sweats
Prolonged cough (> two–three weeks)
Unintended weight loss
(NSTC, 2021)

A CXR should be done (NSTC, 2021). The type/types of CXR that should be done – posterior–anterior only, posterior–anterior, and lateral – depend on patient characteristics (NSTC, 2021). Treatment should only be done if no radiographic findings suggest or confirm the presence of active TB (NSTC, 2021).

Baseline laboratory studies that assess the hematologic status and hepatic function should be done if the patient is at risk for hepatic impairment or an immunocompromised state (NSTC,

2021). Testing for the presence of HIV should be done if the patient's HIV status is unknown, and serologic testing for hepatitis A, B, and C should be done if there is a need (NSTC, 2021).

Evaluate the benefits and risks of treatment and determine if the patient has pre-existing medical conditions that would be a contraindication to treatment. Drug-drug interactions could occur between medications the patient is taking and anti-tubercular drugs. The patient's pregnancy status should be determined.

Who Should be Treated?

1. Patients with latent TB, as determined by a positive blood test or a TST reaction ≥ 5 mm and with any of these conditions/risk factors (CDC, 2021a):
 - Fibrotic changes on a CXR
 - Organ transplant
 - People living with HIV
 - Prolonged immunosuppressive therapy – corticosteroids ≥ 15 mg/kg a day or anyone taking TNF- α antagonists
 - Recent contact with someone who has infectious TB
2. Patients who have latent TB as determined by a positive blood test or a TST reaction ≥ 10 mm and who have any of these conditions/risk factors (CDC, 2021a).
 - Children < 5 years of age, infants, and adolescents exposed to an adult at high risk of having TB
 - Drug abuse
 - Employment in a mycobacterial laboratory
 - People who were born in a country where TB is common
 - People who have lived or now live in a high-risk congregate setting (correctional facility, homeless shelter, nursing home)
 - People who have a medical condition that increases the risk of developing TB, *e.g.*, certain cancers, diabetes mellitus, low body weight (< 90% of ideal weight), silicosis, and severe kidney disease
3. People with latent TB as determined by a positive blood test or a TST reaction ≥ 15 mm and without known risk factors (CDC, 2021a).
4. Persons living with HIV who have had contact with someone with latent TB should be treated, regardless of their blood test or TST results (CDC, 2021a). "Treatment can be discontinued if the second blood test or TST result is negative and 8–10 weeks have passed since the last exposure to someone with infectious TB disease. However, HIV-infected persons might be anergic (*i.e.*, there is impairment in cell-mediated immune responsiveness to stimulation by an antigen) and thus unable to manifest a positive blood test or TST result even if infected. In these instances, medical providers might prescribe a complete course of treatment, even if the second blood test or TST result is negative, particularly if the exposure to TB is substantial (*e.g.*, prolonged, frequent exposure to a patient with highly infectious TB disease)" (CDC, 2021a).

Drug Therapy Regimens

For latent TB, the CDC and the NSTC preferentially recommend short-course, rifamycin-based 3- or 4-month treatment regimens (CDC, 2020; NSTC, 2021).

The NSTC recommends short-course regimens that include rifampin or rifapentine; regimens that only use INH are alternatives (NSTC, 2021).

There are three preferred regimens: 3HP, 4R, and 3HR. The 3HP and 4R have the strongest recommendation, and the 3HR has a conditional recommendation because it may cause hepatic damage (NSTC, 2021).

- 3HP: INH and rifapentine, once a week for three months.
- 4R: Rifampin once a day for four months.
- 3HR: INH and rifampin, once a day for three months.

Longer regimens of six-month or nine-month duration can be used, but they have an inferior completion rate and a higher risk of hepatotoxicity compared to the shorter duration regimens (CDC, 2021a; NSTC, 2021). The nine-month treatment regimen (INH once a day or twice a week) ". . . is probably more efficacious and is commonly recommended for patients who are immunosuppressed, tolerating treatment at six months, and willing to continue (NSTC, 2021). No single regimen is the best choice for all patients. Each patient must be evaluated based on individual characteristics, some of which may influence the choice of regimens" (NSTC, 2021).

Patients Living with HIV

Treatment of a patient who is living with HIV and who has latent TB should be done with consultation with a clinician who has expertise in managing this situation (CDC, 2021a).

The drug regimens that can be used to treat patients living with HIV and who have latent TB are the 3HP, 4R, 3HR, and a nine-month regimen of INH, taken once a day (CDC, 2023d; CDC, 2021a).

- 3HP: INH and rifapentine, once a week for three months (CDC, 2021a; CDC, 2023d). This regimen is recommended for patients who are living with HIV and who are taking antiretroviral medications and if there are . . . acceptable drug-drug interactions with rifapentine, such as efavirenz or raltegravir (CDC, 2023d; CDC 2021a). Rifapentine should not be used for HIV-infected patients who are taking antiretroviral drugs that have a significant drug-drug interaction with rifapentine or antiretroviral drugs for which the drug-drug interaction with rifapentine is not known (CDC, 2023d; CDC, 2021a).
- 4R: Patients who cannot tolerate INH or have been exposed to INH-resistant *M. tuberculosis* can be treated with rifampin once a day for four months (CDC, 2023d; CDC, 2021a). If rifampin cannot be used, rifabutin is an acceptable substitute (CDC, 2023d; CDC, 2021a).
 - Rifampin should not be used if the patient takes integrase strand transfer inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, or maraviroc. "Given the theoretical risks of rifamycin monotherapy in undiagnosed early-stage TB disease and the relatively poor performance of symptom screens alone in HIV-infected patients, clinicians may consider performing a sputum culture before starting the 4R treatment regimen. Chest radiography should be evaluated to ensure there is no radiographic evidence of abnormalities that could be consistent with TB disease" (CDC, 2021a).
- 3HR: The 3HR regimen consists of INH and rifampin once daily for three months.

Drug-drug interactions between the anti-tubercular drugs used in these regimens and the antiretroviral medications a patient takes can be clinically significant. The issue was briefly mentioned, and clinicians should refer to the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV for up-to-date information about antiretroviral medications and drug-drug interactions.

DOT is recommended for all HIV-positive TB patients (CDC, 2023d). Pyridoxine (vitamin B6), 25–50 mg orally daily, should be administered to patients at risk of developing INH-induced

peripheral neuropathy, *e.g.*, patients living with HIV (Nahid et al., 2016).

Pregnant Patients

Pregnant women should be screened to determine if they have risk factors for latent TB (NCTA, 2021a), and they should be tested for the presence of TB only if they have risk factors (NCTA, 2021). If a patient has a positive IRGA test or TST, a medical evaluation, including a CXR, should be done. The timing of when to do a CXR varies. For details on this topic, see the NSTC's publication, "Testing, and Treatment of Latent Tuberculosis Infection in the United States: Clinical Recommendations."

For many pregnant women, treatment of latent TB can begin during the postpartum period (CDC, 2021a); this is preferable because during pregnancy and in the first two to three months of the postpartum period, there is an increased risk of drug-induced hepatotoxicity (CDC, 2021a).

If a pregnant woman with latent TB has a high risk of developing active TB, drug therapy should be started immediately, even during the first trimester (CDC, 2021a).

The drug regimens that can be used for pregnant women who have latent TB include the following (CDC, 2021a; NSTC, 2021):

- 3HR: INH and rifampin, once a day for three months.
- 4R: Rifampin, once a day for four months.
- A six-month or nine-month regimen of once-a-day INH.

The 3HP regimen is not recommended for pregnant women or women who might become pregnant while taking the 3HP regimen; there is insufficient information about its safety during pregnancy (CDC, 2021a; NSTC, 2021).

INH can cause peripheral neuropathy; pregnancy may increase the risk of this adverse effect, and pregnant women taking INH should take pyridoxine as a prophylactic (CDC, 2021a; Drew, 2021a; NSTC, 2021).

Breastfeeding can be done safely if the mother is taking any of the approved drug regimens (NSTC, 2021). The infant does not need pyridoxine supplementation unless the infant is being given INH (NSTC, 2021).

"Some studies have shown an increase in hepatotoxicity in the first three months postpartum in women taking INH...; however, no studies have been done on the tolerance of other regimens given in the postpartum period" (NSTC, 2021). The NCTA states that during pregnancy and in the postpartum period, laboratory monitoring of a patient's hepatic function should be considered if a patient is taking INH (NSTC, 2021).

Bacille Calmette–Guérin Vaccine

The BCG vaccine is used to prevent TB (CDC, 2016a). The BCG vaccine is commonly used in countries with a high TB prevalence (CDC, 20216c), and its primary use is to prevent childhood TB meningitis and miliary TB (CDC, 2016a). Vaccination with BCG is ineffective at preventing adult TB, latent TB, or TB in adults with many common morbidities (Flores–Valdez et al., 2022; Singh et al., 2022; Yadav et al., 2023).

Vaccination with BCG is recommended for children who have a negative TST and who are continually exposed to, and cannot avoid contact with, adults who are not being treated with TB, adults who are being ineffectively treated, or who have INH- or rifampin-resistant TB (CDC,

2016a). Because TB is relatively uncommon in the US, routine BCG vaccination is not recommended (CDC, 2016a).

Vaccination with BCG is recommended on a case-by-case basis for healthcare workers in situations such as caring for a high number of patients who have INH- and rifampin-resistant TB, ongoing transmission of drug-resistant *M. tuberculosis* to healthcare workers, or TB infection control techniques have not been successful (CDC, 2016a). The BCG vaccine is contraindicated in immunosuppressed patients or patients who may become so and in pregnant patients (CDC, 2016a).

Patient Monitoring During Treatment

Note: Monitoring for adverse drug effects is discussed in this section. Adverse drug effects are discussed in more detail in the next section of the module.

Active Tuberculosis

Patients receiving drug therapy for the treatment of active TB should be clinically evaluated at least once a month (CDC, 2021a). The clinical evaluation should focus on two issues:

1. the patient's response to and adherence to drug therapy and
 2. monitoring for adverse drug effects (CDC, 2021a).
1. Patient response to therapy is made by a clinical examination, bacteriologic examination, and radiographic examination, *i.e.*, CXR (CDC, 2021a).
 - The clinical examination should focus on the presence (or absence) of signs and symptoms that indicate that the drug therapy is or is not working and if the patient is adhering to the drug regimen.
 - "If a patient's symptoms do not improve during the first two months of treatment or if symptoms worsen after initial improvement, the patient should be evaluated for nonadherence to, or malabsorption of, the treatment regimen; development of drug resistance; or symptoms consistent with immune reconstitution" (CDC, 2021a).
 - Routinely monitoring the liver, renal function, or platelet counts for patients treated with "first-line anti-TB drugs is unnecessary unless abnormalities are detected at baseline or clinical reasons exist for obtaining measurements. Patients with stable hepatic or renal function abnormalities at baseline should have repeat measurements early in the treatment course, then less frequently to ensure conditions have not worsened" (CDC, 2021a).
 - The bacteriologic examination is done by examination of a sputum culture (CDC, 2021a). The CDC Core Curriculum on Tuberculosis has information about when and for whom a sputum culture should be done and the correct response to the sputum culture results.
 - Example: The patient had a positive sputum culture before treatment. A sputum culture should be done at least once a month until two consecutive specimens are negative (CDC, 2021a).
 - A CXR can be done after two months of treatment if the patient had a positive sputum culture before beginning treatment (CDC, 2021a), and a CXR should be done when treatment has been completed (CDC, 2021a). If the patient had a negative sputum culture before treatment, a CXR should be done after two months of treatment. A CXR after treatment is desirable (CDC, 2021a).
 - Follow-up after completion of therapy is usually unnecessary.

2. Monitoring for adverse drug effects should be done during every clinical evaluation. In addition, the patient's knowledge of adverse drug effects should be reinforced.
 - In particular, the clinician should make sure that the patient
 - knows the signs and symptoms of potentially serious adverse drug effects, *e.g.*, visual changes if the patient is taking ethambutol, and signs and symptoms of hepatotoxicity, and
 - knows what to do if these signs and symptoms occur, *e.g.*, when to stop taking the drug and when to call a healthcare professional.
 - Suppose a patient takes a dose of ethambutol > 15 mg to 20 mg/kg or has been taking ethambutol for > 2 months. In that case, their visual acuity and color vision should be checked once a month. Use a Snellen chart to check visual acuity and the Ishihara color vision test (CDC, 2021a).
 - The CDC's Core Curriculum has guidelines clinicians can use to determine when to discontinue some anti-tuberculars.
 - Example: The use of INH should be stopped if the serum transaminase levels are > three times the upper limit of normal and the patient is symptomatic or if they are > five times the upper limit of normal in an asymptomatic person (CDC, 2021a).
 - Treatment of active TB is complete when the total number of doses has been taken (CDC, 2021a). Follow-up is unnecessary if the patient responds well to a six-month or nine-month regimen. Patients who had drug-resistant TB should be followed for two years after treatment, and if the patient had resistance to INH or rifampin – but not both – follow-up evaluations should be done on a case-by-case basis (CDC, 2021a).

Latent Tuberculosis

Patients being treated for latent TB should be evaluated at least once a month, and the evaluation should include the following (NSTC, 2021).

1. A review of signs and symptoms that could indicate an adverse drug effect or TB (CDC, 2021a; NSTC, 2021).

Table 6: Clinical Monitoring during Treatment for Latent TB: Signs/Symptoms

Abdominal pain, especially right upper quadrant
Anorexia
Bruising (rifampin and rifapentine can cause thrombocytopenia)
Chills
Dark urine
Fever
Flu-like symptoms
Jaundice
Nausea

Paresthesia of the feet or hands
Rash
Vomiting
Weakness
Weight loss
(CDC, 2021a; NSTC, 2021)

- Adherence to the drug regimen (CDC, 2021a; NSTC, 2021). If a patient has not been following the dosing schedule, determine if they understand the importance of complying and the risk of missing doses and ask them why they have missed doses. Consider using a shorter drug regimen and DOT (NSTC, 2021).
- Routine laboratory testing of hepatic function is not needed for most patients who are being treated for latent TB (CDC, 2021a) unless their baseline transaminases are abnormally high, if they have signs and symptoms of hepatotoxicity, if they have continued heavy alcohol use, or if they are at risk for liver disease or hepatotoxicity (CDC, 2021a; NSTC, 2021).
- Monitor for adverse drug effects (CDC, 2021a, NSTC, 2021). During the periodic evaluations, clinicians should monitor patients for adverse drug effects. The NSTC has guidelines for when and for whom drug therapy should be stopped if there is evidence of drug-induced hepatic damage (NSTC, 2021).
 - Examples: Counsel all patients to immediately stop treatment and return to the clinic for evaluation if they develop symptoms of drug-induced hepatotoxicity. If the patient may have optic neuritis, discontinue the drug and consult an ophthalmologist (NSTC, 2021).
- Treatment is complete when the prescribed doses have been taken. Unless the clinician determines a need, no follow-up is needed once treatment is done (NSTC, 2021).

Adverse Effects

The first-line anti-tuberculars can cause many adverse effects; this module will discuss those frequently mentioned in published guidelines. Monitoring for adverse effects is important because adverse effects like hepatotoxicity are common to many anti-tuberculars; some, like visual defects caused by ethambutol, are serious. Adverse effects are a common reason patients stop taking the drugs (Akkerman et al., 2022).

- Ethambutol:** Ethambutol can cause optic neuropathy and defects in visual acuity and color vision (Srithawatpong et al., 2023). The incidence of optic neuropathy associated with the use of ethambutol has been estimated to be 0.5–2.25%, and even after the use of the drug has been stopped, the visual damage may be irreversible (Srithawatpong et al., 2023). Srithawatpong et al. (2023) and Sabhapandit et al. (2023) found that only 39.13% and 35.4% of patients fully recovered their vision after stopping ethambutol.
- INH:** The INH prescribing information contains a US Boxed Warning stating that INH can cause severe hepatitis and, occasionally, fatal hepatitis (Drew, 2021a). Temporary elevations of the serum transaminases occur in 10–20% of patients taking INH (CDC, 2021a; LiverTox, 2018a), but these will typically self-correct, even if therapy with INH continues (CDC, 2021a; LiverTox, 2018a). Acute liver injury has been reported to occur in

0.5–2.6% of all patients, and fatal hepatitis has occurred in 0.05–0.1% of all patients (CDC, 2021a; LiverTox, 2018a; Oscanoa et al., 2023). Pregnant women and women in the postpartum period, especially in the first two to three months, are at risk for developing clinical hepatitis from INH (CDC, 2021a). Peripheral neuropathy is a common adverse effect of INH. The neuropathy usually resolves with discontinuation of use and pyridoxine supplementation (Drew, 2021a).

- **Pyrazinamide:** Pyrazinamide can cause liver damage and even liver failure (Hussain et al., 2021), but because it is used concurrently with other anti-tuberculars that are also hepatotoxic, it is difficult to determine the level of risk of hepatic damage from this drug (Hussain et al., 2021). Pyrazinamide can cause increased serum uric acid levels and gout (Ben Salem et al., 2017). This appears to be a common adverse effect, but as this drug is typically used concurrently with ethambutol – which can also cause hyperuricemia and gout – determining the incidence of these adverse effects with the use of Pyrazinamide is difficult (Ben Salem et al., 2017).
- **Rifampin:** Rifampin will often cause mild and temporary elevations of serum transaminases (LiverTox, 2018b). Serious and clinically obvious liver damage, including fatal liver damage, can occur, but this is a rare adverse effect (LiverTox, 2018b). Rifampin and rifapentine have significant drug–drug interactions with many medications: There are at least 209 medications that are contraindicated for concurrent use with rifampin, and rifampin and rifapentine have drug–drug interactions with many commonly used medications like antihypertensives, oral contraceptives, and warfarin (CDC, 2021a). Rifampin and rifapentine can have drug–drug interactions with many of the medications that are used to treat patients who are living with HIV (CDC, 2021a). These three resources can be used to check drug–drug interactions between anti-tubercular drugs and antiretroviral medications:
 - [HIV Drug Interactions](#)
 - [Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV](#).
 - [Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis](#)
 -

Extrapulmonary Tuberculosis

The *M. tuberculosis bacterium* can infect any organ system (Chatterjee et al., 2021; Nardell, 2022a; Raviglione & Gori, 2022). Extrapulmonary TB is uncommon; it has been estimated that between 17–20% of all TB infections are extrapulmonary (Chatterjee et al., 2021). Extrapulmonary TB can occur in the bones, central nervous system/meninges, gastrointestinal tract, genitourinary tract, liver, lymph nodes (the most common site), pericardium, pleura, skin, and upper airways (Chatterjee et al., 2021; Manjate et al., 2019; Nardell, 2022a; Raviglione & Gori, 2022).

Miliary TB, aka disseminated TB, is caused by the hematogenous spread of *M. tuberculosis* (Nardell, 2022b; Raviglione & Gori, 2022), and miliary TB can be caused by a new infection or reactivation of latent TB (Nardell, 2022a; Raviglione & Gori, 2022). Children < four years of age, older adults, people who are immunocompromised or who have a medical condition like diabetes mellitus or end-stage renal disease that can impair immune system function, and people who are living with HIV have the highest risk of developing miliary TB (Nardell, 2022b). In most cases, the lungs and the bone marrow are affected by miliary TB (Nardell 2022b), but there are many other possible presentations (Ilyas et al., 2022; Nardell, 2022b; Raviglione & Gori, 2022).

The clinical presentation varies depending on the site of the infection (Nardell, 2022b; Raviglione & Gori, 2022). The diagnostic workup for extrapulmonary TB, aside from tests appropriate to the site of the infection, is the same for pulmonary TB: AFB smears of respiratory specimens and tissue specimens, CXR, NAAT, IRGA, and TST (Nardell, 2022a).

Patient Education

Patient education and counseling should be done before and during the treatment of TB, and education and counseling should be provided, as needed, to patients' families, caregivers, and acquaintances (Akkerman et al., 2022). Education and counseling can help patients adhere to the drug treatment regimen, identify and report adverse effects, and prevent transmission of TB (Akkerman et al., 2022).

The basic components of patient education would be essentially the same for all TB patients. However, structuring and delivering education and counseling should be done in an age-specific and gender-sensitive manner and the patient's preferred language and literacy level (CDC, 2016a; Akkerman et al., 2022). Education should include the following:

- The basics of TB: What TB is, how it is transmitted, and how it is treated.
- Infection control.
- Signs and symptoms of a TB relapse, what they are, and when to call the provider.
- The stigma of TB and self-esteem: The association of TB to certain populations, *e.g.*, people who are incarcerated, or someone who has a substance abuse disorder, can impart a stigma to someone who has TB and negatively affect their self-esteem. In addition, infectious diseases have long been associated with a negative stigma (Fischer et al., 2019).
- Adherence to drug regimens: Clinicians should identify issues that can or may prevent treatment adherence to the drug regimen (CDC, 2016a). It is critically important to recognize barriers to adherence, and it is critically important that patients understand that nonadherence can have serious consequences. In addition, patients should be advised to call the provider when doses of their anti-tuberculars are not taken.
- Factors that can or may be barriers to adherence include the following (Akkerman et al., 2022; Alipanah et al., 2018; CDC, 2016a):
 - Adverse drug effects
 - The complexity of the drug regimen
 - Duration of the drug regimen
 - Financial resources, *i.e.*, cost of treatment
 - Health beliefs and practices
 - Language barrier
 - Misinformation about TB
 - Real or perceived stigma of TB treatment
 - Social isolation
- Adverse drug effects: Patients should be informed about the adverse effects of anti-tubercular drugs (Akkerman et al., 2022; CDC, 2016a). Patients need to know what adverse effects are serious and when and whom they call about an adverse effect.
- Risk of alcohol and illicit drug use.
- If DOT is used, the patient should be educated about why this approach is necessary.

Summary

TB is an infectious disease caused by the *M. tuberculosis* bacteria. TB primarily affects the lungs, but it can infect and damage almost any organ. TB is the leading cause of death from infectious

diseases worldwide but is relatively uncommon in the US. TB is primarily transmitted by inhalation of infected droplets that are exhaled when an infectious person coughs, sneezes, or talks.

When infected droplets are inhaled, one of these situations can occur:

- The TB bacterium can be cleared from the body
- Primary progressive TB can occur. An infection can occur, and the patient can rapidly develop active TB
- A TB infection occurs; this is called primary TB
- The TB bacteria are contained, and the patient develops latent TB
- Latent TB reactivation

Approximately 5% to 10% of all persons infected with TB will eventually develop TB, and the risk of this is higher in patients who are immunocompromised or who have a comorbidity that negatively affects the immune system.

The signs and symptoms of TB are non-specific, *e.g.*, cough, fatigue, fever, malaise, and productive cough.

The diagnosis of TB depends on four criteria: Patient risk factors/index of suspicion, signs/symptoms, radiographic evidence, and bacteriologic evidence. Bacteriologic evidence of TB can be obtained by an AFB smear, a TST, an IRGA test, or culturing. Culturing is the definitive proof of a TB infection.

TB infections are drug-susceptible or drug-resistant. Drug-resistant TB is caused by *M. tuberculosis* organisms that anti-tubercular drugs cannot eliminate. There are two types of drug-resistant TB, MDR-TB and XDR-TB. Drug-resistant TB is uncommon in the US.

All suspected and confirmed TB cases should be promptly reported to local and state public health authorities.

Patients treated for active TB do not need to be hospitalized unless certain conditions are present. Hospitalized TB patients can transmit the disease, and infection control requires using an airborne infection isolation room, standard precautions, airborne precautions, respiratory precautions, and PPE.

With prompt identification of a TB infection and proper care, TB is easily cured. Treatment of TB is done by multi-drug regimens with an initiation and a continuation phase, and depending on the patient's circumstances, the treatment regimens can last at least four months or much longer. Every effort should be made to ensure patient adherence, including DOT, and there are guidelines for handling missed doses and treatment lapses. Adherence to the drug regimen is critically important, as treatment lapses can cause TB relapse, treatment failure, and other serious consequences.

At the minimum, patients receiving drug therapy to treat TB should be evaluated monthly. Clinicians should evaluate the patient's clinical condition, determine if the patient is adhering to the treatment regimen, and look for adverse effects like hepatotoxicity, peripheral neuropathy, and visual changes.

Case Studies

Case Study #1

A 45-year-old female who emigrated to the US from Southeast Asia six months ago visits a primary care clinic because she has had a headache and an occasional cough for the past three days. The patient states she has no chronic medical problems. She does not smoke, abuse alcohol, or use illicit drugs. She has a prior hysterectomy. She does not take any prescription medications, and aside from the headache and cough, she has been in good health. The patient states that she has never been tested for TB. She thinks – but is not sure – that close relatives with whom she lived with may have been treated for TB, and she does not know if she had been given the BCG vaccine when she was a child.

The nurse practitioner diagnoses the patient as having a stress headache and that the cough may be likely caused by mild reactive airway disease. She consults with an infectious disease specialist. The infectious disease specialist notes that the patient has been living in an area where TB is endemic, and access to anti-tubercular medications may be difficult. She recommends testing the patient for hepatitis B and C, HIV, and TB. A TST or IRGA can be used, but the IRGA is preferable if it is likely that the patient may not return for a TST reading within the prescribed time. In addition, a CXR, complete blood count, DST, pregnancy test, and liver function tests are performed, and the patient's visual acuity and color vision are checked.

The IRGA is positive. The CXR and liver function tests are normal, as are her color vision and visual acuity; the patient does not have hepatitis B or C or HIV and is not pregnant. The results of the DST indicate susceptibility to INH and rifampin. In addition, her headache and cough have resolved, and based on the initial testing, she does not have active TB. The infectious disease specialist was consulted again. Because of where the patient was born and had recently lived and the possibility of close contact with persons who may have had active TB, she likely has latent TB, and if so, she is at high risk for reactivation. The culture test results have yet returned, but the infectious disease physician has decided to prescribe the 3HP drug regimen. The patient is advised not to become pregnant while taking anti-tuberculars. The regimen is easy to do and has a minimal risk of hepatotoxicity. The 3HP regimen includes INH and rifapentine once a week for three months. The physician decides that DOT should be done, and arrangements are made for DOT and other evaluation/monitoring appointments.

Case Study #2

A 19-year-old male self-refers to an emergency room. He has had a productive cough, fever, fatigue, and night sweats for approximately two weeks. The patient has a past medical history of alcohol use disorder, IV drug use, and a chronic, untreated hepatitis C infection. In addition, he is living with HIV and is taking antiretrovirals. He lives in a homeless shelter.

The patient is admitted to the hospital, placed in a private room, and airborne, respiratory, and standard precautions are put in place.

The CXR is suggestive of but not diagnostic for a cavitary disease of TB; the results of all laboratory tests are normal except for an elevated white blood count and mildly elevated alanine transaminase. His TST result is > 10 mm (Note: He has not previously had a TST). He does not have hepatitis B. His CD4 count is > 600 cells/ μ L. The DST indicates that the TB bacteria are susceptible to INH and rifampin.

Because there is a high index of suspicion that the patient has active TB, and there are no contraindications to its use, the patient is started on a four-month drug regimen: An eight-week initiation phase of INH, moxifloxacin, Pyrazinamide, and rifapentine, orally, taken once a day, every day, and a nine-week continuation of INH, moxifloxacin, and rifapentine, once a day every day is started. A daily dose of pyridoxine is prescribed, as well. Because the patient is on

antiretrovirals, a clinical pharmacologist is consulted before beginning the TB drug therapy to determine if adjustments should be made.

It is decided to delay treatment of the hepatitis C infection. The public health department is notified of the case, and efforts are made to locate people who had contact with the patient and would be at risk for transmission of TB. The patient's condition stabilizes, two AFB smears are negative, and he is discharged to supervised living. DOT at a local health clinic is arranged.

✓Take Test

Your approval agency or organization requires you to take the test.

Implicit Bias Statement

CEUFast, Inc. is committed to furthering diversity, equity, and inclusion (DEI). While reflecting on this course content, CEUFast, Inc. would like you to consider your individual perspective and question your own biases. Remember, implicit bias is a form of bias that impacts our practice as healthcare professionals. Implicit bias occurs when we have automatic prejudices, judgments, and/or a general attitude towards a person or a group of people based on associated stereotypes we have formed over time. These automatic thoughts occur without our conscious knowledge and without our intentional desire to discriminate. The concern with implicit bias is that this can impact our actions and decisions with our workplace leadership, colleagues, and even our patients. While it is our universal goal to treat everyone equally, our implicit biases can influence our interactions, assessments, communication, prioritization, and decision-making concerning patients, which can ultimately adversely impact health outcomes. It is important to keep this in mind in order to intentionally work to self-identify our own risk areas where our implicit biases might influence our behaviors. Together, we can cease perpetuating stereotypes and remind each other to remain mindful to help avoid reacting according to biases that are contrary to our conscious beliefs and values.

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