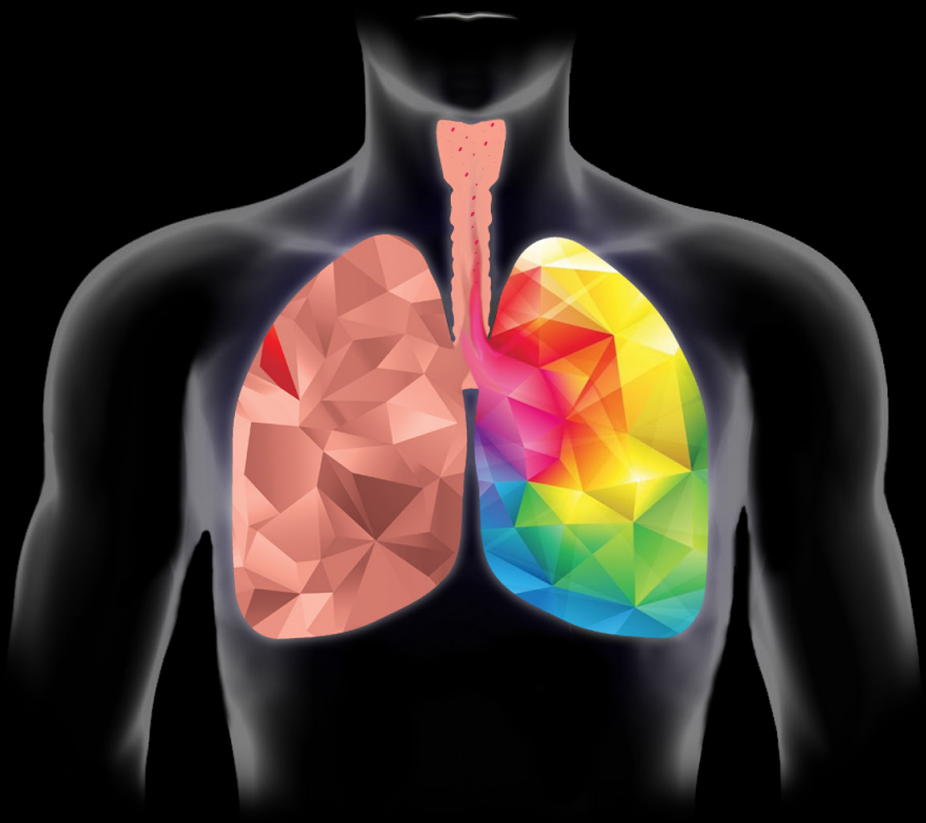
The Spectrum of Tuberculosis from Infection to Disease



TB at a Glance

3rd Edition

HEARTLAND NATIONAL TB CENTER
THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT TYLER

MAYO CLINIC

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The Spectrum of Tuberculosis from Infection to Disease

TB at a Glance | 3rd Edition

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Healthcare providers may access consultation services, technical assistance, and submit requests for training/education by contacting Heartland at 1-800-TEX-LUNG (1-800-839-5864). Staff contact information can also be found on the Heartland website (www.heartlandntbc.org).

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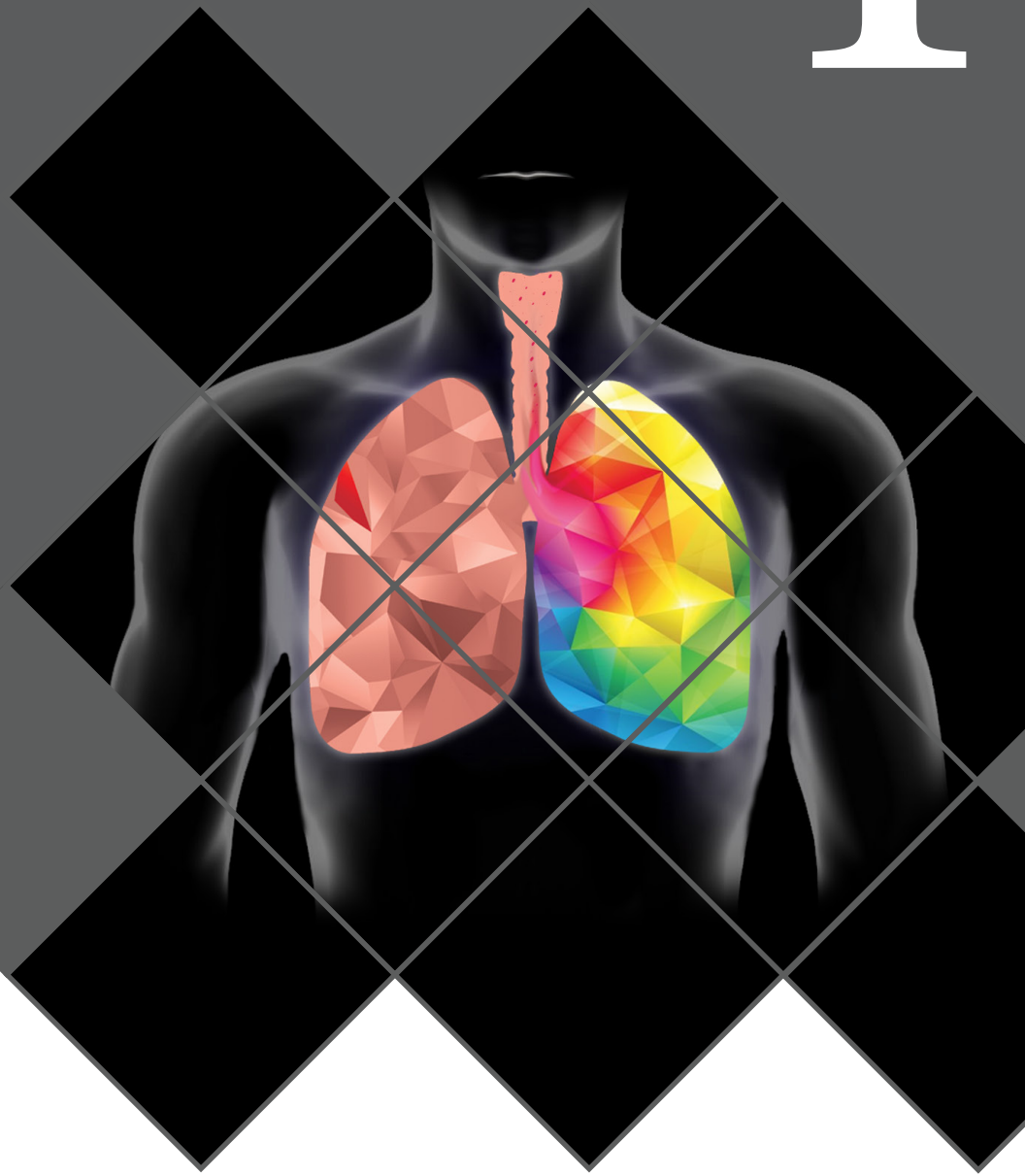
Acronyms and Abbreviations

ADA	adenosine deaminase
AFB	acid-fast bacilli
AII	airborne infection isoloation
ART	antiretroviral treatment
BCG	Bacillus Calmette–Guérin
BMI	body mass index
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CMP	comprehensive metabolic panel
CLIA	Clinical Laboratory Improvement Amendments
cm	centimeters
CO2	carbon dioxide
CT	computed tomography scan
CXR	chest x-ray
DOPT	directly observed preventive therapy
DOT	directly observed therapy
DR-TB	drug resistant TB
DST	drug suscpetibility testing
EMB	ethambutol
FNA	fine needle aspiration
GUTB	genitourinary TB
HIV	human immunodeficiency virus
IGRA	interferon gamma release assay
INH	isoniazid
IRIS	immune reconstitution inflammatory syndrome
LFT	liver function tests
LTBI	latent TB infection
LZD	linezolid
M. tuberculosis	*Mycobacterium tuberculosis*
MAOI	monoamine oxidase inhibitors
MDDR	molecular detection of drug resistance
MDR	multi-drug resistant
MIC	minimal inhibitory concentration
ml	millileters
mm	millimeters
MTBC	*mycobacterium tuberculosis* complex
MTD	*Mycobacterium tuberculosis* Direct Test
NAA	nucleic acid amplification
NTM	*non-tuberculous mycobacteria*
PAPR	Powered Air-Purifying Respirator
PET	positron emission tomography
PI	protease inhibitor
PLWHA	people living with HIV/AIDS
PPD	purified protein derivative
PZA	pyrazinamide
QFT-plus	QuantiFERON® Gold Plus
RPT	rifapentine
RR	rifampin-resistant
RRDR	rifampin-resistant determining region
SAT	self-administered therapy
TB	tuberculosis
TDM	therapeutic drug monitoring
TNF	tumor necrosis factor
T-SPOT®	T-SPOT.TB® test
TST	tuberculin skin test
U.S.	United States
v-DOT	video-directly observed therapy
XDR	extensively drug resistant
Xpert®	Cepheid GeneXpert®

Chapter 1



Testing for TB Infection

Chapter 1

Testing for Tuberculosis Infection

Edward Graviss, PhD, MPH

I. Introduction

A. The diagnosis of latent tuberculosis infection (LTBI) and the diagnosis or exclusion of active tuberculosis (TB) disease requires a combination of epidemiologic, historic, medical, and diagnostic findings.

B. The tuberculin skin test (TST) and interferon gamma release assay (IGRA) should be used as aids in diagnosing LTBI.

II. Who to Test

A. Two purposes for performing a TST or an IGRA are:

1. Identify persons with a clinical diagnosis of latent TB infection who would benefit from preventative treatment
2. Provide partial evidence for or against the diagnosis of TB disease; a positive test could provide evidence of latent TB infection or possibly TB disease. A negative test result by itself does not rule out TB disease in any context, especially if there is clinical suspicion of TB disease

B. Targeted testing should be performed to detect:

1. Those likely to be infected
2. Those with TB infection who have an increased risk of progression to TB disease

C. Screening should not be done in individuals without risk factors for TB exposure unless part of a continuing workplace screening program (e.g., select healthcare workers, correctional workers).

D. Persons at risk for recent TB infection include:

1. Contacts of patients with active pulmonary, pleural or laryngeal TB
2. People from a country where TB disease is common (most countries in Latin America, the Caribbean, Africa, Asia, Eastern Europe, and Russia) or frequent travellers to these areas
3. Employees or residents of high-risk congregate settings (e.g. correctional facilities, long-term care facilities or nursing homes, and shelters for persons experiencing homelessness)
4. Health care workers who have patient contact in settings with increased occupational risk for TB exposure

5. Infants, children and adolescents exposed to individuals who are at increased risk for TB disease

E. Conditions or individuals associated with increased risk for progression to TB disease are:

1. People infected in the past two years
2. People with fibrotic chest x-ray (CXR) lesions of old untreated TB
3. HIV infection
4. Children < 5 years
5. Injection drug users
6. Organ transplant recipients
7. People with immunosuppressive disorders
8. Immunosuppressive therapy (equivalent to prednisone ≥ 15 mg/day for more than one month)
9. Treatment with tumor necrosis factor (TNF) alpha antagonists, and other immunosuppressing biologic therapies
10. Diabetes, especially those with poor glycemic control
11. Chronic kidney disease
12. Leukemia, lymphoma, cancer of the head, neck or lung
13. Silicosis
14. Malnourishment

III. Tuberculin Skin Test

A. A TST is the intra-dermal injection of a 200+ mycobacterial antigen purified protein derivative (PPD) that measures an immune response (delayed-type hypersensitivity).

B. A positive reaction is based on induration measured in millimeters (mm).

C. Expertise in placing and reading a TST is decreasing in the United States due to increasing use of IGRAs and the decreasing prevalence of TB disease.

D. TST Administration

1. TST placement
   a. Locate volar surface of the forearm, 5–10 cm (2–4 inches) below the elbow joint
   b. Place forearm palm-up on a firm, well-lit surface
   c. Select an area free of barriers (e.g. scars, sores, veins) for placement and reading
   d. Clean the proposed injection site with an alcohol swab and allow to air dry

2. Prepare 1 ml Tuberculin Syringe
    a. Check the expiration date on PPD vial and ensure vial contains tuberculin PPD-S (5 TU/0.1 ml)
    b. Use a single-dose tuberculin syringe with a short (¼- to ½-inch) 27-gauge needle with a short bevel
    c. Clean the top of the vial with a sterile swab
    d. Fill the syringe with 0.1 ml tuberculin (PPD solution)
3. Tuberculin (PPD) Injection
    a. Insert the needle slowly, bevel up, at an angle of 5–15°
    b. Needle bevel should be visible just below skin surface
    c. Inject the tuberculin slowly
4. Check Injection Site
    a. After injection, a flat intra-dermal wheal of 8–10 mm in diameter should appear
    b. If the wheal does not appear, repeat the injection at a site at least 5 cm (2 inches) away from the original site
5. Document Above Information
6. TST Reading
    a. The skin test reaction should be read 48 to 72 hours after administration.
    b. A patient not returning within 72 hours should be rescheduled for another TST.
    c. The TST reaction should be measured with a small tuberculin ruler and induration, if present, recorded in millimeters. Induration is the palpable, raised, hardened area or swelling occurring at or near the injection site. The reader should not measure erythema (redness). If no induration, report 0 mm.
    d. The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis).
7. TST Interpretation
    a. TST interpretation depends on two factors: 1) the induration size and 2) the person's risk for TB infection or progression to TB disease.
    b. In persons suspected to have TB disease, an induration ≥ 5 mm is considered positive.
    c. For infants, children, and adolescents in contact with adults in high risk categories, an induration of ≥ 10 mm is considered positive.

Table 1. TST Interpretation

Induration ≥ 5 mm considered positive in:	Induration ≥ 10 mm considered positive in:	Induration ≥ 15 mm considered postive in:
HIV infected individuals	Immigrants from high-prevalence countries	Any person, including persons with no known risk factors for TB. **Note:** Targeted skin testing programs should only be conducted among high-risk groups.
A recent contact of a person with TB disease	Persons with clinical conditionis that place them at high risk (See Section II.E, bullets #10-14)	
Persons with fibrotic changes of CXR consistent with prior TB	Residents and employees of high-risk congregate settings	
Patients with organ transplants	Mycobacteriology laboratory personnel	
Individuals immunocompromised for other reasons (e.g. taking TNF-alpha inhibitors, taking equivalent of ≥15 mg/day of prednisone for ≥ 1 month)	Infants, children, and adolescents to adults in high-risk categories	
	Children < 5 years old	
	Injection drug users	

8. Boosting and Two-Step Testing

   a. Adults infected with *M. tuberculosis* in the distant past may have diminished TST reactivity. In some, an initial TST gives a negative or weakly positive reaction, but "boosts" the immune system so that subsequent TSTs may cause a greater degree of induration and be classified as positive, thus the term "booster effect."

   b. Because of the potential booster effect, persons such as healthcare workers and others who undergo periodic tuberculin skin testing should receive an initial two-step TST.

      i. If the first test is positive, no further testing is needed.

      ii. If the first test is negative, a second test is placed 1-3 weeks later.

      iii. If the second test is positive, the person may have TB infection. This "boosted" response is the valid baseline for the individual.

      iv. If the second test is negative, the person is likely uninfected, but immunosuppressed individuals can have false negative TST results.

IV. Interferon Gamma Release Assay

A. Background

1. IGRAs are in-vitro blood assays developed to improve the accuracy and simplicity of diagnosing TB infection.

   a. IGRAs detect a biomarker (i.e. interferon-gamma) that is released when memory lymphocytes react to a mixture of peptides of the secretory proteins CFP-10 and ESAT-6 (encoded by the region of difference RD1), which are produced only by the *M. tuberculosis* complex (representative species include: *M. tuberculosis*, *M. bovis* {wild type}, *M. africanum*) and a few other non-tuberculous mycobacteria (NTM) species.

   b. Bacille Calmette-Guérin (BCG) mycobacteria (attenuated *M. bovis*) vaccines and most environmental NTM do not produce these RD1 proteins, and thus, IGRAs do not cross-react in patients with prior BCG vaccination and infection with most NTM.

   c. IGRAs can give false positive results in some unusual NTM infections that produce RD1 proteins:

      i. *M. kansasii, M. szulgai, M. marinum*, and *M. leprae*

2. Although Food and Drug Administration (FDA) approved only for the diagnosis of LTBI, an IGRA can be used in some clinical scenarios to evaluate for TB disease along with clinical and radiological assessment.

3. Currently there are two IGRA assays:

   a. QuantiFERON® Gold Plus (QFT-Plus) which uses an enzyme linked immunoSorbet Assay (ELISA)

   b. T-SPOT®.TB which uses an enzyme linked immunoSPOT method (ELISPOT)

B. QuantiFERON® Gold Plus - The QFT-Plus assay is performed in two stages. Whole blood is collected into four (4) QFT-Plus Blood Collection Tubes: a nil tube, TB1 tube, TB2 tube and a mitogen tube. Alternatively, blood may be collected in a single tube that contains lithium-heparin and then transferred to the 4 QFT-Plus Blood Collection Tubes in the laboratory.

1. The TB1 tube has a mixture of ESAT-6 and CFP-10 peptides that trigger mostly CD4 T-lymphocyte activation (similar to those used in earlier assay versions of the QuantiFERON®).

2. The TB2 tube has a mixture of peptides with a short length that triggers both CD4 and CD8 T-lymphocyte activation.

   a. The QFT-Plus Blood Collection Tubes are:

   b. Shaken to mix antigens in the tube with the blood

c. Incubated at 37°C as soon as possible (in 16 hours) for 16 – 24 hours

d. Centrifuged, plasma is removed, and quantity of IFN-γ (IU/ml) is measured

C. QFT-Plus Interpretation (Table 2) - Both the qualitative test interpretation and the quantitative assay measurements should be reported together with the criteria used.

Table 2. Interpretation of QuantiFERON®-TB Gold Plus

Nil (IU/ml)	TB1-Nil (IU/ml)	TB2-Nil (IU/ml)	Mitogen-Nil (IU/ml)	QFT-Plus Result	Interpretation
≤8.0	≥ 0.35 and ≥25% of Nil	Any	Any	Positive	*M. tuberculosis* infection likely
	Any	≥0.35 and ≥25% of Nil			
	<0.35 or ≥0.35 and <25% of Nil	<0.35 or ≥0.35 and 25% of Nil	≥0.50	Negative	*M. tuberculosis* infection NOT likely
	<0.35 or ≥0.35 and <25% of Nil	<0.35 or ≥0.35 and 25% of Nil	<0.50	Indeterminate	Likelihood of *M. tuberculosis* infection cannot be determined
≥8.0	Any				

D. Indeterminate QFT-Plus Results

1. An indeterminate result may occur when: The Nil well is ≥ 8.0 IU/ml or when there is a low mitogen response (Mitogen – Nil < 0.50 IU/ml).

2. Potential causes of indeterminate results include:

a. Host factors such as elevated levels of circulating IFN-γ or the presence of heterophile antibodies

b. Medical conditions associated with suppressed cellular immunity and/or production of IFN-γ such as severe lymphopenic states, HIV with low CD4 cell counts, malnutrition, anergy, viral infections, and others

c. Technical factors (pre-analytical conditions)

i. Incorrect handling of blood (poor shaking, transportation temperature)

ii. Delayed time to incubation

iii. Inappropriate filling of tubes leading to low mitogen results

E. Conversions and Reversions with QFT-Plus Assay

1. Conversion is used to describe the clinical situation when a previously negative assay becomes positive.

Table 3. Advantages and Disadvantages of the QFT-Plus Assay

Advantages	Disadvantages
Lack of cross-reactivity with BCG and most NTM	Blood samples should be processed as soon as possible or within 16 hours
Single visit needed	Errors in collecting or transporting blood specimens or in processing the assay can decrease the accuracy of the assay
QFT-Plus uses CD8 polypeptides in the TB2 blood tubes which may possibly increase sensitivity and predict progression of infection	Requires 4 ml of whole blood (1 ml per 4 assay tubes); in some immunocompromised patients, lymphocyte depletion may cause indeterminate results due to lack of sensitized cells
	A negative assay does not exclude TB disease in immunocompromised patients

2. Reversion is used to describe the clinical situation when a positive assay becomes negative.
3. IGRA conversion can be a marker of incident infection but often represents false positive results in individuals at low risk of infection (e.g. low-risk healthcare workers).
   a. In both low- and high-burden countries where serial testing for incident TB infections has been studied, higher than expected conversion rates have been reported as well as high rates of reversions after documented conversions.
   b. Most of these IGRA conversion and reversions occurred near the threshold of the older QuantiFERON® Gold Assay (0.35 IU/ml).
   c. Recent data has shown the conversion/reversion phenomena also occurs with the QFT-Plus. ATS/IDSA/CDC guidelines recommend repeating an IGRA if a false positive is suspected in low-risk settings.

F. T-SPOT.TB® Assay

1. The T-SPOT.TB® assay (T-SPOT®) detects effector T cells that respond to stimulation by a mixture of ESAT-6 and CFP-10 peptides in plate-wells covered with antibodies against IFN-γ to form "spot forming units" that represent immune cells releasing IFN-γ.
2. This assay is performed in two stages. Whole blood is drawn; peripheral blood mononuclear cells (PBMCs) are isolated, washed and enumerated.
   a. The processing of blood should occur within 8 hours of blood draw.
   b. If processing is delayed (up to 32 hours) then a preserving reagent (T-Cell Xtend®) should be used.

c. Approximately, 1 million PBMCs are needed for the T-SPOT® assay (≈250,000 cells in each of the 4 plate-wells or panels: a positive control, a nil control, and two separate panels for each ESAT-6 and CFP 10 peptide mixtures).

d. The specimen is incubated overnight (16-20 hours) under CO_2 conditions and released IFN-γ is captured by antibodies reacting with the IFN-γ that covers the well.

e. Wells are washed, a conjugate is added, and after washing, a substrate is added forming a dark blue spot at the site of the antigen-specific IFN-γ–producing cells.

f. Spots are counted and results reported in spot forming units (SFU).

G. T-SPOT® Interpretation (Table 4) - Both the standard qualitative test interpretation and the quantitative assay measurements should be reported together with the criteria used for test interpretation.

Table 4. Interpretation of T-SPOT®.TB Assay

Nil (Spots)	Mitogen-Nil (spots)	Panel A - Nil (spots)	Panel B - Nil (spots)	T-SPOT® Result	Interpretation
≤ 10 spots	≥ 20 spots	≥ 8 spots	≥ 8 spots	Positive	*M. tuberculosis* infection likely
	< 20 spots				
	≥ 20 spots	5, 6, or 7 spots	5, 6, or 7 spots	Borderline	Equivacol
	< 20 spots				
	≥ 20 spots	≤ 4 spots	≤ 4 spots	Negative	*M. tuberculosis* infection NOT likely
	< 20 spots	≤ 4 spots	≤ 4 spots	Invalid	Repeat Test
> 10 spots	Any			Invalid	Repeat Test

H. Borderline and Invalid T-SPOT® Results

1. As noted in the table above a borderline result may occur if the Nil well is ≤ 10 spots and either Panel A – Nil or Panel B – Nil have 5, 6, or 7 spots.

2. A Borderline result should be repeated with a new specimen.

3. If a second borderline result is reported, another diagnostic assay, such as the QFT-Plus or TST, and clinical information should be used to help determine TB infection status of the patient.

4. Borderline results may reflect early or compartmentalized immunologic reactivity to TB infection; clinicians and providers may wait 6 - 8 weeks before retesting.

5. An invalid result occurs when the Nil panel has > 10 spots (High Nil) or the Nil panel ≤ 10 spots and mitogen panel has < 20 spots and all other panels have ≤ 4 spots.

a. Potential causes of invalid results where the Nil panel has > 10 spots include technical factors (pre-analytical conditions) such as incorrect handling of blood samples or cross contamination in the laboratory.

b. Potential causes of invalid results with low mitogen response includes anergy and immunosuppression.

6. An invalid result should be repeated with a new patient specimen.

I. Conversions and Reversions with T-SPOT® - Although T-SPOT® conversion and reversions have been reported, in the hands of experienced ELISPOT laboratorians, conversion rates in nearly 20,000 healthcare workers were < 1% and the mean reversion rate was 17.6%, with positivity and conversion rates correlated with known TB risk factors.

Table 5. Advantages and Disadvantages of the T-SPOT®.TB Assay

Advantages	Disadvantages
Lack of cross-reactivity with BCG and most NTM	Blood samples should be processed within 8 hours or within 32 hours with the T-Cell Xtend™ reagent after collection, while white blood cells are still viable
Single visit needed	A CO_2 incubator is required for incubation
≈ 1 million PBMCs are needed. If the patient is immunocompromised and/or has lymphopenia, a cell count can be run to determine the volume of blood needed to perform the T-SPOT® assay. Counting cells corrects for low PBMC	Errors in collecting or transporting specimens or in running and processing the assay can decrease the accuracy of the assay
	A negative assay does not exclude TB disease in immunocompromised patients

V. Follow-up Assessment (chest radiography, clinical exam)

A. In persons with a positive TST or positive IGRA, a clinical evaluation and a chest radiograph (CXR) should be done to evaluate the possibility of active TB. (See Chapter 2 - Diagnosis of TB Disease)

B. In a number of U.S. jurisdictions, LTBI is a reportable condition.

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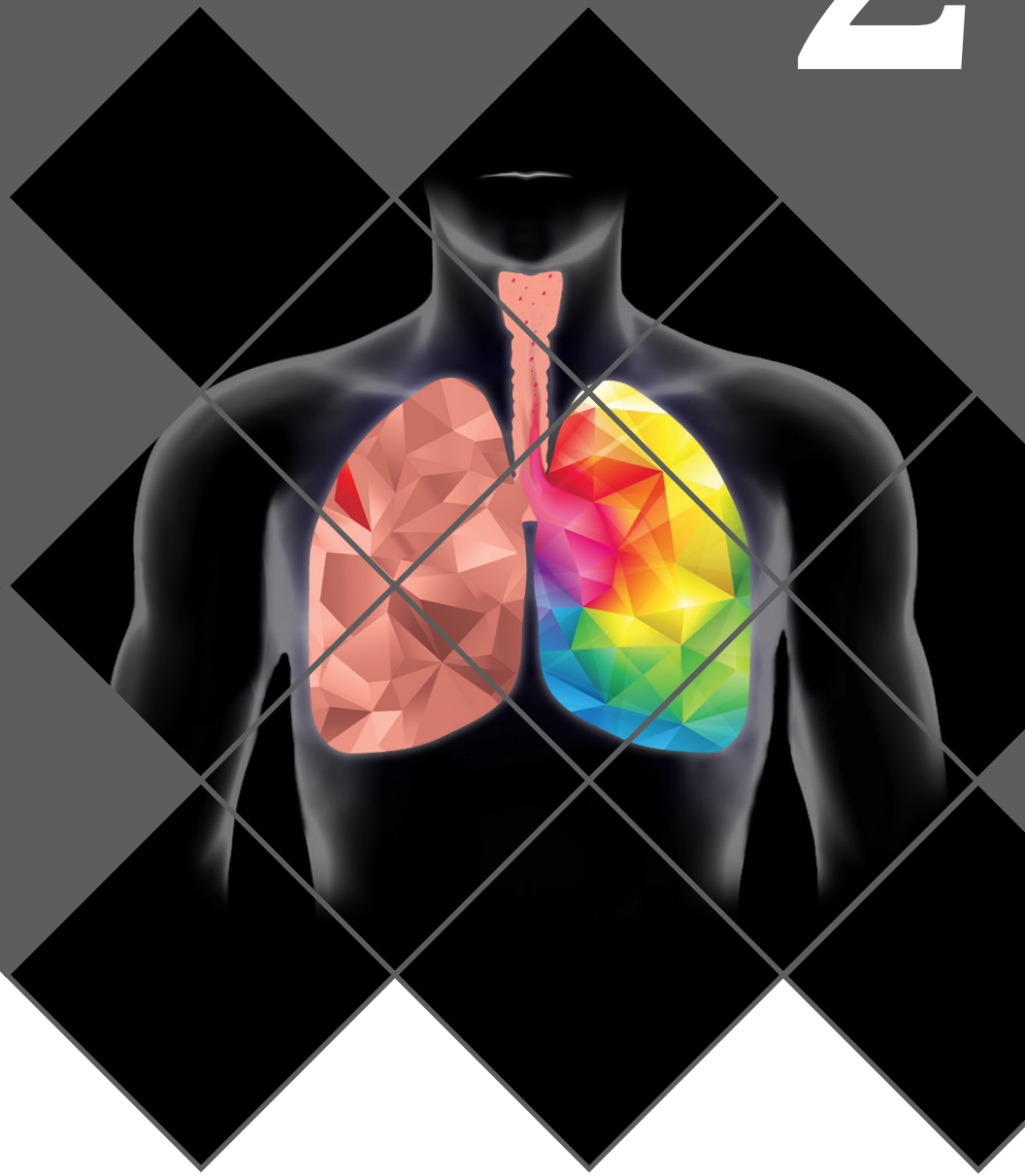
Chapter 2



Diagnosis of TB Disease

Chapter 2

Diagnosis of Tuberculosis Disease

Lisa Y. Armitige, MD, PhD

I. Evaluating for TB Disease

A. A positive tuberculosis (TB) screening test, (i.e. a tuberculin skin test (TST) or interferon gamma release assay (IGRA)), is frequently one of the first tests pursued in the evaluation for TB disease. These tests are covered extensively in Chapter 1.

1. In the setting of compatible symptoms or radiographic findings, a positive TST or IGRA offers compelling evidence of TB disease.
2. It is important to note that historic data shows 15-20% of patients with TB disease will have a negative TB screening test. Though no data exists for false negative IGRAs in these instances, it is thought that a similar percent (about 15-20%) of patients with active TB disease will be IGRA negative as well.
3. A negative screening test is more common in small children with active TB, individuals with disseminated TB disease (thought to be due to high antigen burden) and immune compromised individuals with TB disease.

B. Though there are no physical examination findings specific for TB disease, every patient suspected of having active TB should have a respiratory exam and examination for lymphadenopathy at minimum.

1. TB can occur in any part of the body so special attention should be given to any body parts with persistent pain, swelling or discomfort.
2. Fever of unknown origin (FUO) is another manifestation of TB disease and should be investigated during the workup of FUO.

C. Specimens from body sites suspected of being infected with *Mycobacterium tuberculosis (M. tuberculosis)* should be submitted to the laboratory for acid-fast bacilli (AFB) smear and culture. An AFB positive smear is suggestive of TB but not definitive; like *M. tuberculosis*, non-tuberculous mycobacteria (NTM) stain positive by AFB staining methods such as Ziehl-Neelson, Kinyoun and auramine-rhodamine stains.

D. Growth of *M. tuberculosis* in culture from sputum or other body sites is definitive for TB disease. An AFB culture cannot be considered negative before 6-8 weeks of incubation and a negative culture does not rule out active TB disease. Approximately 20% of TB cases are AFB culture negative. In these individuals the diagnosis is determined when there is a patient at risk for TB disease, usually with a positive TST or

IGRA, an abnormal chest x-ray (CXR), who responds clinically and/or radiographically after 2 months of standard treatment for TB (isoniazid, rifampin, ethambutol, and pyrazinamide).

E. Diagnostic accuracy can be improved using a nucleic acid amplification (NAA) test. The Cepheid GeneXpert® (Xpert®) MTB/RIF assay is used for its ease of operation and in the United States, is rapidly replacing older *mycobacterium tuberculosis* complex (MTBC) NAA tests, though some labs may use in house developed NAA tests as well.

Table 6. Interpreting Nucleic Acid Amplification Test Results

Result	Interpretation
NAA test positive and AFB smear positive	The patient should be presumed to have active TB disease, and anti-tuberculosis treatment should be started while awaiting culture results. The positive predictive value of an FDA-approved NAA test in this situation for TB is >95%.
NAA test positive and AFB smear negative	Clinical judgment is required to determine whether to begin anti-tuberculosis treatment before the culture results are available. Many experts would consider starting treatment for TB unless another diagnosis is evident. A second specimen can be tested to confirm the NAA test result. If two specimens are NAA test positive, the patient can be presumed to have TB, and treatment for TB should be started while the culture is pending.
NAA test negative and AFB smear positive	A second NAA test should be considered on a new specimen. If the second test is also NAA negative, clinical judgment should be used to determine whether to begin anti-tuberculosis treatment until culture results are available and to determine if additional diagnostic testing is needed. Usually, however, a patient can be presumed to be infected with an NTM if a second specimen is also smear positive and the NAA test is negative.
NAA test negative and AFB smear negative	TB cannot be excluded with the use of either the NAA test or AFB smear. Clinical judgment should be used to determine whether to begin anti-tuberculosis treatment until the results of the culture and additional diagnostic tests are available.

1. NAA testing can reliably detect *M. tuberculosis* in specimens at least one week earlier than culture for 80% of those patients who have disease confirmed with a positive culture. As few as 1 to 10 organisms/ml may give a positive result. Results should be made available within 24-48 hours.

2. The NAA test can confirm the presence of *M. tuberculosis* in 50-80% of AFB smear-negative, culture-positive specimens and can provide confirmation of the presence of *M. tuberculosis* in smear-positive specimens in clinical situations in which an NTM infection are also common.

3. Use of NAA tests can impact patient care and TB control efforts, reducing unnecessary contact investigations or respiratory isolation for patients whose AFB smear-positive specimens do not contain *M. tuberculosis*.

4. Currently available NAA tests are not sufficiently sensitive (detecting 50%–80% of AFB smear-negative, culture-positive pulmonary TB cases) in excluding the diagnosis of TB in AFB smear-negative patients suspected to have TB.

5. NAA test results often remain positive after culture results become negative during therapy. A positive NAA test result does not give any information on the viability of mycobacteria in a particular patient and subsequent NAA testing is not helpful in determining response to, or duration of, therapy. NAA testing is not recommended for diagnostic purposes for one year after completion of TB therapy.

II. Pulmonary TB Disease

A. A presumptive diagnosis of pulmonary TB can be made when a patient presents with classic clinical symptoms of cough, fever, night sweats and weight loss and is found to have a positive TST or IGRA, an abnormal CXR, and a reasonable exclusion of alternative causes of infection. Suspicion is augmented in the presence of demographic risk factors for TB.

B. Sputum smears for AFB are positive approximately 50% of the time with pulmonary TB. This varies with the quality of sputum sample submitted, extent of radiographic disease and immune status of the individual patient.

   1. A series of at least 3 quality sputum specimens should be collected 8-24 hours apart (at least one should be obtained in the early morning and, if possible, one should be observed).

   2. Sputum specimens should be submitted for AFB smear and culture with at least one of the 3 sputa submitted for NAA testing.

   3. Sputum induction may be performed for patients who are unable to spontaneously produce an adequate sputum sample.

   4. Collecting sputum is preferred over bronchoalveolar lavage with respect to safety and cost. Bronchoscopy with bronchoalveolar lavage should be reserved for patients unable to give sufficient/quality sputum samples by spontaneous or induced sputum and for patients with negative sputum studies or absence of cough in the setting of a high clinical suspicion for pulmonary TB.

C. Patients with pulmonary infiltrates and clinical symptoms who have no risk factors for TB disease and who have negative TST or IGRA results should continue to be evaluated for the etiology of their disease. Clinical judgment is needed.

III. Extra-pulmonary TB Disease

A. Extra-pulmonary TB is reported more often in specific groups of individuals such as children, persons living with HIV/AIDS (PLWHA) or other immunosuppression conditions (e.g. those taking anti-tumor necrosis factor agents, receiving antineoplastic chemotherapy, patients with chronic renal disease, especially dialysis, etc.), and those with disease due to *M. bovis*.

B. The diagnosis of extra-pulmonary TB can be difficult to make as it generally presents with non-specific symptoms and requires a higher index of suspicion and more diagnostic acumen than pulmonary TB. Additionally, it is a more 'paucibacillary' form of disease than pulmonary TB. Depending upon the severity of disease, AFB/Fite staining and cultures performed on extra-pulmonary tissue and body fluids (e.g. blood, urine, tissue from biopsy, cerebrospinal, pleural or peritoneal fluid) can often be negative. NAA testing and/or multiple sampling may increase the diagnostic yield.

C. On pathologic exam, granulomatous inflammation, especially necrotizing or caseating granuloma increases the likelihood of TB disease but is not specific for TB. NTM, fungal infections and notably rare forms of sarcoidosis can give similar necrotizing granulomas on biopsy. AFB smears on tissue (e.g. Fite stain) are frequently negative even when significant granulomatous inflammation is present. The absence of AFB in a tissue biopsy should never exclude a diagnosis of TB disease.

D. When available, NAA testing should be performed on specimens collected from sites of suspected extra-pulmonary TB. A positive NAA test result can be considered as evidence of extra-pulmonary TB and can help guide decision making to start therapy.

E. Pleural, pericardial, abdominal and spinal fluids collected for evaluation of TB should be sent to the laboratory for NAA testing, cell counts, protein, glucose and, when appropriate, lactate dehydrogenase (LDH), in addition to AFB smear and mycobacterial culture, and other appropriate testing for alternative diagnoses. Adenosine deaminase and free IFN-γ levels in pleural and spinal fluid may also be considered. It is especially important to ensure that tissue specimens have a portion allotted for mycobacterial culture and are not completely placed in formalin.

F. Culture remains the gold standard for laboratory confirmation of TB and is required for isolating bacteria for drug-susceptibility testing and genotyping. It is important that sufficient portions of specimens are reserved for mycobacterial culture.

G. Consider a consultation with a TB expert in case of suspected TB and inconclusive testing results for both pulmonary and extra-pulmonary TB.

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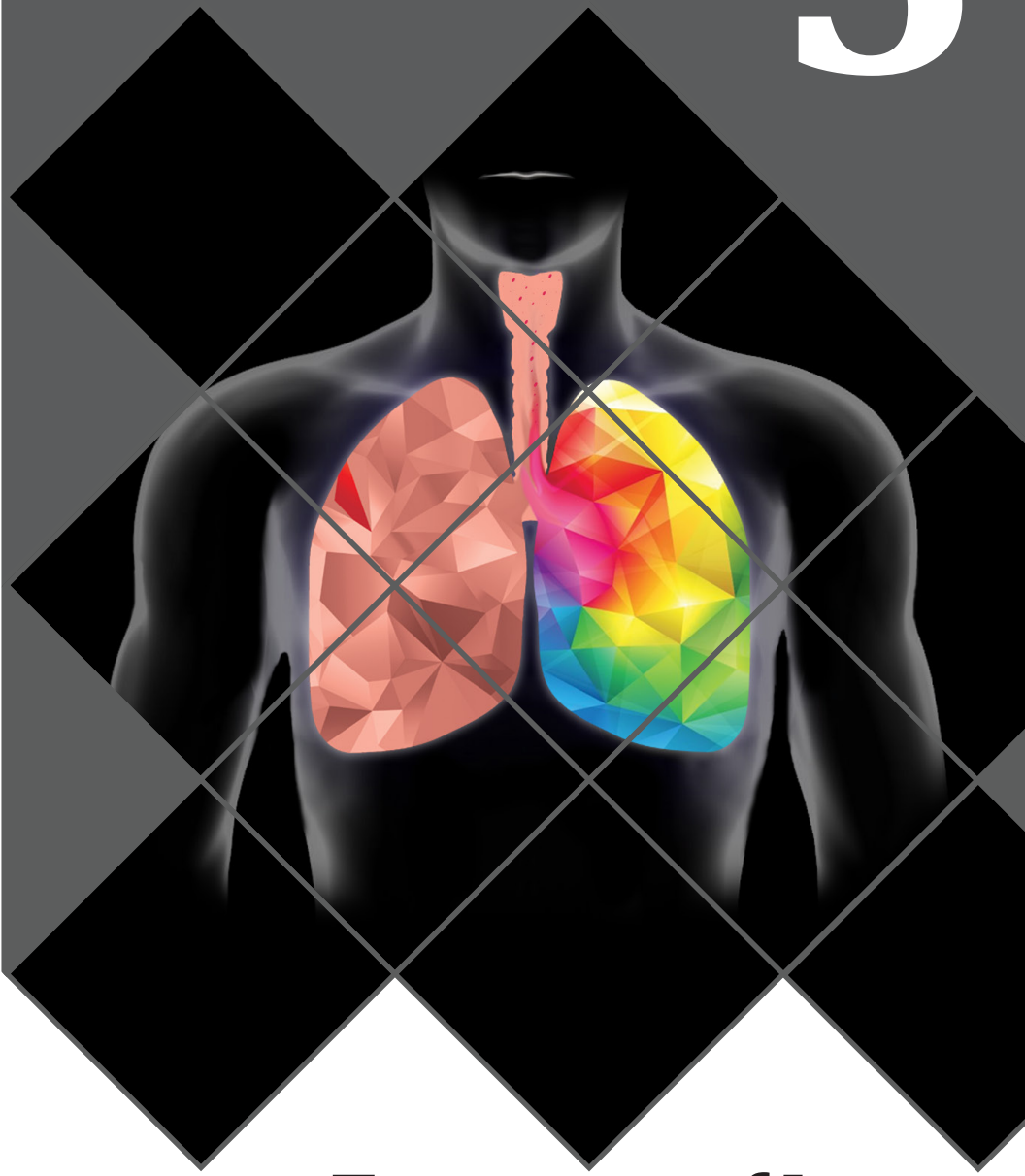
Chapter 3



Treatment of Latent TB Infection

Treatment of Latent Tuberculosis Infection

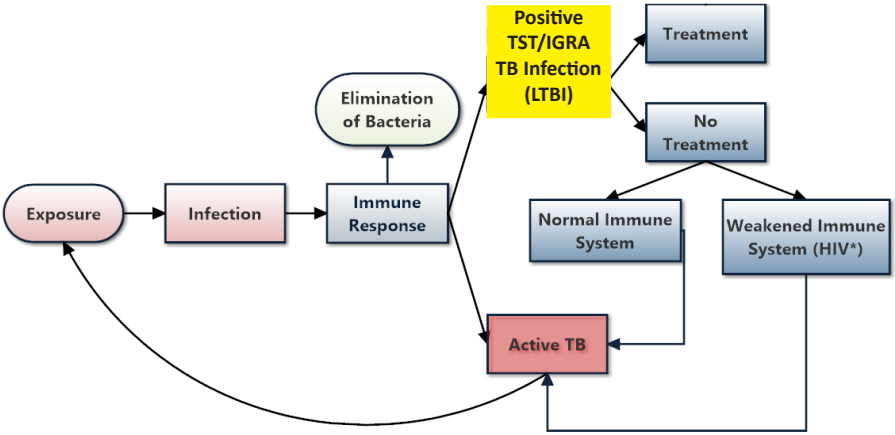
Juzar Ali, MD, FRCP(C), FCCP; Jeremy M. Clain, MD

I. Introduction

A. Latent tuberculosis infection (LTBI) is an asymptomatic infection with *Mycobacterium tuberculosis* (*M. tuberculosis*).

1. Affected individuals are not infectious, but are at risk of developing active tuberculosis (TB) disease.
2. Most individuals who develop active TB disease pass through a period of LTBI (Figure 1).

Figure 1. Latent TB Infection Flow Chart



Adapted from Core Curriculum on Tuberculosis: What the Clinician Should Know, 5th ed. Atlanta, GA: US Department of Health and Human Services, CDC; 2011. with addenda and modifications by authors

B. Distinguishing Characteristics of LTBI

1. An individual with LTBI harbors low numbers of viable MTB organisms without clinical or radiologic findings of active disease.
2. The TB infection is contained by active engagement of the adaptive immune system.
   a. Engagement of the adaptive immune system generates immune memory to *M. tuberculosis* antigens, which allows for indirect detection of possible LTBI via immune-mediated tests such as tuberculin skin test (TST) or an interferon gamma release assay (IGRA).

b. All individuals with LTBI have potential to progress to active TB disease (approximately 5-10% lifetime risk among immunocompetent persons), and the risk of progression is increased if there are disruptions to the individual's adaptive immune system (by immunosuppressing conditions or medications).

C. The identification and treatment of LTBI comprises a key component of a successful TB control program.

1. Since those affected by LTBI are asymptomatic, the identification of LTBI cases depends on effective screening (i.e. TST and/or IGRAs) along with appropriate clinical and radiological assessments.

a. TB screening efforts should focus on individuals who are at high risk of *M. tuberculosis* infection and those who would be at high risk for progressing to active TB disease once infected.

b. Efforts should be dedicated to include foreign born individuals and racial and ethnic minorities in screening programs, given that members of these groups bear a disproportionately high burden of TB.

2. With few exceptions, screening for LTBI should be performed with the intention to treat identified cases, in order to reduce the affected individual's potential to progress to active TB disease. Treatment of LTBI prevents progression to active TB disease.

II. Diagnosis of Latent TB Infection

A. General Criteria (**Figure 2**)

1. History of exposure or potential exposure(s) to patients with pulmonary TB

2. Positive TST or positive IGRA

3. Exclusion of active TB disease

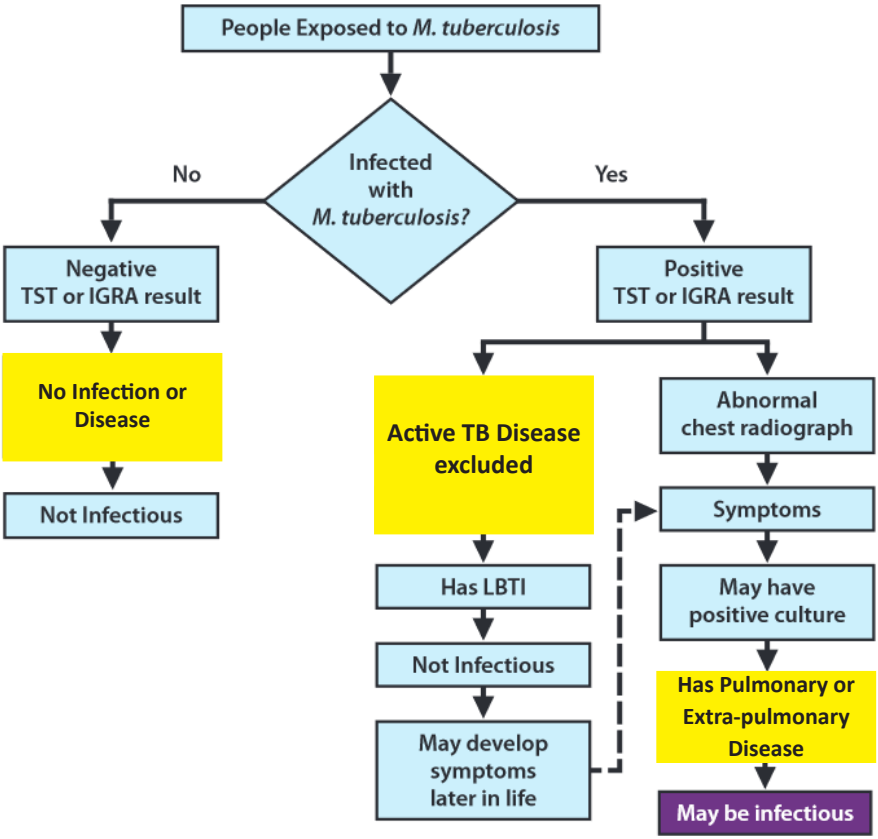
B. In a patient with a positive TST or IGRA, a careful clinical evaluation is needed to rule out active TB disease and to establish a diagnosis of LTBI, based on CDC/IDSA guidelines (**Figure 3**).

1. All patients with a positive screening test should undergo a thorough symptom review, a physical examination, and a chest x-ray (CXR).

2. In an asymptomatic individual, active TB disease is ruled out if the CXR is negative for signs of pulmonary TB and the history and physical examination are negative for signs of extra-pulmonary TB.

3. Individuals who have signs or symptoms compatible with active TB disease require additional evaluation.

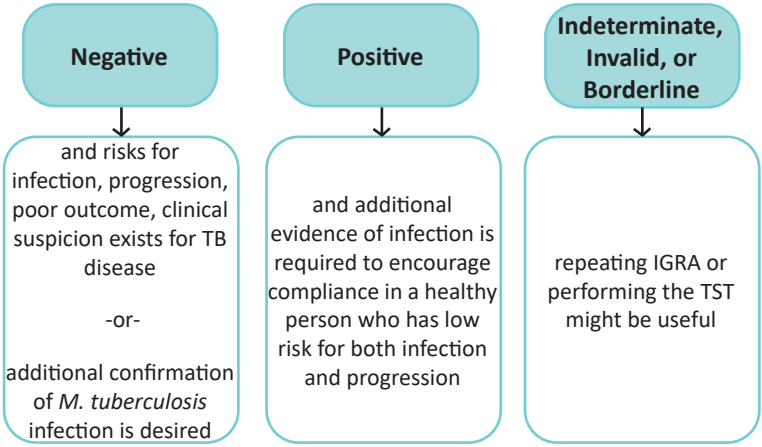
Figure 2. Progression of Tuberculosis



Core Curriculum on Tuberculosis: What the Clinician Should Know, 5th ed. Atlanta, GA: US Department of Health and Human Services, CDC; 2011. Figure 2.4. with Addenda and modifications by authors

Figure 3. Testing with Both IGRA and TST

Testing with both IGRA and TST may be considered when initial test result is:



C. Special Cases

1. Individuals recently exposed to TB who are at the highest risk for rapid progression to TB disease (**Table 7**).

Table 7. Risk Factors with Highest Risk of Progression to Active TB

Risk Factors	
Age less than 5 years	HIV infection
Organ transplant	Silicosis
Treatment with a biologic agent or other immunossuppresive medications	

a. These patients may have false-negative TST and false negative or indeterminate IGRA results.

b. Once active TB disease has been ruled out, window prophylaxis is indicated for children less than 5 years of age. (See Chapter 7 - Tuberculosis in Children)

c. Some individuals may be considered for full treatment of LTBI even if an IGRA or TST is not positive. Expert consultation should be considered.

2. Individuals who undergo TST or IGRA testing but have neither an elevated risk of *M. tuberculosis* infection nor an increased likelihood of TB disease.

a. False-positive TST and IGRA tests represent a considerable percentage of positive test results in such individuals.

b. To avoid over-diagnosis of LTBI, a second confirmatory test (TST or IGRA) is recommended.

III. Testing for Latent TB Infection

A. Placing and interpreting TSTs should be performed by trained personnel, and individuals collecting blood samples for the serum IGRA must be aware of the collection and processing requirements to avoid erroneous results.

B. LTBI screening should be targeted, focusing on the following individuals and populations

1. Persons with increased risk of having been exposed to *M. tuberculosis*, including:

a. Close contacts (including direct household and those with confined space exposures) to patients with active pulmonary or airway TB disease

b. Immigrants from, or frequent travelers to, countries where TB is endemic (> 20 cases/100,000 population)

c. Residents and employees of high risk congregate settings (including homeless shelters, correctional facilities, migrant camps, and transitional venues; depending upon local epidemiological data)

d. Healthcare workers in centers where the risk of exposure to TB is high

e. Individuals whose chest imaging studies demonstrate fibrotic changes consistent with prior active pulmonary TB (not including minimal apical scarring or small calcified granulomas as the only abnormalities), who have no history of documented TB treatment

f. Mycobacteriology laboratory personnel

2. Persons with risk factors for progression to active TB disease once infected, including:

   a. Chronic disease states known to impair the ability to contain LTBI

      i. HIV infection

      ii. Diabetes mellitus

      iii. End stage renal disease requiring dialysis

   b. Long-term immunosuppressive therapy

      i. Organ transplant recipients (and prospective recipients)

      ii. Chemotherapy (anti-neoplastic)

      iii. Biologic agents

      iv. Other immunosuppressive therapy equivalent to ≥ 15 mg/day of prednisone for ≥ 1 month

   c. Silicosis

   d. Intravenous drug use

   e. Malnutrition or underweight status (BMI < 20)

3. Note that patients with prior documented LTBI or active TB should not receive additional/repeated TST or IGRA testing (as results can remain positive, even after successful prior therapy).

C. Those providing LTBI screening tests must have processes in place to further evaluate patients with positive results or refer them to TB program clinics or to providers with experience managing treatment for latent TB infection.

D. Those interpreting LTBI test results should be aware of the possibility of false-positive and negative results and of conversions and reversions. Consider consultation with a TB expert in case of discordant or unclear screening results, especially in immunosuppressed individuals.

IV. Deciding Whether to Treat Latent TB Infection

A. Nearly all individuals who are diagnosed with LTBI should be offered treatment, unless specific contraindications are identified.

1. The effectiveness of LTBI treatment for reducing the incidence of active TB varies from 60-90%, and its efficacy is dependent upon adherence to treatment and available support of the healthcare system implementing the program.
2. The durability of protection is variable depending upon regional prevalence, population groups, and risk for repeat exposure to new *M. tuberculosis* infection.
3. Treatment for LTBI is not mandatory, and thus, an informed and culturally-sensitive shared decision is often necessary.

B. There are few absolute contraindications to therapy, but relative contraindications (which must be considered on an individualized basis) include:

1. A history of serious adverse reactions to both isoniazid and rifampin
2. Severe liver disease
3. Prior treatment for active TB disease or LTBI, except in recently re-exposed immunocompromised individuals or children < 5 years of age

C. Special Considerations

1. Pregnant Women (See Chapter 12: TB and Pregnancy)
   a. In women with an average/low risk of TB disease progression, treatment of LTBI can be deferred until after delivery (which generally necessitates close coordination with a primary care provider to ensure follow-up with a TB clinic post-delivery).
   b. Those with a high risk of TB disease progression (especially those with HIV or close household contact to an active case) should be offered LTBI therapy during pregnancy.
   c. While LTBI therapy during pregnancy is generally safe, all pregnant and peripartum women receiving treatment should have monthly clinical monitoring with LFTs (and a CBC if taking rifampin).
2. Close Contacts of Active TB Cases
   a. High risk contacts of contagious patients should be initiated on LTBI treatment irrespective of the result of the initial LTBI screening test (**Table 7**).
   b. Children under 5 years but over 6 months who are initiated on empiric LTBI therapy should be reassessed as to the need for a complete therapeutic course after 8-10 weeks, with treatment discontinued if the following conditions are met:

i. Repeat TST or IGRA is negative

ii. Contact with the index TB case has been broken for at least 8 weeks

iii. The child has no significant co-morbid medical conditions

3. Diagnostic Uncertainty

   a. When it is not possible to distinguish between LTBI and active TB disease, an individual should be considered to have active TB disease until proven otherwise.

   b. In such cases, a trial of multi-drug therapy for active TB disease is appropriate, with reassessment as to response to treatment at a later date (e.g. 2-3 months).

4. Potential Reinfection

   a. Generally, an individual previously treated adequately for active TB disease or LTBI should not be treated for possible recurrent LTBI at a later date.

   b. However, immunocompromised individuals (including those infected with HIV) who have experienced a significant recent exposure, should be considered for a repeat course of LTBI therapy. Clinical judgment is required to identify those at risk of developing active TB after repeated exposure and despite successfully completing prior therapy.

V. General Principles of Latent TB Infection Treatment

A. The choice of LTBI treatment regimen depends on host factors and preferences, as well as susceptibility data from the index source case, when available.

B. In many cases, the source index case is unknown, and any of the standard therapeutic regimens would be reasonable options.

C. Treatment of LTBI linked to a drug-resistant TB index case should be individualized and tailored (based on culture sensitivity data from the index case), and consultation with experts in the field is recommended.

VI. Latent TB Infection Treatment Regimens (Table 8)

A. Isoniazid (INH) and rifapentine (RPT) combination therapy (3HP)

1. Preferred regimen with strong recommendations with the shortest duration of therapy and the lowest pill burden, but the treatment regimen with which there is the least experience.

2. Centers for Disease Control and Prevention (CDC) recommendations for 3HP include:

   a. Use in persons with LTBI ages 2 to Adult

b. Use in persons with LTBI who have HIV infection, including AIDS, and are taking antiretroviral medications with acceptable drug-drug interactions with RPT

c. Can be taken either by directly observed therapy (DOT) or self-administered therapy (SAT) in persons in certain populations aged ≥ 2 years

d. Not recommended for children under 2 years of age or pregnant women

3. Hypersensitivity and flu-like syndrome reactions have been reported, especially in malnourished, elderly, or white individuals.

4. Caution with respect to drug-drug interactions with rifapentine, similar to those with rifampin.

B. Rifampin monotherapy (4R)

1. Rifampin daily for 4 months is the only currently recommended schedule for rifampin monotherapy.

2. Benefits as compared to INH monotherapy include:

a. Shorter duration of treatment

b. Higher completion rates

c. Lower rates of hepatotoxicity

3. Attention must be given to numerous possible drug-drug interactions

a. Necessitates substituting rifampin with rifabutin in persons with HIV infection on select antiretroviral agents.

b. Requires caution when considering rifampin in women using oral contraceptives for birth control and in patients undergoing methadone therapy for opiate addiction.

4. Patients should be made aware of the expected orange discoloration of the urine (which is not a drug toxicity) and possible permanent staining of soft contact lenses while taking rifampin.

5. Rifabutin may be substituted for rifampin

C. INH and rifampin combination therapy (3HR)

1. INH and rifampin daily for 3 months is used more commonly to treat LTBI in the United Kingdom than it is in the United States

2. Regimen offers shorter treatment length than either rifampin monotherapy or INH monotherapy

3. As with rifampin monotherapy, attention must be given to potential drug-drug interactions

4. Hepatotoxicity may be more frequent in INH and rifampin together than with either drug given alone

5. Rifabutin may be substituted for rifampin

D. INH monotherapy (6H/9H)

1. LTBI regimen with the most accumulated data substantiating its efficacy
2. Requires the longest duration of therapy of the available regimens and has the lowest completion rates
3. Four potential dosing schedules; daily therapy for 6 months is the preferred INH regimen for most patients
4. Regimen with most potential for hepatotoxicity

Table 8. Treatment Regimens for Latent TB Infection

Drug(s)	Duration of Treatment	Dosing Schedule	Dose	Notes
Isoniazid and Rifapentine (3HP)	12 weeks (11-12 doses within 16 weeks)	Once-weekly (via DOT or SAT)	INH 15 mg/kg (ages ≥12) 25 mg/kg (ages 2-11) Maximum dose: 900 mg RPT (dose by weight) 10.0-14.0 kg: 300 mg 14.1-25.0 kg: 450 mg 25.1-32.0 kg: 600 mg 32.1-49.9 kg: 750 mg ≥50.0 kg: 900 mg	Preferred regimen Strong recommendation Not recommended for children under two or pregnant women
Rifampin[1] (4R)	4 months (120 doses within 6 months)	Daily	10 mg/kg Maximum dose: 600mg 15-20 mg/kg (ages 2-17) 20-30 mg/kg (ages <2 years)	Preferred regimen Strong recommendation
Isoniazid and Rifampin (3HR)	3 months 90 doses	Daily	INH Adults: 5 mg/kg Children: 10-15 mg/kg Rifampin Adults: 10 mg/kg Children: 15-20 mg/kg (ages 2-17) 20-30 mg/kg (ages <2 years)	Alternative regimen Conditional recommendation

Table 8. Treatment Regimens for Latent TB Infection

Drug(s)	Duration of Treatment	Dosing Schedule	Dose	Notes
Isoniazid (6H/9H)	6 months[2] (180 doses within 9 months)	Daily	Adults: 5 mg/kg Children: 10-15 mg/kg Maximum dose: 300 mg	Preferred regimen Conditional recommendation for HIV *negative* Alternative recommendation for HIV *positive*
	9 months (270 doses within 12 months)			Alternative regimen
	6 months[3,4] (52 doses within 9 months)	Twice-weekly (via DOT)	Adults: 15 mg/kg Children: 20-30 mg/kg Maximum dose: 900 mg	Alternative regimen Conditional recommendation
	9 months[4] (270 doses within 12 months)			Alternative regimen

[1]As compared to INH therapy, a recent clinical trial using rifampin demonstrated higher completion rates, fewer adverse effects in children and adults and similar efficacy compared to isoniazid
[2] Use with caution in pregnant patients; avoid in persons who are living with HIV/AIDS
[3]Not recommended for individuals living with HIV/AIDS
[4]Avoid in pregnant patients who are living with HIV/AIDS

VII. Interruptions of Therapy

A. Missed doses are a major cause of LTBI treatment failure.

B. Causes of missed doses must be identified and overcome, whenever possible.

C. When treatment has been interrupted, the same regimen should be restarted, either from the beginning or from the point of last treatment (depending on the duration of interruption and the parameters of duration and number of doses outlined in (**Table 8**).

VIII. Treatment Counseling

A. Successfully guiding an individual through LTBI therapy requires establishing realistic patient expectations and strategies for overcoming barriers for optimal treatment adherence.

B. Sufficient time should be dedicated to individualized patient education and shared decision making prior to initiating any LTBI mediations and during the treatment.

Table 9. Patient Education Topics

Topics for Education, Counseling, and Discussion Prior to and During Treatment of Latent Tuberculosis Infection
Culturally sensitive explanation of latent tuberculosis infection, with emphasis on the logic of treating an asymptomatic condition and the goals of therapy
Description of potential minor and major adverse effects
Instructions regarding when to hold therapy and seek immediate in-person evaluation
Counseling regarding abstinence from alcohol and other hepatotoxic substances
Information regarding avoiding pregnancy during treatment, if applicable
Discussion of logistical barriers to successful treatment, including issues related to healthcare access
Appreciation of potential cultural barriers to completion of therapy
Emphasis on regular communication between the healthcare provider and the patient

IX. Minimizing Harm During Latent TB Infection Therapy

A. To reduce the risk of INH-induced peripheral neuropathy, the use of pyridoxine (vitamin B6) 25-50 mg daily is recommended for certain patients (Table 10).

B. Limiting alcohol use

1. The most important risk factor for liver toxicity during LTBI treatment is alcohol consumption, especially with binge drinking and in patients with chronic liver disease.

2. Appropriate counseling with realistic expectations should be provided to patients.

Table 10. Indications for Pyridoxine Supplementation

Risk Factors for Isoniazid-Induced Peripheral Neuropathy	
Pregnancy	Chronic kidney disease
Breast feeding	History of neuropathy
Diabetes mellitus	History of seizures
HIV infection	Malnourishment
Poor diet	Substance Abuse

X. Monitoring for Drug Toxicity

A. Baseline laboratory testing

1. Baseline liver function tests (LFTs) should be obtained in all individuals with an elevated risk of hepatotoxicity. These include patients with:

   a. Pre-existing liver disease

   b. History of alcohol abuse

c. HIV infection

d. Concurrent treatment with other hepatotoxic medications

e. Current or recent pregnancy

f. Individuals who were born in areas with high rates of viral hepatitis (e.g. countries in Asia and Africa)

2. Consultation with a hepatologist and TB expert are recommended for patients with severe liver disease (e.g. cirrhotics or liver transplant candidates).

3. Baseline complete blood count (CBC) and serum creatinine should be obtained in patients who will be treated with rifampin or 3HP.

B. Laboratory testing during treatment

1. Liver Function Testing (LFT)

a. Routine LFTs during LTBI treatment is not necessary for most patients (but is at the discretion of the provider taking into account the clinical circumstances of individual patients); however, serial LFTs (at least monthly) should be obtained in the following circumstances:

i. History of liver disease

ii. Concern for alcohol use during LTBI treatment or concomitant use of other potential hepatotoxic drugs

iii. Pregnancy

iv. Abnormal baseline LFTs

b. Patients with signs or symptoms of drug induced liver injury should stop their LTBI therapy and undergo immediate clinical and laboratory test evaluation

c. Indications to stop LTBI therapy due to drug induced liver injury:

i. Transaminases ≥ 5 times normal in an asymptomatic patient

ii. Transaminases ≥ 3 times normal in a symptomatic patient

iii. Total bilirubin ≥ 2

2. Complete Blood Count (CBC)

a. In addition to LFTs, patients treated with rifampin or 3HP who have lab abnormalities identified on baseline testing are recommended to have periodic CBC checks during therapy.

b. Decisions regarding the frequency of testing and the threshold for discontinuation of rifampin or 3HP are individualized.

C. Evaluation of Rash

1. Rash is a common adverse effect reported during LTBI treatment with either INH or rifampin.
2. A patient report of rash should always prompt clinical evaluation; mild skin eruptions can often be managed with topical treatment and/or oral antihistamines, without interrupting LTBI therapy.

D. Clinical Monitoring During Treatment

1. All patients receiving treatment for LTBI should be seen in person by healthcare personnel at least monthly. Clinical monitoring is the most effective strategy for reducing drug toxicity and is an essential element in all LTBI treatment programs, regardless of other monitoring efforts.
2. Clinical evaluations during LTBI treatment should assess for:
   a. Adverse drug reactions, especially hepatotoxicity
   b. Adherence to therapy
   c. Signs or symptoms concerning for active TB disease
   d. Need for continued patient education

XI. Completion of Latent TB Infection Therapy

A. A medical clearance letter documenting the completion of LTBI treatment should be given to the patient and placed in the medical records. No TB clinic follow-up for these patients is necessary.

B. Future Screening

1. Subsequent screening and follow up should focus on checking for active TB disease based on symptom questionnaire, in accordance with local policies.
2. Repeat TST or IGRA testing should not be performed as they typically remain positive after treatment.
3. Re-establish continuity of care with primary care team.

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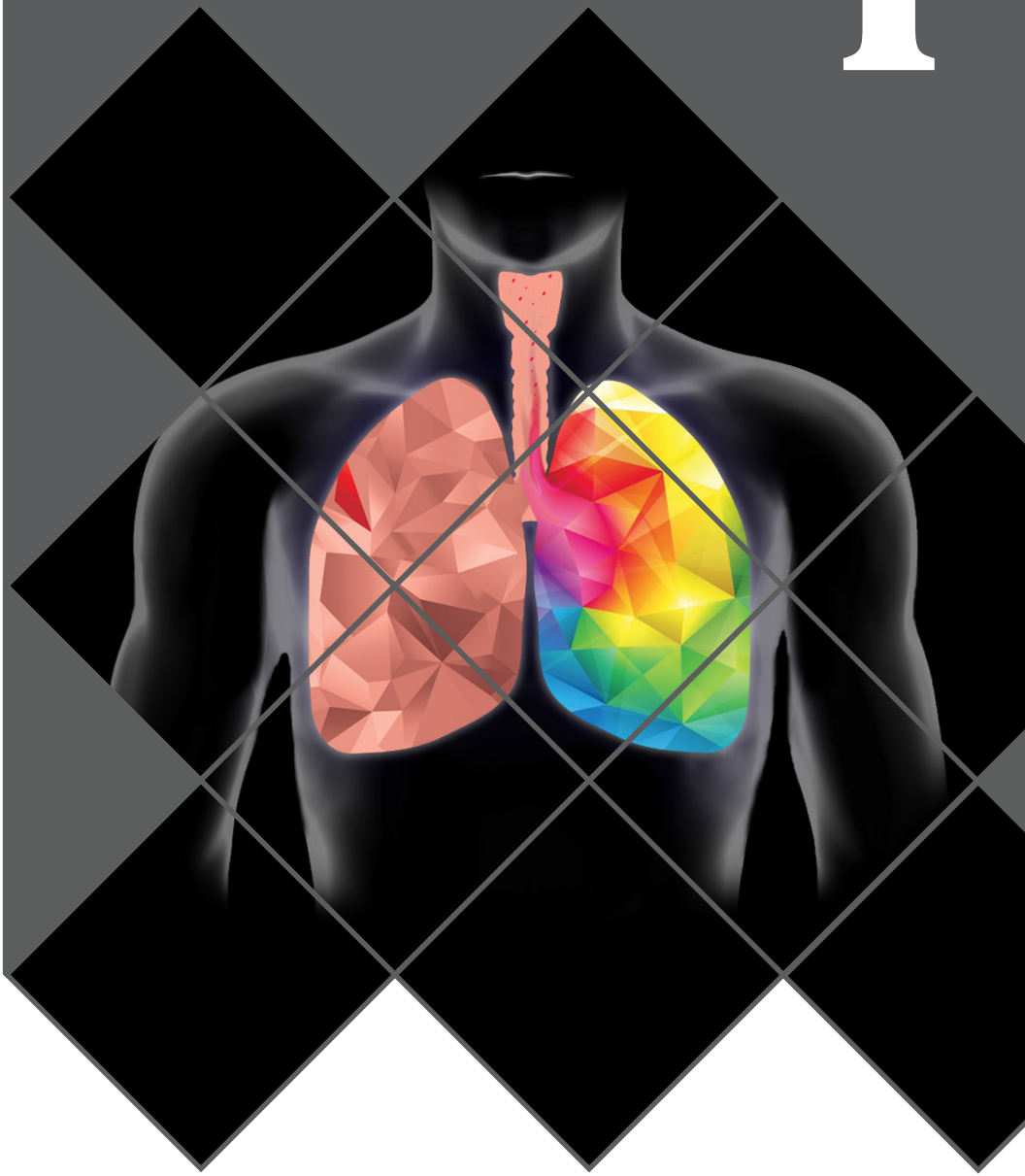
Chapter 4



Treatment of TB Disease

Chapter 4

Treatment of Tuberculosis Disease

Thomas C. Bailey, MD; Douglas B. Hornick, MD

I. General Considerations

A. Reportable Condition: report any patient with suspected or confirmed active tuberculosis (TB) to the appropriate State Tuberculosis Elimination Division and/or the local health authority within 24 hours.

B. Manage active TB in consultation with an experienced TB clinician.

C. Test all TB patients for HIV infection. Those confirmed should be co-managed with a clinician experienced in the treatment of HIV disease. (See Chapter 6: Tuberculosis and HIV for further information).

1. The CDC/ATS/IDSA and WHO TB management guidelines both recommend starting anti-retroviral therapy (ART) as soon as possible in all patients with drug susceptible TB and HIV; ideally within 2 weeks of starting TB therapy for patients with CD4 counts under 50 cells/uL and by 8-12 weeks for patients with CD4 counts of 50 cells/uL or higher.

2. An exception is with central nervous system (CNS) TB/meningitis and HIV. Because early ART initiation may be detrimental in patients with TB meningitis, it has been recommended to delay starting ART in patients with CNS TB and HIV by up to 8 weeks after starting TB therapy. If there is evidence of increased intracranial pressure further delay may be needed. Consultation with an expert may be necessary.

D. Send the initial TB isolate from any patient with active TB for drug susceptibility testing (DST), and report results to the appropriate State Tuberculosis Elimination Division and the local health authority.

1. Rapid resistance testing is recommended particularly for previously treated patients, and for patients from countries with a high prevalence of drug resistance. (See Chapter 5: Principles of Drug Resistance)

2. Rapid molecular drug resistance testing is available through State and reference laboratories and includes the Cepheid GeneXpert® (Xpert®) MTB/RIF and Xpert® MTB/RIF Ultra assays (Cepheid, Sunnyvale, USA); Line probe assays, including the INNO-LiPA RIF TB (Innogenetics, Ghent, Belgium), the GenoType MTBDRplus (Hain Life-Science, Nehren, Germany) and the GenoType MTBDRs (Hain Life-Science, Nehren, Germany); Pyrosequencing and Sanger sequencing (including through the CDC's Molecular Diagnostic Drug Resistance (MDDR) testing platform and whole genome sequencing).

E. The most common cause of treatment failure and relapse is non-adherence to therapy. Adherence must be monitored carefully in all patients.

F. Treat every patient using directly observed therapy (DOT). Daily therapy refers to administering by DOT 5 or 7 days per week. Patients may self-administer medications on weekends and/or holidays.

G. Apply case management interventions wherever possible. These may include patient reminders/incentives/enablers, field or home education/counseling as well as enhanced coordination and integration of care with specialists. (See Chapter 13: Section VI. Basic Principles of Case Management).

H. Educate each patient about the toxicities of the medications. Instruct each patient to report any suspected adverse event or toxicity immediately to their providers. (See Chapter 11: Clinical Monitoring and Toxicity Management for information on drug toxicities)

I. Patients with extensive TB lung disease (e.g., bilateral cavitation; multi-lobe consolidation) and/or delayed response to therapy (i.e., culture positive at 2 months) require 9 months or longer treatment (consultation with physician experienced in TB management is recommended).

J. Add corticosteroids only in select patients with extra-pulmonary TB. These would include patients with meningitis and select patients with pericarditis (those with large effusions, high levels of inflammatory cells in pericardial fluid, or those with early signs of constriction).

K. As with drug-susceptible pulmonary TB, 6 months of treatment is needed for most forms of extra-pulmonary TB. However, meningitis, some with bone/joint TB and drug-resistant TB, require longer durations of therapy. (See Chapter 9: Extra-pulmonary TB)

L. Treatment of TB in Special Situations - refer to the following chapters:

1. Drug resistant TB (Chapter 5)
2. HIV infection and TB (Chapter 6)
3. Children with TB (Chapter 7)
4. Pregnancy/Breastfeeding and TB (Chapter 12)

II. Specific Treatment Regimens

A. Routine TB cases complete treatment after taking the prescribed number of doses, rather than after taking treatment for a prescribed length of time.

B. The standard regimen for drug-susceptible TB starts with an "intensive phase", consisting of isoniazid (INH), rifampin, pyrazinamide (PZA) and ethambutol (EMB). This phase treats the rapidly replicating and large number of TB organisms (especially in lung cavities). The longer "continuation phase" follows and continues with INH and RIF to eradicate

the more slowly replicating residual TB organisms in macrophages and caseous foci.

C. Table 11 lists the first-line anti-tuberculosis medications and recommended doses for adults.

Table 11. First-Line Medication Doses for Adults

Drug	Daily (Max)	Thrice Weekly (Max)**	Twice Weekly (Max)**	Adverse Effects
Ethambutol PO Tabs 100, 400 mg	40-55 kg: 800 mg 56-75 kg: 1200 >75 kg: 1600	40-55 kg: 1200 mg 56-75 kg: 2000 >75 kg: 2400	40-55 kg: 2000 mg 56-75 kg: 2800 >75 kg: 4000	Decreased red-green color discrimination, decreased visual acuity, rash; renal dysfunction increases risk; dose adjustment required for eGFR <30
Isoniazid* Tabs 100, 300 mg Elixir 50 mg/5 ml IV/IM 100 mg/ml	5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	Hepatotoxicity, peripheral neuropathy, headache, anorexia, nausea, rash, drug induced lupus, hematologic toxicity
Pyrazinamide PO Tabs 500 mg	40-55 kg: 1000 mg 56-75 kg: 1500 >75 kg: 2000	40-55 kg: 1500 mg 56-75 kg: 2500 >75 kg: 3000	40-55 kg: 2000 mg 56-75 kg: 3000 >75 kg: 4000	Nausea, hepatotoxicity, arthralgias, gout, rash
Rifampin Caps 150, 300 mg Suspension can be made from powder IV+ (various strengths)	10-20 mg/kg (600 mg)	10-20 mg/kg (600 mg)	10-20 mg/kg (600 mg)	Fever, rash, hepatotoxicity, renal failure, thrombocytopenia, flu-like syndrome; increases metabolism of many drugs, e.g. methadone, many HIV medications, coumadin; oral contraceptives unreliable

*Add Pyridoxine (vit B6) 25-50 mg/day to prevent neuropathy: Malnourished, diabetes, alcoholism, elderly, chronic renal failure, pregnant, HIV Give 100 mg/day to those with peripheral neuropathy
+Rifampin 20-30 mg/kg IV for TB meningitis due to poor CSF penetration
**Use daily treatment in all patients, if possible. Avoid twice weekly unless only possible option.

D. Intensive phase: administer INH, rifampin, PZA, and EMB for suspected or confirmed pan-susceptible TB (Table 12).

Table 12. Medication Regimens Listed in Descending Order of Effectiveness

	Intensive Phase		Continuation Phase[2]	
	Drugs[1]	Schedule of Doses	Drugs	Schedule of Doses
I	INH, RIF, PZA, EMB	7 days/wk for 56 doses (8 weeks) OR 5 days/wk for 40 doses (8 weeks)	INH, RIF	7 days/wk for 126 doses (18 weeks) OR 5 days/wk for 90 doses (18 weeks)
II	INH, RIF, PZA, EMB	7 days/wk for 56 doses (2 weeks) OR 5 days/wk for 40 doses (2 weeks)	INH, RIF	3 days/wk for 54 doses (18 weeks)
III	INH, RIF, PZA, EMB	3 days/wk for 24 doses (8 weeks)	INH, RIF	3 days/wk for 54 doses (18 weeks)
IV	INH, RIF, PZA, EMB	7 days/wk for 14 doses THEN twice weekly for 12 doses	INH, RIF	Twice weekly for 36 doses (18 weeks)[3]

[1]EMB can be stopped once drug susceptibility to INH and RIF is confirmed.
[2]Extend continuation phase to 31 weeks for cavitation on initial chest x-ray AND positive culture obtained at 2 months of therapy.
[3]Use daily treatment in all patients, if possible. Avoid twice weekly unless only possible option.

1. EMB is included in the initial 4-drug regimen to protect against the emergence of RIF resistance if INH resistance is present, but not yet diagnosed. EMB can be discontinued if isolate confirmed to be pansusceptible.
2. PZA must be included in the regimen in the intensive phase to permit a 6-month (26-week) treatment regimen. If PZA cannot be administered, the continuation phase should be extended to at least 7 months (i.e. 31 weeks for the continuation phase), 9 months, (39 weeks) total duration of therapy. (See Section E).
3. Daily DOT (either 5 or 7 days/week) is prefered over intermittent regimens (Regimens I & II, Table 12). Customary expectation for U.S. TB Control Programs: Patients must complete the total designated number of doses within 2.5 months.
4. Only consider using thrice-weekly regimen (Regimen III, Table 12) for HIV negative patients with non-cavitary and/or Acid Fast Bacilli (AFB) stain negative disease.
5. The twice-weekly regimen (Regimen IV, Table 12) must only be used when daily or thrice-weekly DOT is impossible or extremely difficult, after 14 days of daily DOT, and only for the HIV negative patient with non-cavitary and/or AFB stain negative disease.

E. Continuation phase: Customary expectation for U.S. TB Control Programs: Patients must complete the total designated number of doses within 6 months (i.e., the entire regimen within 9 months).

1. Daily INH and RIF is preferred, however thrice-weekly DOT regimen can be used in circumstances where daily therapy is difficult programmatically and only for drug-susceptible tuberculosis (Regimens I & II, **Table 12**).
2. Extend the continuation phase from 18 weeks to 31 weeks when initial chest x-ray (CXR) shows cavitation AND the culture obtained at 2 months on treatment remains positive.
3. Consider prolongation from 18 weeks to 31 weeks for immunocompetent patients with initial cavitary chest x-ray OR positive culture at 2 months, particularly when response to treatment delayed, and especially cases with extensive disease, poorly controlled diabetes, late culture conversion, or severe malnourishment per BMI. (See BMI chart at https://www.heartlandntbc.org/assets/products/bmi_card_oct_2008.pdf.)
4. Consider decreasing from 18 weeks to 9 weeks in HIV negative patients with culture-negative, non-cavitary pulmonary TB.
5. Regimen III, **Table 12** uses thrice-weekly therapy in the continuation phase, and is less preferable. Avoid using in patients with HIV and those with cavitary disease.
6. The twice-weekly regimen (Regimen IV, **Table 12**) results in higher relapse rates if any doses are missed and must only be used in HIV negative patient with non-cavitary and/or AFB stain negative disease.
7. Intermittent dosing regimens should not be used for drug-resistant disease.

F. Managing treatment interruptions: Send sputum for AFB stain, culture, and susceptibility when resuming therapy after being lost to follow-up. Consider the following approaches based on timing and duration of interruption:

1. During intensive phase, if interruption:
   a. ≤ 14 days: Continue & complete total number doses intended (must be completed by 2.5 months)
   b. > 14 days: Start over from beginning
2. During continuation phase, if patient completed:
   a. ≥ 80% intended doses & initial sputum AFB stain negative: Further treatment may be unnecessary
   b. ≥ 80% intended doses but initial sputum AFB stain positive: Must complete total number of doses intended

c. < 80% intended doses & hiatus < 3 months plus consecutive lapse ≤ 2 months: Must complete total number doses intended. If unable to complete w/in 6 months, start over with the intensive followed by continuation phase

d. < 80% intended doses and hiatus ≥ 3 months: Start over with the intensive followed by continuation phase

G. Follow-up post treatment: Routine follow-up is not recommended by the CDC for patients demonstrating satisfactory bacteriologic response (negative cultures after 2 months of therapy) and completing a 6- or 9-month INH and rifampin-containing regimen. However, patients with the following characteristics may benefit from at least one year follow-up: poorly controlled diabetes, HIV, those with drug-resistant, disseminated or extensive TB, and those re-treated for TB.

III. Patients with Drug Intolerance, Treatment Failure, or Relapse

A. Treat any patient with these conditions in close consultation with an expert in TB.

B. Patients with drug intolerance(s) require individualized regimens.

C. Identify as treatment failure patients who fail to convert sputum cultures to negative after 4 months of standard therapy.

1. Augment treatment with at least 2, and preferably 3 new drugs to which the isolate is known to be susceptible.
2. Review adherence and evaluate for factors interfering with absorption of medication.
3. Consider therapeutic drug level monitoring.
4. Request new cultures and rapid/molecular and standard/phenotypic DST.

D. Patients who relapse following successful treatment most likely have drug susceptible TB if they were adherent to the standard 4 drug regimen (RIPE) given by DOT.

1. Obtain rapid molecular and standard DST on the TB isolate from these patients.
2. Administer the standard TB regimen (rifampin, INH, PZA, and EMB) when the prior regimen was a rifampin-based regimen given by DOT. If poor adherence for the initial treatment suspected or documented, consider initiating an expanded regimen in consultation with an expert in TB.

IV. Monitoring for Efficacy of Treatment

A. Obtain 3 sputum specimens for AFB stain and culture initially. Every 1-2 weeks collect 2-3 sputum specimens for AFB stain and culture until stains are negative.

B. Discontinue airborne infection isolation (AII) for patients with pulmonary TB after:

   1. 3 consecutive quality sputum samples submitted for AFB stains become negative, AND
   2. 2 weeks of effective therapy completed (1 week if baseline AFB smear negative), AND
   3. Clinical improvement is evident.
   4. The duration of isolation will be prolonged for patients with suspected MDR or rifampin-resistant (RR) TB.

C. For patients with persistently positive AFB stains but negative cultures, 2 consecutive negative cultures define non-infectiousness. (See Chapter 13: Hospitalization, Isolation, Public Health Case Management)

D. Every month collect 2-3 sputum samples for AFB stain and culture until cultures are negative for 2 consecutive months. Note the critical importance of the specimen for culture obtained at 2 months of therapy. Treatment duration hinges on the result.

   1. In patients whose original sputum cultures are negative, obtain a CXR after 2 months of therapy to assess the radiographic response to therapy.
   2. In patients with cavitary disease; if culture is positive at 2 months treatment must be extended to a total of at least 9 months.

E. If sputum specimens collected after 2 months of therapy remain positive and the patient is not improved clinically, evaluate for issues with adherence, drug-resistant TB, or malabsorption. Repeat rapid and standard drug susceptibility studies, place patient on DOT if not already on it, and consult an expert in treating tuberculosis. Consider therapeutic drug monitoring (TDM) to optimize drug dosing.

F. Document at least monthly an assessment of the clinical response to therapy and include the following: weight, general health, and whether symptoms improved or resolved. Patients who have negative initial cultures at two months treatment require documentation of clinical and radiological response to establish the diagnosis of culture-negative clinical pulmonary tuberculosis.

G. Patients who respond slowly to therapy require prolonged treatment, consisting of extending the continuation phase of therapy as indicated in **Table 13**.

Table 13. Indications for Altering Duration of the Continuation Phase

Patient Features	HIV Status	Duration
Cavitary disease AND Positive 2 month culture	Positive or Negative	INH and RIF for 31 weeks
Cavitary disease AND Negative 2 month culture	Positive or Negative	INH and RIF for 18 - 31 weeks*
Non-cavitary disease AND Positive 2 month culture	Negative	INH and RIF for 18 - 31 weeks*
Non-cavitary disease AND Positive 2 month culture	Positive	INH and RIF for 31 weeks
Non-cavitary disease AND Negative 2 month culture	Positive or Negative	INH and RIF for 18 weeks

**Depends on clinical assessment and clinical or radiographic response*

V. Monitoring for Drug Toxicity

(See Chapter 11: Clinical Monitoring and Toxicity Management)

A. Check baseline transaminases, total bilirubin, complete blood count and serum creatinine for all patients initiating treatment. Note that TB itself can involve the liver and in those cases abnormal liver tests will improve on treatment.

B. Each month during therapy check for signs and symptoms of hepatotoxicity, neuropathy, and any other adverse reactions.

C. Obtain monthly liver tests in patients with risk factors for hepatotoxicity (e.g. baseline abnormalities, chronic medical problems, daily alcohol use, and chronic liver disease).

D. Perform additional lab testing based on clinical judgment.

E. For patients receiving EMB, assess visual acuity and color discrimination monthly. Note that up to 10% of males of European ancestry may exhibit baseline abnormalities in red-green color discrimination, which is not a contraindication to administration of EMB.

F. Managing medication induced liver toxicity. If symptoms of hepatotoxicity develop, re-evaluate hepatic transaminases and bilirubin levels. In addition, consider checking for viral hepatitis, alcohol, acetaminophen, and other toxicities.

G. Stop therapy if the transaminases are more than 5 times the upper limit of normal in the absence of symptoms (nausea, anorexia), or ≥ 3 times normal in the presence of symptoms.

1. Hold all potentially hepatotoxic medications
    a. Until ALT < 2x upper limits of normal, then start rifampin (assuming fully drug susceptible disease) and EMB.
    b. If liver enzymes do not increase after 1 week, add INH.
    c. Treat for 9 months (39 weeks).
2. For patients with advanced liver disease, consider regimens that remove both INH & PZA; for example rifampin, moxifloxacin or levofloxacin, and EMB. These regimens require longer duration (9-12 months) and introduce potential for other toxicities. These regimens are described in more detail in Chapter 10 and should be undertaken with consultation from a TB expert.

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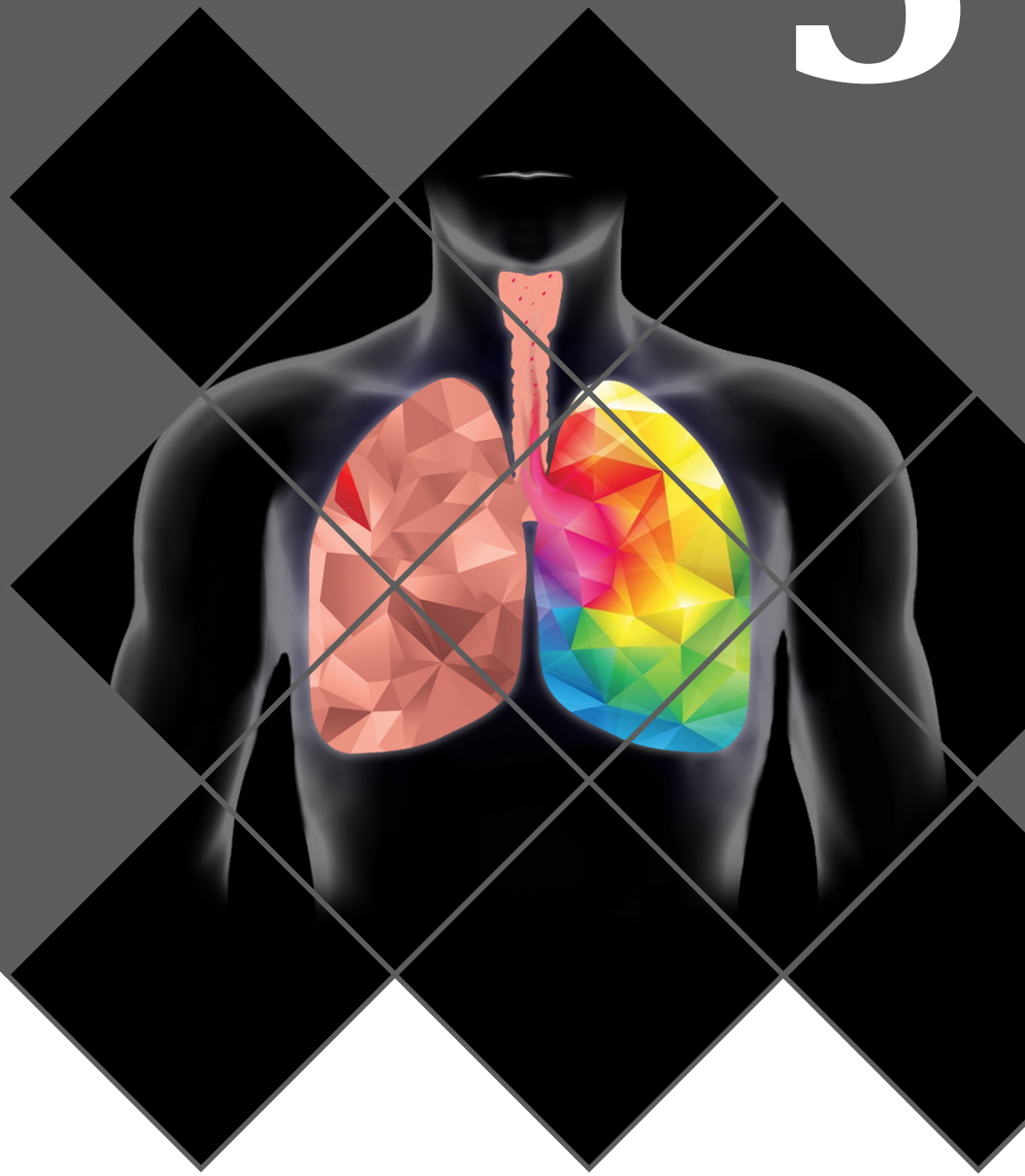
Chapter 5



Principles of Drug Resistance

Chapter 5

Principles of Drug Resistance

Quratulain (Annie) Kizilbash, MD, MPH; Adriana Vasquez, MD

I. Overview

A. Multi-drug resistant tuberculosis (MDR-TB) is caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) resistant to at least isoniazid (INH) and rifampin.

B. Pre-extensively drug resistant tuberculosis (pre XDR-TB) is caused by MDR-TB resistant to either a fluoroquinolone or a second line injectable TB drug (i.e. amikacin).

C. Extensively drug resistant tuberculosis (XDR-TB) is caused by MDR-TB resistant to both a fluoroquinolone and a second line injectable TB drug (i.e. amikacin).

D. Other drug resistance

1. Rifampin-resistant (RR) TB is caused by *M. tuberculosis* resistant to rifampin with or without resistance to other drugs but susceptible to INH.
2. INH resistant TB is caused by *M. tuberculosis* resistant to INH with or without resistance to other drugs but susceptible to rifampin.

E. RR, MDR, pre-XDR and XDR-TB require longer treatment with medications that are more expensive, have additional toxicities and are less effective.

II. Epidemiology

A. World Health Organization (WHO) Global Report 2019

1. Globally 588,000 cases of RR-TB were diagnosed in 2018, of which > 80% were MDR-TB.
2. Almost half of the global burden of MDR-TB occurs in India, China and the Russian Federation.
3. One in three persons with MDR-TB in 2018 were enrolled in treatment.
4. Although the reported global cure rate for MDR-TB is only 56%, many sites are reporting much better outcomes (80-90%) with newer drugs and all oral regimens.
5. By June 2017, 89 countries and territories had started using Bedaquiline and 54 had used Delamanid.
6. At least 35 countries have implemented shorter MDR regimens.

7. The WHO has identified an all oral shorter regimen for MDR-TB which replaces the injectable with Bedaquiline.
8. Approximately 80 high burden countries have adopted Cepheid GeneXpert® (Xpert®) MTB/RIF as the initial diagnostic test for all people with signs and symptoms of TB.

B. Risk Factors for Drug Resistant TB

1. Foreign born persons or those with history of travel to countries with a high prevalence of drug resistant TB.
2. History of TB treatment failure, self-administered therapy, poor adherence to directly observed therapy (DOT), treatment with inadequate doses of medication or inadequate drug regimens.
3. Contact to patients with drug resistant TB.

III. Evaluation of the Patient at Risk of Drug Resistant TB

A. Clinical Evaluation - Identification of patient's baseline symptoms, clinical status, weight, co-morbid illnesses, laboratory assessment (includes HIV and pregnancy test and HbA1c if appropriate), and radiographic exam (preferably within 2 weeks or less than treatment start date).

B. Mycobacteriological Laboratory Evaluation

1. Appropriate specimen collection from each site of disease
   a. Prior to initiation of treatment
   b. At time drug resistance is recognized
2. Whole Genome Sequencing (WGS) or molecular-based assays (Xpert® MTB/RIF or MTBDR*plus* line probe assay) for rapid molecular detection of *M. tuberculosis* and resistance to rifampin.
3. When WGS or molecular testing suggests rifampin-resistance a full panel of drugs detected by molecular testing is done.
4. Conventional phenotypic culture-based susceptibility testing to first and second-line drugs. If specimen is identified as rifampin-resistant and referred to CDC, their lab will do further molecular testing and extended battery of susceptibility tests to include minimal inhibitory concentration (MIC) for levofloxacin, moxifloxacin, bedaquiline, linezolid, and clofazimine.
5. Discordant susceptibility reports may occur, and the gold standard depends on the specific drug.
6. A laboratory expert and a clinical expert should be consulted regarding diagnosis and management of MDR/XDR.

IV. Molecular Detection of Drug Resistance

A. Molecular assays detect *M. tuberculosis* gene mutations associated with drug resistance.

B. These tests differ in the variety of mutations detected and each has some limitations.

   1. Failure to detect a mutation associated with drug resistance does **NOT** exclude resistance.

   2. Some mutations are not associated with drug resistance.

C. Molecular tests should always be combined with phenotypic drug resistance testing to best identify drug susceptibility and resistance in *M. tuberculosis* isolates.

D. Select Rapid Molecular Assays for Detection of Drug Resistance

   1. Xpert® MTB/RIF and Xpert® MTB/RIF Ultra

      a. Molecular tests that detect both *M. tuberculosis* and rifampin resistance by select rpoB gene mutations by real time PCR in rifampin-resistance determining region (RRDR).

      b. The World Health Organization (WHO) recommends the use of Xpert® MTB/RIF or Xpert® MTB/RIF Ultra as the initial diagnostic test for all adults and children with signs and symptoms of TB and for testing of extra-pulmonary specimens (CSF, lymph nodes and tissue).

      c. Xpert® MTB/RIF is FDA approved in the United States for use on smear positive or negative sputum specimens and isolates of *M. tuberculosis*. It is not approved in the U.S. for extra-pulmonary specimens, but some laboratories have laboratory approved tests for use on these specimens.

         i. False positive detection of resistance can occur

         ii. Although uncommon, RR can be missed (2 – 3%)

      d. Xpert® MTB/RIF Ultra is not approved for use in the United States at this time. It has a higher sensitivity in *M. tuberculosis* detection in cases of AFB smear negative, culture positive TB.

      e. CDC recommends confirmation with a sequence-based method, molecular detection of drug resistance (MDDR) if RR is detected by Xpert® MTB/RIF.

   2. MTBDR*plus* (Hain LifeScience, RUO) line probe assay utilizes paper strips with microbial DNA hybridization to identify both *M. tuberculosis* and select drug resistance via multiple gene mutations. Rifampin-resistance detected in the RRDR.

3. Sequencing

   a. MDDR is offered through the CDC and can perform targeted DNA sequencing to identify resistance to isoniazid, rifampin, pyrazinamide, ethambutol, the fluoroquinolones and injectable agents. Soon they will add additional testing that includes newer drugs (Bedaquiline, linezolid, clofazimine).

      i. Pyrosequencing detects mutations in the rpoB and RRDR

      ii. Sanger Sequencing detects mutations in the the rpoB

      iii. Next Generation Sequencing detects mutations in the rpoB and its promoter region

      iv. Whole Genome Sequencing detects mutation in rpoB and assesses entire genome for other genetic predictors of drug resistance

E. Common Mutations (nucleic acid substitutions) that confer select drug resistance have been identified. A listing of many of the common mutations and their effect on the susceptibility of the MTB isolate are described in Curry International Tuberculosis Center and California Department of Public Health, 2016: Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, Third Edition, Chapter 3, Table 3, page 46-47.

V. General Principles of MDR/XDR-TB Treatment

A. Individualized treatment regimens based on genotypic and phenotypic DST are associated with better outcomes.

B. Increased treatment success was found in patient who received linezolid, bedaquiline and a newer generation fluoroquinolone.

C. Good Practice Statements

1. When there is suspicion or documentation of drug resistant TB (DR-TB) request consultation from an expert or regional CDC-designated TB Center of Excellence https://www.cdc.gov/tb/education/tb_coe/ or through local health department TB programs https://www.cdc.gov/tb/links/tboffices.htm.

2. Obtain molecular drug susceptibility tests for rapid detection of mutations associated with resistance. If RR is detected, additional testing should be performed (see above).

3. Use only drugs to which the patient's *M. tuberculosis* isolate has documented or high likelihood of susceptibility.

4. Monitor treatment response clinically, radiographically and bacteriologically. Obtain cultures at least monthly for pulmonary TB throughout treatment.

5. Ask patients about adverse effects at each visit. Investigate and work to ameliorate these effects.
6. Patient-centered case management is the standard of care.

D. Treatment Recommendations for Individualized Treatment (not Short Course Therapy)

1. Use at least 5 drugs in the intensive (initial) phase of treatment and 4 drugs in the continuation phase.
2. The intensive phase, during which 5 drugs are recommended, should last for 5 – 7 months after culture conversion.
3. The total duration of treatment should be between 15 and 21 months after culture conversion.
4. Consider extending total treatment duration to 15 – 24 months in those with pre-XDR and XDR-TB especially if there is extensive disease or a slow response to treatment.
5. Treatment regimen should generally, when isolate is susceptible, include:
   a. Later generation fluoroquinolone (levofloxacin or moxifloxacin)
   b. Bedaquiline
   c. Linezolid
   d. Clofazimine
   e. Cycloserine
6. When resistance is excluded or highly unlikely, and other more effective drugs noted above cannot be used to achieve the recommended initial regimen of 5 drugs or the continuation phase of 4 drugs, the following drugs can be utilized:
   a. PZA
   b. Ethambutol
   c. Delamanid
7. When oral options are not available to adequately treat the patient
   a. Amikacin or streptomycin (when isolate documented to be susceptible) can be included in the regimen. These drugs have moderate efficacy but significant toxicity.
   b. Carbapenem (always give amoxicillin clavulanate with each dose of carbapenem); Imipenem and meropenem both have been associated with treatment success as evaluated in an individual patient data meta-analysis.
   c. Kanamycin and capreomycin are not recommended.

8. Older oral drugs should be avoided
    a. Ethionamide should only be used if more effective drugs (noted above) are not available.
    b. PAS (p-aminosalicyclic acid) should rarely, if ever, be used. This drug is used only when other available options are not possible.
    c. Amoxicillin-clavulanate should not be used unless paired with a carbapenem.
    d. Macrolide antibiotics, azithromycin and clarithromycin should not be used.

E. Pretomanid was approved by the FDA in 2019 for use as part of the Bedaquiline, Pretomanid Linezolid regimen (BPaL) in selected patients, such as adult patients with:
    1. Pulmonary XDR-TB
    2. Treatment-intolerant or nonresponsive MDR-TB
    3. Approval was based on limited clinical safety and efficacy data
    4. CDC guidelines to be released in late 2020

F. Patient Centered Care
    1. Patient centered case management has been associated with better outcomes; completion of successful therapy and fewer adverse effects.
    2. Employs a collaborative process that plans, coordinates and evaluates services to meet the patient's needs.
    3. Includes shared decision making on composition of treatment regimen.
    4. DOT should be used in all patients with DR-TB
        a. A patient centered approach includes patient input into the timing and place of DOT.
        b. Video DOT (v-DOT) has been successfully used in treatment of DR-TB patients.
    5. Involves education of the patients and family on the risks and benefits of medications proposed for treatment.

G. Toxicity Monitoring (**Table 14**)
    1. Educate patients on known side effects, adverse effects and the importance of reporting these to their healthcare provider.

Table 14. Monthly Toxicity Monitoring by Medication Type

Medication	Assessment								
	Visual Acuity and Color Vision Assessment	Neuropathy Screening	Changes in Mental Status	EKG	Ca++ K+ Mg++	Thyroid Stimulating Hormone	Renal Function[1]	Audiometry from 1000 Hz to 8000 Hz	Vestibular Toxicity Assessment
Amikacin					BL/Monthly		BL/Monthly	BL/Monthly	BL/Monthly
Bedaquiline				BL/Monthly	BL/Monthly	BL/q 3 Months			
Clofazimine			BL/Monthly[2]	BL/Monthly					
Cycloserine		BL/Monthly	BL/Monthly				BL/Monthly[1]		
Delamanid				BL/Monthly	BL/Monthly	BL/q 3 Months			
Ethambutol	BL/Monthly						BL/Monthly[1]		
Ethionamide	BL/Monthly	BL/Monthly				BL/q 2-3 Months			
Fluoroquinolones		BL/Monthly	BL/Monthly[3]				BL/Monthly[1,4]		
Isoniazid		BL/Monthly							
Linezolid	BL/Monthly	BL/Monthly							
PAS						BL/q 2-3 Months	BL/Monthly[1]		
Pretomanid				BL/Monthly	BL/Monthly[5]				
Streptomycin					BL/Monthly		BL/Monthly	BL/Monthly	BL/Monthly

BL-Baseline Ca-Calcium K-Potassium Mg-Magnesium

[1]-BL and monthly renal function assessment recommended for all drugs that require renal adjustment

[2]-Some patients become depressed due to skin color changes

[3]-especially high-dose

[4]-Levofloxacin

2. All patients should have the following monitored at baseline and at least monthly:
    a. Weight
    b. Sputum smear and culture
    c. CBC, CMP and if appropriate HbA1c, pregnancy test
    d. HIV status
    e. Symptoms of TB
    f. New concerns or problems that interfere with treatment
    g. Adherence assessment

H. Surgery to Treat Drug Resistant TB
1. Severe hemoptysis
2. Bronchopleural fistula
3. Extensive drug resistance, slowly responding disease (positive culture after 4-6 months of treatment), weak treatment regimen
4. Generally, patients who are good surgical candidates will have localized disease and have adequate pulmonary function to tolerate removal of part of lung
5. Lobectomy is preferred procedure; pneumonectomy should be avoided
6. Decision to perform resectional surgery should be made in consultation with a MDR-TB expert and an experienced thoracic surgeon. Culture conversion or at least response to therapy is important prior to surgical resection to allow adequate healing of bronchial stump to occur postoperatively

I. Therapeutic Drug Monitoring (TDM) (See Chapter 10: Drug Therapy for TB)
1. Allows optimization of a dose with less toxicity, especially helpful with second line injectable drugs, trough level of linezolid and when absorption may be compromised.
2. For TDM, TB medications are administered under supervision and blood samples are collected for most drugs at 2 and sometimes 6 hours post medication administration.
    a. For Linezolid and injectable drugs, the trough level is very important.
    b. Accurate documentation of the time of medication, time of blood draw, and the dose is necessary.

3. TDM is recommended in the following situations:
    a. Cycloserine peak
    b. Linezolid trough (some experts also monitor peak level)
    c. Amikacin or streptomycin trough
    d. Moxifloxacin when levofloxacin resistance is noted, or MIC of moxifloxacin is 1.0 ugm/ml
    e. Patients with CNS disease
    f. Document absorption and peak levels especially of fluoroquinolones, linezolid
    g. Gastrointestinal disease that may impact absorption
    h. Poor response to treatment
    i. Unclear target for clofazimine, bedaquiline at present; monitoring may become recommended in future

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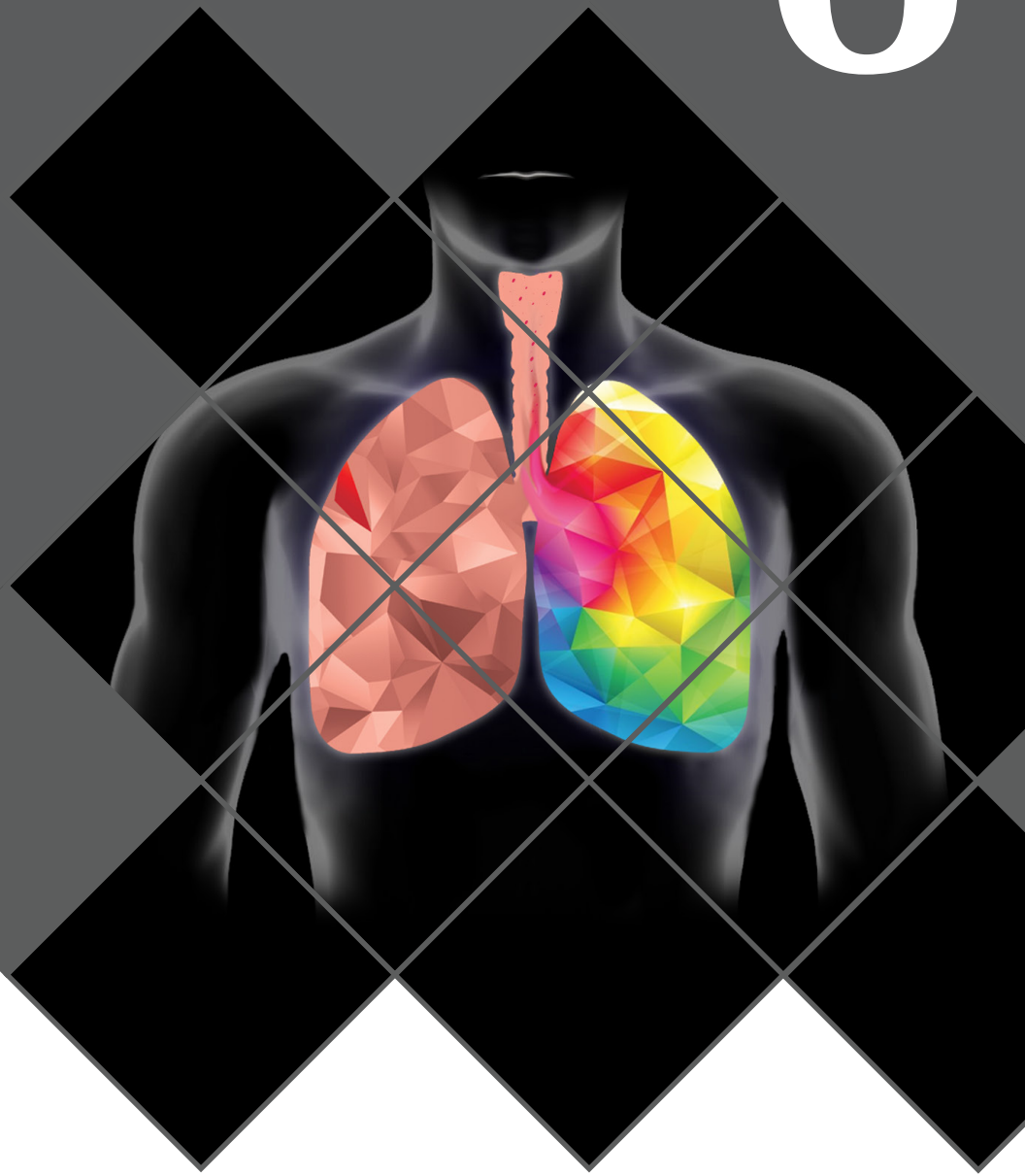
Chapter 6



TB and HIV

Chapter 6

Tuberculosis and HIV

Jennifer Whitaker, MD, MS

I. General Considerations

A. Tuberculosis (TB) is the primary cause of morbidity and mortality worldwide among Persons Living With HIV/AIDS (PLWHA). In 2017, in the United States, 5.5% of persons with active TB who were tested for the human immunodefeciency virus (HIV) were found to have TB/HIV co-infection in 2017.

B. HIV infection increases the risk of progression from TB infection to active TB. In persons with untreated HIV, the estimated annual risk of TB reactivation in PLWHA and TB infection is 3-16% per year. TB reactivation can occur with any CD4 count. The risk does increase with progressive immunologic decline (lower CD4 counts). All PLWHA diagnosed with either latent TB infection or active TB should be treated regardless of CD4 count.

C. All persons with LTBI or active TB should be screened for HIV infection. The HIV status of every patient with active TB should be documented.

D. All PLWHA should be treated with antiretroviral therapy (ART) regardless of their CD4 count. The initiation of ART in persons with HIV and active TB should be done early (within 2 weeks from time of TB diagnosis for those with CD4 count <50 cells/µl and within 8 weeks for those with CD4 count >50 cells/µl). An exception is for patients with TB meningitis and HIV, where consideration should be given for delaying the start of ART for up to 8 weeks after starting TB therapy. This is to reduce the incidence of Grade 4 adverse events.

E. There are potential drug interactions between TB medications and ART (**Table 15**). The clinician should be cognizant of these interactions. Consultation with a TB, HIV, or infectious disease expert (or pharmacist) with experience with these medications is recommended.

F. Clinicians need to be aware of the potential for additional concomitant opportunistic infections in persons with TB/HIV co-infection. A consultation with an infectious disease expert may be helpful in those special clinical circumstances.

G. People with HIV and TB may experience a paradoxical worsening of symptoms known as Immune Reconstitution Inflammatory Syndrome (IRIS) while on therapy for HIV and TB. Clinicians should be familiar with the evaluation of IRIS and that it is a diagnosis of exclusion.

Table 15. Rifamycin and Antiretroviral Drug Interactions

Antiretroviral agents	Interaction with Rifamycins	Comments
Tenofovir alafenamide (TAF)	Rifamycins are potent inducers of P-glycoprotein and decrease TAF levels.	• Do not use rifampin or rifabutin with TAF. • Tenofovir disoproxil fumarate (TDF) may be administered with rifamycins.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Rifampin decreases levels of all NNRTIs. Efavirenz decreases rifabutin levels.	• Many experts recommend that efavirenz be given at standard dose of 600 mg daily. (FDA recommends increasing dose to 800 mg daily in persons >60 kg.) • Increase the dose of RFB to 600 mg daily if using it with efavirenz. Rifampin use is preferred with efavirenz. • Do not use rilpivirine or etravirine with rifampin. • Rifabutin can be used with etravirine at usual dose. • Rifabutin should not be used with rilpivirine • Consider TDM for rifampin/rifabutin combinations with NNRTIs.
Protease inhibitors (PIs)	Rifampin decreases protease inhibitor levels significantly. PIs increase rifabutin levels.	• Do not use rifampin with PIs. • Rifabutin may be used with PIs but the dose should be decreased to 150 mg daily or 300 mg thrice weekly. Consider TDM of rifabutin when lab resources are available.
Integrase strand transfer inhibitors (INSTIs)	Rifampin decreases INSTI levels. Rifabutin does not alter levels of raltegravir or dolutegravir.	• Raltegravir 800 mg twice daily should be used when combined with rifampin. • Elvitegravir with cobicistat should not be used with rifampin or rifabutin. • For patients on dolutegravir 50 mg daily; dose increase to 50 mg twice daily is recommended with rifampin. • For those on dolutegravir 50 mg twice daily for INSTI resistance, do not use rifampin. Use rifabutin if a rifamycin is needed. • Avoid using bictegravir for patients taking rifampin or rifabutin.
CCR5 Inhibitor Maraviroc	Rifampin decreases maraviroc levels.	• Rifampin should not be used with maraviroc. • Rifabutin may be used with maraviroc.

II. Diagnosing Latent TB Infection in Patients with HIV

A. All PLWHA should be evaluated for TB infection at the time of HIV diagnosis, due to the increased risk of progression to active TB. The evaluation should include an assessment of any active symptoms for TB,

a comprehensive physical examination and either a TB skin test (TST) or interferon gamma release assay (IGRA). In select cases, both tests can be used if there is high suspicion for TB infection (e.g. prior or ongoing potential exposure(s) to a person with active TB) where a positive result from either assay would be considered a true positive. The definition of a positive TST in a PLWHA is defined as ≥ 5 mm induration.

1. Indeterminate and false negative IGRA and TST results can occur in PLWHA, especially if patients are substantially immunocompromised. A negative TST or IGRA result never excludes a diagnosis of TB. Using both tests can detect more TB infection cases in this population.
2. In PLWHA who have negative initial TB infection testing performed at CD4 counts < 200 cells/µl, TB infection testing should be repeated at time of immune reconstitution (when CD4 ≥ 200 cells/µl) to confirm the initial test was a true negative test result.
3. Annual screening for TB infection is recommended for PLWHA who are at high risk for repeated exposure to persons with active TB.

B. All persons who test positive for TB infection must be carefully evaluated for active TB disease with a symptom screen, physical examination and chest x-ray (CXR).

1. A CXR alone is insufficient to rule out active disease. About 10% of patients with pulmonary TB/HIV co-infection have an unrevealing CXR.
2. PLWHA can have extra-pulmonary TB, such as lymphatic TB, without pulmonary TB involvement and with very few symptoms.

III. Diagnosing Active TB in Patients with HIV

A. The presentation of active TB in PLWHA may be influenced by the immunodeficiency caused by HIV. Compared to patients without HIV, those with HIV and TB can present with:

1. A shorter duration and more rapid progression of symptoms related to TB.
2. More variable CXR patterns, including a higher incidence of:
   a. Primary TB complex pattern (hilar adenopathy, mid-to-lower lung infiltrates, pleural effusions)
   b. Miliary TB with diffuse bilateral micronodular (“millet seed”) patterns
   c. Non-cavitary pulmonary involvement with confluent or patchy infiltrates
   d. Normal CXR

3. Higher incidence of extra-pulmonary disease such as TB pleuritis, lymphadenitis, meningitis, renal involvement, bone and joint involvement, peritonitis, genital involvement and others.

B. All PLWHA who are pregnant and suspected of having TB should have a CXR, even if they have no pulmonary symptoms. The CXR is done with appropriate precautions. Patients with HIV and TB could also present with unrevealing physical examination, particularly if they have advanced immunosuppression.

C. Sputum acid-fast bacilli (AFB) smear, sputum mycobacterial culture, and sputum nucleic acid amplification (NAA) test should be performed in PLWHA who are being evaluated for possible TB disease.

1. These tests should be considered even in those who have a normal CXR and in those with no pulmonary symptoms but evidence of TB disease elsewhere.

2. Sputum AFB smear-negative pulmonary TB, and culture-negative pulmonary TB, is more common among PLWHA, particularly in those with advanced immunodeficiency and non-cavitary pulmonary disease.

3. If available, sputum testing with Cepheid GeneXpert® (Xpert®) MTB/RIF Assay is more sensitive and accurate than sputum AFB smear alone to detect pulmonary TB, and also provides rapid diagnostic information for rifampin-resistance (RR), which is a marker of multi-drug resistant TB (MDR-TB).

D. Extra-pulmonary and disseminated TB are more common in PLWHA, particularly those with low CD4 counts. Blood cultures may be positive in patients with advanced HIV. Appropriate tissue and/or fluid samples from the site of suspected infection should be collected for AFB staining, mycobacterial cultures, and NAA testing.

IV. Treatment of Latent TB Infection in Patients with HIV

A. PLWHA with a positive TB infection test result, no active TB disease, and no prior TB infection treatment should be treated for LTBI.

B. PLWHA who are a close contact to persons with active TB, should be treated for LTBI once active TB is ruled out, regardless of their TB infection test results.

C. In the U.S., 3 treatment regimens for LTBI are recommended:

1. INH treatment with 300 mg daily for 6-9 months is one treatment option for TB infection. Also, PLWHA should receive pyridoxine at dose of 25-50 mg/day to prevent peripheral neuropathy.

2. Rifampin 600 mg daily for 4 months may also be used as treatment for TB infection. However, close attention to potential ART drug interactions, in particular protease inhibitors, cobicistat (boosting agent) and select integrase strand transfer inhibitors (INSTIs), is

necessary (Table 15). In select cases where a patient cannot tolerate isoniazid and there are ART interactions with rifampin, rifabutin 300 mg daily may be used for 4 months. Rifabutin also has ART drug interactions (Table 15) but these are often more manageable.

3. Rifapentine and INH given by either self-administered therapy (SAT) or directly observed therapy (DOT) is now recommended as an alternative regimen.

   a. Drug-drug interactions with rifapentine are similar to those with rifampin. Rifabutin cannot be substituted for rifapentine.

   b. Contraindications include known source case resistance to INH and/or rifampin, pregnancy, or a known reaction to either INH or a rifamycin.

   c. A consultation with a TB or infectious disease expert, or pharmacist experienced with ART, can be helpful.

D. PLWHA who are treated for LTBI should be seen by a clinician on a monthly basis to assess medication adherence and possible adverse effects of treatment.

1. Baseline liver enzymes should be checked prior to initiating LTBI treatment in patients with HIV.

2. If liver enzymes are abnormal at baseline, then they should be checked at least monthly during treatment. Some experts check liver enzymes monthly even if baseline laboratory results are normal.

3. Persons with viral hepatitis have a higher risk of hepatotoxicity with TB infection treatment. All persons with HIV should also be screened for hepatitis B and C infection. Persons with hepatitis B or C co-infection should have close monitoring of liver enzymes during LTBI therapy.

4. PLWHA that are pregnant should not receive INH as treatment for LTBI during pregnancy or in the post-partum period.

E. Shorter courses of therapy for LTBI are being studied in people with HIV. At the time of publication, current U.S. guidelines do not recommend shorter courses of therapy than what has been outlined above.

F. INH preventive therapy is not recommended for pregnant women until after delivery unless they are a contact to a person with active TB disease.

V. Treatment of TB in Patients with HIV

A. Treatment of suspected or confirmed TB is generally the same for PLWHA as it is for persons who do not have HIV infection. One exception is in the use of intermittent therapy.

1. Intermittent dosing (twice- or thrice-weekly dosing during the intensive phase of therapy) and (once- or twice-weekly dosing during the continuation phase of therapy) has been associated with increased risk of TB treatment failure or relapse in PLWHA.
2. Daily therapy (5-7 days per week) administered via DOT is recommended during the intensive and continuation phases of TB therapy in PLWHA.

B. PLWHA with suspected or confirmed TB should be started on TB therapy immediately. If a patient is already on therapy with ART, ART should not be stopped. ART regimens may need to be modified due to drug interactions with TB medications. Assessment for ART and TB drug interactions, and any modifications to the patient's ART should be performed in consultation with an HIV specialist.

C. The duration of TB therapy for PLWHA is generally the same as for those without HIV infection. The reasons to extend HIV therapy for PLWHA are the same as those without HIV infection, with two exceptions:

1. In the unusual event that a PLWHA does not receive ART during TB treatment, it is recommended that the continuation phase be continued for an additional 3 months, resulting in 9 months of therapy for drug-susceptible pulmonary TB.
2. PLWHA can present with disseminated TB disease and high bacillary burden. In some cases, based on the severity of infection and degree of dissemination, regardless of HIV status, clinicians may opt to extend therapy to 9 months duration.

VI. Starting ART in Patients with TB/HIV Co-Infection

A. Treatment of HIV during TB therapy improves survival, decreases opportunistic infections, improves TB treatment outcomes, and is not associated with higher rates of treatment-related adverse events. For patients with newly diagnosed HIV infection or those who were previously diagnosed but are ART-naive at the time of TB diagnosis, the SAPiT, CAMELIA and STRIDE trials all showed that patients with HIV and TB had better outcomes when ART was started early after the initiation of TB treatment. Current guidelines recommend the following:

1. For ART-naive persons with CD4 count < 50 cells/µl, ART should be started within 2 weeks after TB treatment initiation.
2. For ART-naive persons with CD4 count ≥ 50 cells/µl, ART should be started within 8 weeks of TB treatment initiation.
3. In PLWHA and TB meningitis, early ART may pose a higher risk for more severe adverse reactions. ART treatment initiation should generally be delayed up to 8 weeks after initiation of TB therapy and should be initiated with close monitoring. Treatment is delayed to

reduce central nervous system (CNS) events related to IRIS. Patients should have careful ongoing monitoring after initiation of ART.

VII. Drug Interactions

A. The rifamycin class of antibiotics (rifampin, rifabutin, and rifapentine) has significant drug interactions with multiple antiretroviral medications. Nonetheless, rifamycins are the most important drug class in drug-susceptible TB therapy and every attempt should be made to include a rifamycin in the TB treatment regimen. To address rifamycin-ART drug interactions, dosing adjustments, and even a change in the ART regimen in consultation with an HIV specialist, may need to be considered. **Table 15** reviews potential rifampin-ART drug interactions, lists which drug combinations should be avoided, and outlines medication dose adjustments.

B. For patients on a ritonavir-boosted protease-inhibitor (PI)-based regimen, dose-reduced rifabutin may be used in place of rifampin (**Table 15**). Close monitoring for adverse effects of rifabutin (uveitis and neutropenia) is recommended during treatment.

VIII. Immune Reconstitution Inflammatory Response

A. Persons with TB/HIV co-infection are at increased risk of developing paradoxical TB-IRIS reaction, particularly if they are started on TB/HIV treatment with CD4 counts < 100 cells/µl. They may initially experience clinical improvement on TB therapy, but after being on antiretroviral therapy for several weeks or months, they may exhibit new or worsening clinical and radiographic features of TB. Paradoxical TB-IRIS may manifest as recurrent fevers, new or worsening lymphadenopathy, abscess formation, new or worsening radiographic findings of infection, worsening neurologic symptoms and elevated intracranial pressure in those with TB meningitis. In patients with disseminated TB and hepatic involvement, hepatic TB-IRIS may present with cholestatic liver enzyme elevation.

B. The median onset of paradoxical TB-IRIS symptoms is 1-4 weeks after ART is initiated with an average duration of 2-3 months. According to a meta-analysis, TB-IRIS occurs in ~18% of cases when ART treatment is initiated while patients are on TB treatment.

C. Paradoxical TB-IRIS is a clinical diagnosis that relies on the clinical presentation of initial improvement in TB, worsening inflammatory features of TB within weeks after starting ART, demonstration of immune reconstitution with an increase in the CD4 cell count and peripheral blood HIV viral load reduction. TB-IRIS is a “diagnosis of exclusion” that requires a comprehensive evaluation and exclusion of alternative opportunistic infections, drug toxicities, and other non-infectious syndromes, as well as, TB treatment failure due to drug-resistance or poor medication adherence.

D. For patients at high risk for developing TB associated IRIS, preemptive prednisone is recommended as adjunct therapy with the initiation of ART. Prednisone 40 mg daily for 2 weeks followed by prednisone 20 mg daily for 2 additional weeks is recommended. Some patients may need a slower taper.

E. Many cases of paradoxical TB-IRIS require only symptomatic therapy with non-steroidal anti-inflammatory drugs. However, those with significant or severe symptoms often require corticosteroid treatment.

F. Unmasking TB-IRIS occurs in those who are started on ART and have undiagnosed TB at the time they are started on ART. TB may be "unmasked" clinically and radiographically within several weeks after ART is started. These patients may present with rapid symptom onset and sepsis. Persons with this syndrome should be treated with TB therapy and corticosteroids.

G. A consultation with an HIV or infections disease expert can be helpful in special clinical circumstances.

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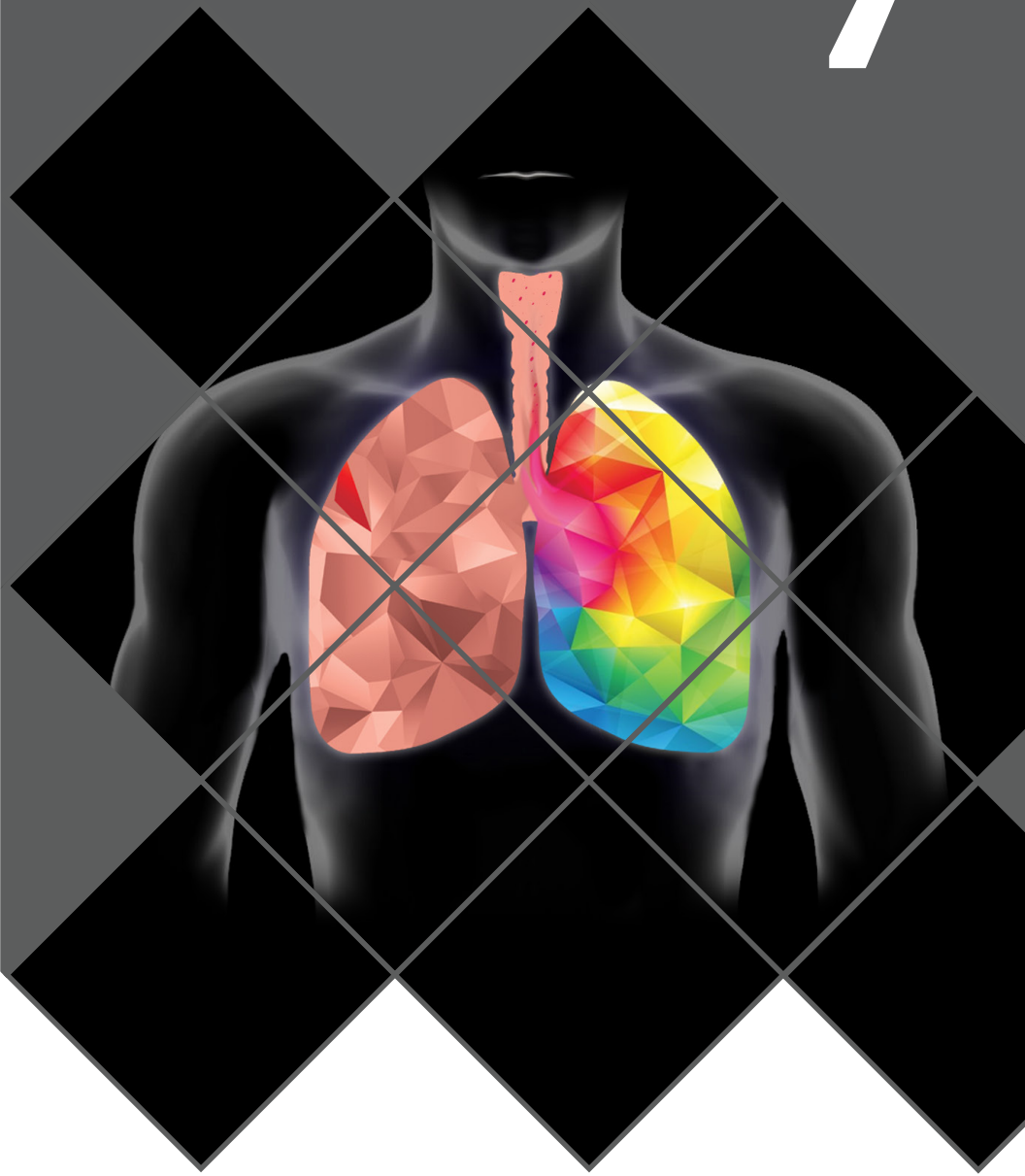
Chapter 7



TB in Children

Chapter 7

Tuberculosis in Children

Ritu Banerjee, MD, PhD; Andrea T. Cruz, MD, MPH; Jeffrey R. Starke, MD

I. General Principles

A. Many of the principles of the diagnosis and treatment of tuberculosis (TB) infection (Chapters 1 and 3) and disease (Chapter 4) are similar for children and adults. This chapter focuses on pediatric-specific considerations.

B. Presentation of Disease

1. Active surveillance for TB in the United States (U.S.) results in many children diagnosed at an earlier stage in the natural history of TB than in children in resource-limited settings, and in adults. This has implications in terms of clinical manifestations and radiographic findings. Compared to adults, children are:

   a. More likely to have subtle clinical findings-often only cough and low-grade fevers

   b. Less likely to expectorate sputum or have hemoptysis

   c. More likely to have extrathoracic disease [up to 25% of cases]

   d. More likely to have an x-ray that looks much worse than the patient looks clinically

   e. More likely to have intrathoracic lymphadenopathy

   f. More likely to have atelectasis (due to compression of bronchi by the adenopathy)

   g. Less likely to have cavitary and apical disease

2. Given the more subtle clinical manifestations and the often 'clinically silent' disease, a high quality chest x-ray (CXR) is an essential component of evaluation prior to children being offered treatment for TB exposure or infection to ascertain that they do not, in fact, have TB disease.

   a. All pediatric CXRs should be frontal and lateral films, as the lateral view is critical for assessing the intrathoracic lymph nodes, particularly in the young child whose thymic silhouette can obscure evaluation of the mediastinum on the frontal view.

   b. Because of the more unique and often subtle radiologic findings of TB in children, CXRs should be read by a radiologist with experience reading pediatric films.

C. Differences in Infectiousness

1. Pre-pubertal children are very rarely contagious even when they have pulmonary tuberculosis. In contrast, the adults who accompany children to the hospital or clinic may have as yet undiagnosed intrathoracic TB and these adults are far more likely to be contagious than the children.

2. The following children should be considered potentially contagious and appropriate infection control precautions (Chapter 13) should be used:

   a. Older adolescents

   b. Children of any age with cavitary disease

   c. Children of any age expectorating sputa

   d. Draining skin lesions (use contact precautions)

   e. Suspected or confirmed laryngeal TB

D. Immunological Vulnerability

1. Children younger than 5 years of age and immunocompromised children are both at higher risk of progressing from infection to disease and of having extrathoracic manifestations of TB (Table 16).

2. As a result, the diagnostic evaluation and management of these children is different from that of older children and adolescents, and physical examination is of paramount importance. TB in a child is a sentinel event, as it is usually indicative of recent community transmission of *Mycobacterium tuberculosis* (*M. tuberculosis*).

Table 16. Risk of Progression from Latent TB Infection to Disease, by Age*

Age at Infection (years)	No Disease (%)	Intrathoracic TB (%)	TB Meningitis (%)
<1	50	30-40	10-20
1-<2	75-80	10-20	2.5
2-<5	95	5	0.5
5-10	98	2	<0.5
≥10	80-90	10-20	<0.5

**Adapted from Marais et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy area. Int J Tuberc Lung Dis. 2004; 8(4):392-402*

II. Diagnosis

A. Tests of infection include tuberculin skin test (TST) and Interferon-Gamma Release Assays (IGRAs). TSTs and IGRAs may be used separately or in combination for children depending on the clinical scenario (Table 17).

Table 17. Suggested Uses of the TST and IGRA*

Suggested Test(s)	Scenario
TST Preferred	Child < 2 years
IGRA Preferred	Child ≥ 2 years
	Child unlikely to return for TST reading
Both TST and IGRA	Initial and repeat IGRAs are indeterminate or invalid
	Initial test is negative and 1) there is clinical suspicion of TB or 2) child is at high risk of progression and a poor outcome if progression occurs
	Initial TST is positive and additional evidence is needed prior to initiation of treatment for TB infection

**Adapted from Pediatrics 2014;134(6):e1763-1773*
***Some experts use IGRA for children ≥ 1 and younger but do not trust a negative test result*

B. Microbiologic Diagnosis

1. Gastric Aspirates

   a. Many young children cannot expectorate sputa. In order to secure a microbiologic diagnosis, gastric aspirates can be obtained. Gastric aspiration is conducted each morning while the child is fasting. The yield of gastric aspiration is low (30-40% even with extensive disease) and the costs are substantial. As such, gastric aspiration should be considered in the following patients:

      i. Children for whom no adults have been identified from whom cultures can be obtained

      ii. Children exposed to more than one adult whose isolates have differing drug-resistance patterns

      iii. Children whose possible source case has drug-resistant TB

      iv. Children (especially immunocompromised children) with a positive test of infection and CXR anomalies that may or may not represent TB

2. Sputum Induction

   a. Sputum induction is another way to obtain samples in children who cannot expectorate sputa. Children are given nebulized hypertonic saline, which results in a strong tussive effect. The posterior pharynx is suctioned before the child has a chance to swallow secretions. It can be performed in the outpatient setting with reduced cough and similar yield to gastric aspiration.

3. Fine Needle Aspiration/Incision and Drainage

   a. Children with TB lymphadenitis may benefit from fine-needle aspiration (FNA): 1) for microbiologic confirmation, 2) to decrease the size of the node in an effort to prevent creation of a fistulous sinus, and 3) to drain pus to improve antimicrobial tissue penetration.

   b. Incision and drainage should never be performed on children with suspected mycobacterial adenitis as it often causes scarring and fistula formation.

   c. Unlike non-tuberculous mycobacteria adenitis where excision is curative, children with TB (or *M. bovis*) adenitis need medical therapy even if a complete excisional biopsy is performed.

4. Lumbar Puncture

   a. Lumbar puncture should be strongly considered to evaluate for TB meningitis in certain groups, as the presence of meningitis alters: 1) treatment duration, 2) the decision to administer systemic corticosteroids, and 3) the selection of antibiotics.

   b. Lumbar puncture for routine studies, acid-fast bacilli (AFB) smear and culture, and TB PCR (glucose, protein, and cell count) should be considered for:

      i. Infants in the first year of life with suspected or confirmed intrathoracic or extrathoracic TB.

      ii. Children of any age with miliary or disseminated TB (obtaining blood or urine mycobacterial cultures in children with disseminated TB may also increase culture yield).

5. Culture Yield

   a. A minority of children with clinically-diagnosed TB disease will have positive cultures (**Table 18**).

   b. Use of NAA (nucleic acid amplification) testing, such as Cepheid GeneXpert® (Xpert®) MTB/RIF Assay, may improve sensitivity and increase rates of positivity.

C. Clinical Diagnosis of Intrathoracic TB

1. Given the paucibacillary nature of childhood TB, the infrequency of positive cultures, and the time required for culture positivity, clinicians should not wait for microbiologic confirmation prior to starting treatment for suspected TB disease in a child.

2. Often, treatment is initiated based on the following constellation of findings:

   a. Positive test of infection

   b. Compatible clinical and/or radiographic findings

Table 18. Culture Yield for *M. tuberculosis* in Children

Specimen	Culture Yield
Gastric aspirate*	30-40%
Sputum induction	5-25%
Broncho-alveolar lavage	10-60%
Pleural fluid	20-40%
Pleural punch biopsy	40-60%
Cerebrospinal fluid*	20-50%
Lymphatic tissue*	75%
Pericardial fluid	0-42%
Ascitic fluid	30%
Bone biopsy	75%
Skin biopsy	20-50%
Blood	0-5%

**If available, GeneXpert MTB/RIF can provide a sensitivity >70% and high specificity for TB with samples from lymph node FNA, lumbar puncture and gastric aspirates.*

c. Epidemiological link to a person with recently confirmed or suspected tuberculosis

D. Evaluation of the Child Exposed to TB

1. Contact tracing is performed by health departments to identify persons in contact with a potentially infectious case. The goal is to identify and treat symptomatic persons to decrease the immediate spread within the community and to identify and treat infected persons to decrease the future reservoir of disease.

2. The following evaluation should be performed for asymptomatic children identified as contacts to a case:

   a. A TST or IGRA is performed for all contacts

   b. CXR performed in:

      i. Children < 5 years, even with a negative TST or IGRA

      ii. Immunocompromised or immunosuppressed children of any age

      iii. Children with any symptoms possibly related to TB

      iv. Children of any age with a positive TST or IGRA

III. Treatment

A. TB Exposure

1. The TST and IGRA can take up to 8-10 weeks to become positive after a child is infected.
2. Given the risk of rapid progression in children younger than 5 years of age (especially younger than 2 years of age) and immunocompromised children of any age, provision of 'window prophylaxis' during the time between the initially negative TST or IGRA and the definitive test of infection is recommended for these groups.
    a. If the 2nd test of infection is negative, the treatment is stopped.
    b. If the 2nd test of infection is positive, medication received to date 'counts' toward the total treatment course for TB infection.
    c. Most experts feel that a second test of infection is reliable by 4-6 months of age.
3. Isoniazid (INH) has been the most common medication used for window prophylaxis but rifampin is increasingly being used by many experts.

B. Latent TB Infection (LTBI)

1. The principles of treatment of LTBI are similar for children and adults.
2. Pediatric considerations include:
    a. Children tolerate treatment for LTBI well. There is no need for baseline hepatic transaminase levels in otherwise healthy children not taking other potentially hepatotoxic medications.
    b. Children receiving other hepatically-metabolized medications or those with hepatic concerns (including morbid obesity with concern for non-alcoholic fatty liver disease) should have baseline transaminases obtained.
    c. While medication tolerance is better for children than adults, adherence is equally poor: approximately 50% of children complete a full 9-month course of INH. Consequently, consideration of shorter-course therapy and therapy observed by health department representatives should be considered (**Table 19**).
    d. Lack of pharmacokinetic data on rifapentine in children < 2 years of age precludes use of the 3HP regimen in this age group.
    e. Do not assume a child can swallow pills or capsules; provide recommendations to families about how to administer pills and capsules to younger children.

Table 19. Regimens Used to Treat Children with Latent TB Infection

Regimen	Dose(s) [Maximum Dose]	Schedule	Optimal Duration	Completion Defined As	Mode of Administration
Isoniazid (INH) and Rifapentine (3HP)	INH: 25 mg/kg (children 2-11 y) [900 mg]; 15 mg/kg (children ≥ 12 y) [900 mg] Rifapentine: 300 mg (10-14 kg); 450 mg (14.1-25 kg); 600 mg (25.1-32 kg); 750 mg (32.1-49.9 kg); 900 mg (≥ 50kg) [900 mg]	Once weekly	12 weeks, 12 doses	Receipt of at least 11 doses over a 16-week period	DOPT, ESAT or SAT
Rifampin (4R)	15-20 mg/kg [600 mg] 20-30 mg/kg Infants/Toddlers [600 mg]	Daily	4 months, 120 doses	Receipt of at least 4 months over a 6 month period	DOPT, ESAT, SAT
Isoniazid (INH) and Rifampin (3HR)	INH: 10-15 mg/kg [300 mg] Rifampin: 15-20 mg/kg [600 mg] 20-30 mg/kg Infants/Toddlers [600 mg]	Daily	3 months, 90 doses		DOPT, ESAT, SAT
Isoniazid (6H)	10-15 mg/kg [300 mg]	Daily	6 months, 180 doses	Receipt of at least 6 months over a 9 month period	ESAT, SAT
	20-30 mg/kg [900 mg]	Twice weekly	6 months, 52 doses		DOPT
Isoniazid (9H)	10-15 mg/kg [300 mg]	Daily	9 months, 270 doses	Receipt of at least 9 months over a 12 month period	ESAT, SAT
	20-30 mg/kg [900 mg]	Twice weekly	9 months, 76 doses		DOPT

DOPT-Directly-Observed Preventive Therapy (therapy provided to family and administration witnessed by health department representative); ESAT-Enhanced Self-Adminstered Therapy (therapy provided to the family by the health department, but family is responsible for administering medication to the child); SAT-Self-Administered Therapy (family has to acquire and administer the medication for the child)

f. Many commercial formulations of INH suspension are sorbitol-based and cause an osmotic diarrhea; try to transition children to crushed tablets when they start consuming any pureed food.

C. TB Disease

1. The treatment of TB disease is similar in children and adults. Children generally tolerate TB medications better than adults. However, given adherence concerns, all children with TB disease should be treated under directly-observed therapy (DOT).

2. Pediatric-specific caveats:

   a. If cultures on a child are negative, they should be treated based on the drug susceptibility results of the infectious adult source case or other available epidemiologic information.

   b. Children require higher mg/kg doses than adults; this may be particularly true for rifampin, where doses on the higher end of the recommended range (closer to 20mg/kg) should be used.

   c. Ethambutol can be used safely in children of any age, even in pre-verbal children in whom assessing for ocular effects can be challenging.

   d. Fluoroquinolones can be used safely in children when MDR-TB infection or disease is suspected.

   e. Drug doses should be based on a child's actual (not ideal) body weight; adult maximum doses should not be exceeded.

   f. Pyridoxine (Vitamin B6) supplementation when receiving INH should be considered in breastfeeding infants, pregnant adolescents, HIV-infected children, and for children whose diet may result in relative pyridoxine deficiency.

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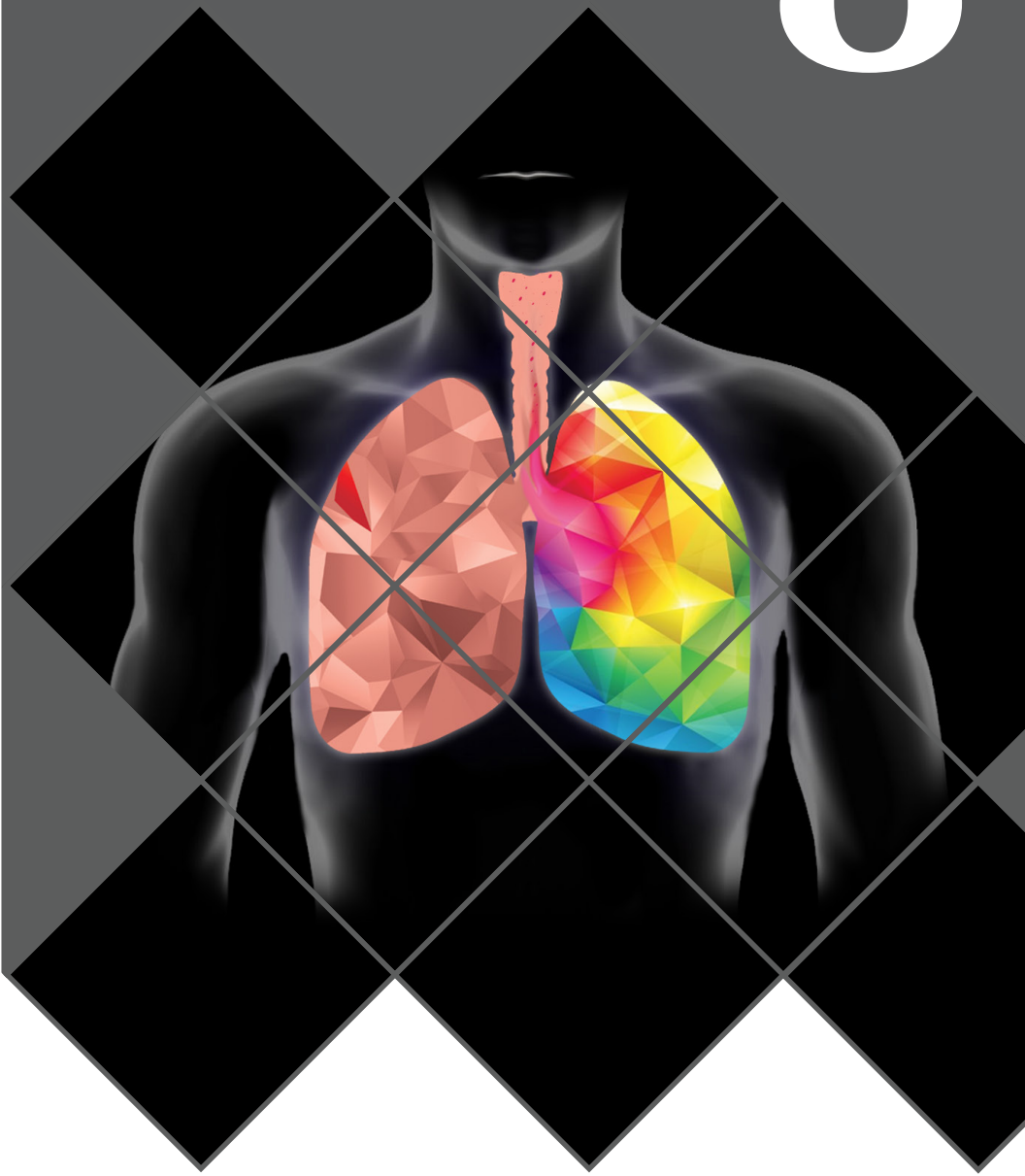
Chapter 8



Radiographic Findings of Pulmonary TB

Chapter 8

Radiographic Findings of Pulmonary Tuberculosis

Dana G. Kissner, MD

I. Introduction

A. Chest radiographs are key to the diagnosis of pulmonary tuberculosis (TB), particularly in pulmonary cases diagnosed by clinical criteria (positive tuberculin skin test (TST) or interferon gamma release assay (IGRA), TB risk factors, compatible chest radiograph, and negative nucleic acid amplification (NAA) test and culture.

B. Chest radiographs are required for all persons with signs or symptoms of TB and all people living with HIV/AIDS (PLWHA) being evaluated for possible TB infection or disease.

C. TB in children is paucibacillary, which makes it difficult to obtain material for microbiologic confirmation. A posteroanterior (PA) and a lateral view should be done for all children < 18 years old.

D. Computerized tomography (CT) is rarely needed for the diagnosis of TB, but it is useful in some circumstances, which will be discussed later in this chapter.

E. Patients with a positive TST or IGRA should undergo chest radiography to help distinguish latent TB infection (LTBI) from disease. TB can be asymptomatic.

1. Chest radiographs often provide the first clue to the presence of TB.
2. Chest radiographs are key components of medical screening for TB in immigrants and refugees overseas, and in persons in the United States (U.S.) applying for adjustment of status to permanent residence.
3. Chest radiograph alone is unable to distinguish active TB disease from chronic changes. Sputum for acid fast bacilli (AFB) smear, mycobacteria culture, and NAA test should be obtained, even for stable radiologic lesions.

II. Performing and Interpreting Chest Radiographs

A. Structures are discernible on chest radiographs because they vary in shade from white to black and contrast with each other. Identification of normal silhouettes is important in interpreting chest radiographs.

1. X-ray beams are directed at a person and photons are absorbed and scattered (attenuated) or pass through and hit the detector.

2. The amount of absorption depends on the density of the tissue and the energy of the x-ray beam.
    a. Where there is little absorption (low attenuation), such as in the lung, the radiograph appears dark gray.
    b. When there is high absorption, such as in the bones, the radiograph appears white.
3. Contrast dye accentuates the difference in shade between structures.
    a. Contrast dye can be given by multiple routes and is very useful in TB.
    b. The iodine or barium in the dye is dense, absorbs photons well, and thus appears very light.
    c. Intravenous (IV) contrast dye, used in chest CT scans, accumulates in vascular areas, including the inflammatory lesions in TB.
        i. TB lesions are inflammatory, but frequently have central necrotic regions.
        ii. Dye collects in the vascular inflammatory regions, but not in the caseating or necrotic ones, producing a contrast that can be highly suggestive of TB.
    d. The term "enhancement" refers to the light, dye-accumulating regions. Darker areas that do not accumulate dye are described as non-enhancing or low attenuation. For these reasons, when performing CT scans in patients with or suspected of having TB, contrast should be used whenever safe and possible.

B. Special techniques can improve visualization of TB lesions. These can be done at the same visit as the standard chest radiograph.
    1. Anteroposterior (AP) lordotic views help move the clavicles and anterior ribs up and away from the apex of the lung, a frequent location of tuberculous lesions. The x-ray beam is aimed at the front of the chest for an AP.
    2. The apical lordotic view may provide a better evaluation of this area which can be obscured by bones. The x-ray beam is either angled upward or the patient leans his/her upper body backward for the lordotic view

C. Special attention should be paid to regions of the lung that are commonly affected by TB.
    1. The initial lung lesion in primary TB occurs most frequently in the mid to lower lung fields.
    2. Post-primary or reactivation TB appears most often in the apical and posterior segments of the right upper lobe, the apicoposterior segment of the left upper lobe, and the superior segments of the lower lobes.

3. The apex of the lung is radiologically defined as the area above the anterior ends of the first ribs on an upright image. One should look for asymmetry in the density of the apices.
4. The hilum or root of the lung may show enlarged lymph nodes.
    a. The hilar point is the V-shaped space created by the apparent merger of the large vessels (the lower lobe pulmonary arteries and the lowest of the upper lobe pulmonary veins) in the hilum.
    b. Obliteration of the hilar point by a lobular density suggests lymphadenopathy or a mass.
5. The mediastinum contains the central chest organs, not including the lungs. Enlarged lymph nodes in TB may be visible anywhere in the mediastinum though they may not be seen on chest radiograph.
6. The right paratracheal stripe is the white line separating the air in the trachea from the air in the lung. It extends from the azygos vein to the clavicle and normally is < 4 mm in width. Thickening of the paratracheal stripe may indicate enlarged lymph nodes.
7. The costophrenic angle is formed by the lateral chest wall and the dome of the diaphragm. Blunting of this angle may indicate a small pleural effusion or thickening of the pleura.

D. Additional Findings
1. TB lesions frequently cause volume loss or shrinkage of a lobe or segment. This can be detected by the displacement of structures in the chest such as:
    a. The mediastinum shifts toward the side of the lesion
    b. The diaphragm moves superiorly
    c. Fissures separating the lobes move toward the lesion
    d. With upper lobe disease the hila move superiorly
2. Healed lesions calcify. Radiologists frequently use the term “calcified granulomas” for small densely calcified nodules. They are not indicative of active TB disease.

III. Radiographic Patterns Typical of TB

A. There are recognizable patterns of chest radiograph abnormalities in TB. They can occur alone, or simultaneously with others.
1. Nodules. These are discrete round or oval opacities 2-30 mm. in diameter. Sometimes the term “tuberculoma” is used.
    a. Nodules may be solitary or multiple and they are frequently confused with malignancies. Nodules can cavitate, in which case the central part of the nodule is replaced by air. Cavitary nodules can be seen in TB, other infections, other types of inflammation and in malignancy.

b. Comparison with prior chest radiographs can be helpful not only to evaluate for TB but also for alternative diagnoses such as malignancies and atypical mycobacteria.

c. In primary TB (Ghon focus), nodules are often associated with ipsilateral lymphadenopathy. When the Ghon focus and lymph nodes calcify the pair is called a Ranke complex. These calcified lesions are not risk factors for subsequent active TB.

d. AP lordotic views are helpful in detecting small nodules in the apex.

e. One should look carefully between the ribs, going from side to side, to detect asymmetry due to subtle nodules.

f. On CT scans done with IV contrast, rim enhancement (dye taken up by the outer edge) and low attenuation centrally (caused by necrosis or caseation) is suggestive of TB.

g. 18-FDG Positron Emission Tomography (PET) scans cannot distinguish malignancy from TB.

2. Consolidation. These are relatively homogeneous opacities in the lung caused by filling and replacement of the air space with fluid, cells, pus, or blood. The term infiltrate is sometimes used but is nonspecific.

   a. Consolidations are generally translucent enough to allow structures such as ribs and lung markings to be visible through them.

   b. Consolidation due to TB is frequently confused with pneumonia.

   c. Air bronchograms are often visible. The air-filled bronchi (dark gray) can be seen (outlined) within areas of consolidation (white) because the air in the lung has been replaced with denser material.

   d. Silhouette signs may be caused by consolidation. A silhouette sign is an absence of the normal silhouette formed by the air in the lung adjacent to the diaphragm, aorta, and heart. Atelectasis, pleural effusion, tumor, or consolidation that replaces the air in the lung that is adjacent to the heart or diaphragm can cause a silhouette sign.

3. Cavities. Cavities are gas filled round or oval spaces that form within an area of consolidation, a nodule, or a mass (i.e. lesion > 3 cm). They are caused by release of necrotic material into the airways. They are among the most well-known lesions in TB.

   a. Cavities caused by TB can be solitary or multiple.

   b. The walls of tuberculous cavities are thin to medium in width. Cysts generally have walls that are < 1 mm thick. Cavities with wall widths of > 16 mm are more likely to be malignant.

c. TB cavities typically contain little fluid, and thus do not have significant air-fluid levels, as commonly seen in lung abscesses.

4. Pleural effusions. Fluid can collect in the pleural space because of elevated hydrostatic pressure (transudate) or inflammation (exudate).

   a. Tuberculous pleural effusions are frequently seen early after infection and thus can be a manifestation of primary disease. They are exudates and can be serous, thick, congealed, or bloody in appearance.

   b. The size of TB pleural effusions is variable and can range from small to massive.

      i. Blunting of the costophrenic angle may indicate a very small effusion.

      ii. Large effusions can shift the mediastinal structures to the opposite side.

      iii. If CT scans are performed, they should be done with IV contrast, unless contraindicated. This helps distinguish compressed lung tissue and inflamed pleura, which pick up some contrast dye, from pleural fluid.

   c. TB pleural effusions can be free-flowing or loculated.

      i. On upright chest radiographs a free-flowing effusion appears as a white crescent or meniscus where the costophrenic angle should be.

      ii. A loculated effusion is caused by fibrotic or inflamed pleura trapping the fluid into compartments.

      iii. Left and right lateral decubitus chest radiographs can be helpful in visualizing pleural effusions, estimating their size, and determining if they are loculated. Lateral decubitus chest radiographs are done with the patient lying with right and left sides down. Free flowing fluid will form a visible dependent layer.

      iv. Ultrasound is helpful in characterizing pleural effusions and guiding needle aspiration (thoracentesis).

5. Miliary TB. This usually occurs during the initial or primary infection due to dissemination via hematogenous spread of TB bacilli.

   a. Most often found in children < 5 years old, can occur in adults with or without immunosuppression.

   b. Can lead to respiratory failure and sepsis and is usually suspected because of the distinctive chest radiograph pattern.

c. Chest radiograph shows a profusion of well-defined, uniformly distributed nodules of similar size that can be 1-5 mm in diameter (average 2 mm). Miliary TB can be difficult to detect on chest radiographs especially if the technique is poor.

d. High Resolution CT (HRCT) can greatly improve detection and characterization of the lesions in miliary TB.

   i. The distribution of miliary TB nodules in the secondary lobule is random.

   ii. Ground-glass opacities, intralobular reticulation, and interlobular septal thickening may also be found.

e. AFB stains, molecular tests for TB, and cultures may be negative, making diagnosis difficult.

f. Miliary TB may affect multiple organs and may be accompanied by thoracic lymphadenopathy or evidence of prior TB lesions.

6. Lymphadenopathy (hilar & mediastinal). Lymph node disease is very common in TB. It is most often seen in primary disease. TB presenting as nodules and lymphadenopathy is frequently mistaken for malignancy.

   a. Identifying lymphadenopathy on a chest radiograph is an important way of diagnosing pediatric pulmonary TB.

   b. In young children it is critical to be aware of the normal appearance of the thymus gland, which can be visible on chest radiograph through age 3.

      i. The thymus gland overlaps other mediastinal structures in infants and toddlers and makes estimating the presence of lymphadenopathy unreliable based on the mediastinal width or paratracheal soft tissue thickness. The thymus gland is soft and does not compress adjacent structures.

      ii. Enlarged lymph nodes are often best visualized on a lateral chest radiograph, especially in very young children.

   c. In TB the distribution of enlarged thoracic lymph nodes is usually asymmetric. Sarcoidosis, which can be confused with TB in adults, usually presents with symmetric lymphadenopathy.

   d. In TB, enlarged hilar and mediastinal lymph nodes can compress and/or displace the trachea, bronchi, and esophagus and can erode through the airways.

   e. The right paratracheal and hilar regions are common locations for TB lymphadenopathy. In older children and adults, a widened right paratracheal stripe (> 4 mm) can suggest TB.

f. Enlarged lymph nodes can also be found in the aortopulmonary window (the space between the aortic knob and the left pulmonary artery seen on a standard chest radiograph), subcarinal space (where enlarged lymph nodes may be visible because of increased density below the carina), and the anterior, superior, and posterior mediastinum.

g. Normally the hilar points should be concave outwardly. The angles should be sharp, and the space should not be occupied by a mass or the point obliterated.

h. Paradoxical reactions in immune competent people are common, as is immune reconstitution inflammatory syndrome (IRIS) in immune suppressed individuals.

   i. Despite appropriate treatment of TB, lymph nodes can appear, enlarge, fluctuate, drain, and form sinus tracts.

   ii. Note that paradoxical reactions can also present as new lung consolidations. This makes chest radiographs a limited indicator of treatment failure.

7. Airways and TB. Effects of TB on airways can sometimes be seen on chest radiography.

   a. TB can be endobronchial.

      i. Chest radiograph may show atelectasis due to an endobronchial lesion that could be seen on bronchoscopy and could mimic cancer. Atelectasis can also be caused by airway compression by lymphadenopathy upon the airway.

      ii. A broncholith is a portion of calcified lymph node that is extruded and erodes into a bronchus. It can be seen on chest radiograph or CT scan.

   b. Bronchiectasis and fibrotic bronchostenosis can be caused by TB.

   c. Tree-in-bud lesions are common in active TB.

      i. These are centrilobular opacities. They are felt to be due to endobronchial spread of bacilli.

      ii. They consist of branching linear opacities in and around terminal and respiratory bronchioles plus inflammatory nodules in the bronchioles and peribronchial alveoli. The combination of the branching linear shadows and the nodules resembles a tree that is budding.

      iii. HRCT scans are the best way to visualize them.

8. Miscellaneous TB conditions that can be found on a chest radiograph.
    a. Enlarged cardiac shadow can suggest TB pericarditis.
    b. TB of the vertebral bodies may be detected.
    c. Volume loss is common in both old healed and active TB.
    d. Before and soon after antibiotics were available for TB in 1948, surgeons performed procedures to collapse TB cavities. Survivors are still living, making it important to recognize the appearance of prior surgery for TB on chest radiograph.
        i. Plombage refers to various techniques to cause collapse of cavities to promote healing. Inert material was inserted in the chest to achieve this.
        ii. Thoracoplasty is another way to collapse cavities. The ribs are removed allowing periosteum to remain. Bone later forms from the collapsed periosteum and stabilizes the chest wall. This was done in stages to prevent flail chest.

IV. Additonal Information

A. For additional information regarding adult TB radiology with images, visit https://www.currytbcenter.ucsf.edu/sites/default/files/radiographic_complete_2nded.pdf, Radiographic Manifestations of Tuberculosis.

B. For additional information regarding pediatric TB radiology with images, visit https://www.heartlandntbc.org/assets/products/pediatric_tb_radiology.pdf, Pediatric TB Radiology for Clinicians.

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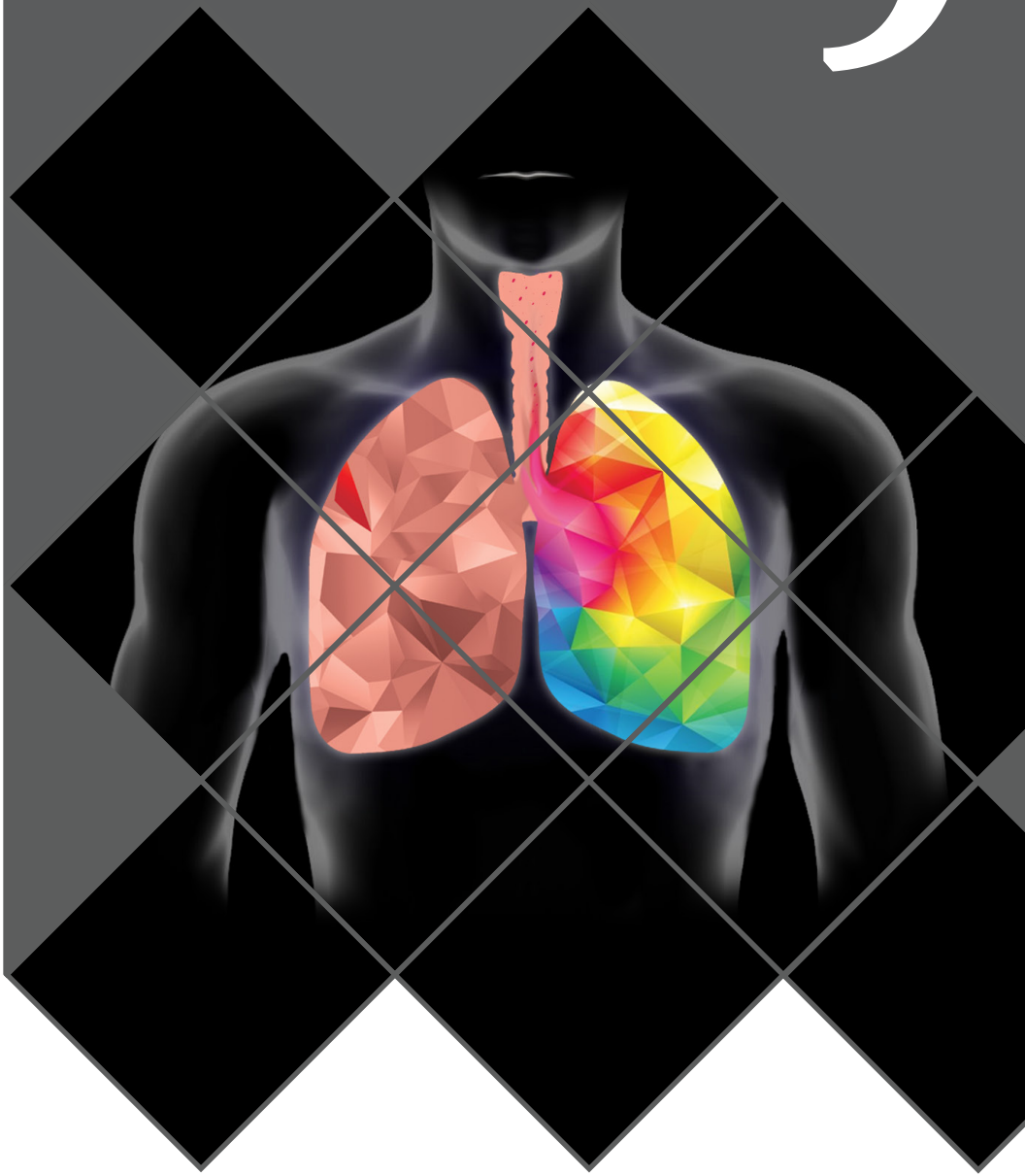
Chapter 9



Extra-pulmonary TB

Chapter 9

Extra-pulmonary Tuberculosis

Linda Williams Dooley, MD;
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I. Diagnosis

A. Tuberculosis (TB) can infect any tissue or organ in the body.

B. A comprehensive patient history, review of systems and thorough physical examination are essential to making the correct diagnosis.

C. Immunosuppression (including HIV infection, select hematologic cancers, antineoplastic chemotherapy, prolonged steroid use, anti-tumor necrosis factor agents, poorly controlled diabetes, chronic renal disease/dialysis, etc.) and an immature immune system due to very young age increase the risk of dissemination. Extra-pulmonary TB, however, is not limited only to patients with immunosuppressive conditions or young children.

D. Extra-pulmonary TB is often "paucibacillary" with lower concentrations of acid fast bacilli (AFB) present.

   1. AFB stains and mycobacteria cultures performed on body fluids (e.g. pleural, peritoneal, spinal, ocular fluids, as well as blood and urine) are commonly negative, but do not exclude a diagnosis of TB.

   2. Although nucleic acid amplification (NAA) tests may adjunctively be helpful in making a diagnosis, there is insufficient published information on non-respiratory samples to compose specific recommendations.

   3. Culture remains the gold-standard for laboratory conformation of the diagnosis and enables antimicrobial drug susceptibility testing (DST) and organism genotyping. Negative culture results do not exclude a diagnosis of TB.

E. Tissue biopsies are often needed to make a diagnosis. Granulomatous inflammation (especially caseating) can further support a diagnosis of TB (but is not specific for TB).

F. Radiographic evaluation including chest X-rays (CXR), ultrasound, CT or MRI may aid in diagnosis.

G. Even when extra-pulmonary TB is suspected or confirmed, there must be an evaluation for concurrent pulmonary TB via assessment for symptoms, CXR and (in many circumstances) sputum collection for acid fast bacilli (AFB) stain, NAA test and culture.

   1. A diagnosis of pulmonary TB may obviate the need for additional extra-pulmonary tissue sampling.

2. Sputum cultures may be positive even with a normal CXR and no immune suppression.

II. Select Extra-pulmonary TB Syndromes

A. TB lymphadenitis - most common (30-40%) forms of extra-pulmonary TB.

1. Cervical lymphadenitis is the most common presentation of TB lymphadenitis, but any lymph node can be involved. Unilateral disease is a more common presentation.
2. Supraclavicular and/or submandibular lymphadenitis may be present with cervical disease or by itself. Hilar adenopathy is a common site with primary pulmonary TB disease, TB in patients living with HIV/AIDS (PLWHA) and other forms of immunosuppression.
3. Fine needle aspirate (may be falsely negative) or excisional lymph node biopsy recommended to make diagnosis. Avoid incision and debridement (e.g. without lymph node removal) as poor healing and secondary draining sinus may form.
4. Paradoxical reaction (IRIS) has been reported during therapy in up to 20-25% of patients, irrespective of HIV or immunologic status.
5. Treatment of TB lymphadenitis is the same (drug composition and duration) as recommended for pulmonary disease.
6. Unlike isolated non-tuberculous mycobacteria (NTM) adenitis in children, TB adenitis in both adults and children requires combination anti-TB drug therapy, irrespective of surgical excision.

B. Pleural TB/TB pleurisy

1. Second leading presentation of extra-pulmonary TB.
   a. Occurs in approximately 15-20% of extra-pulmonary cases.
   b. May present as primary or reactivation TB, with or without concurrent pulmonary parenchymal disease.
2. Usually unilateral; may develop into an empyema (with a higher bacillary load). Chronic disease often associated with thickened, adherent, calcified pleural tissue.
3. TB pleural effusion – straw colored, exudative
   a. WBC pleocytosis, usually with lymphocyte predominance
   b. LDH and protein concentrations elevated
   c. Glucose may or may not be low
   d. Adenosine deaminase (ADA) characteristically elevated but not diagnostic
   e. AFB staining and cultures performed on fluid commonly negative (78-80% and approximately 50% respectively) in patients without HIV

f. Pleural (tissue) biopsy may be needed to make diagnosis

4. TB empyema – thick, purulent, adhesive
   a. WBC pleocytosis may be neutrophil predominant
   b. AFB staining and mycobacterial culture with higher yield
   c. Adjacent pleural tissue may become thick, adherent, calcified and encase lung tissue
5. Treatment of pleural TB is the same (drug composition and duration) as recommended for pulmonary disease.
   a. Steroid use generally not recommended.
   b. Repeat thoracentesis for pleural fluid drainage is preferred to chest tube drainage due to risk of bronchopleural cutaneous fistula with chest tube.
   c. Thoracotomy with pleurectomy is rarely indicated for acute TB effusions. May be necessary after completion of the therapy if fibrothorax and significant restriction occur.
   d. Occasional paradoxical reactions during therapy encountered and require additional therapeutic thoracentesis.

C. Laryngeal TB
1. May develop with or without concurrent pulmonary TB (CXR may be clear).
2. Can be very contagious with high propensity to aerosolize *M. tuberculosis* through coughing, laughing, talking, or singing.
3. Voice hoarseness (especially if chronic) is the most common presenting symptom; odynophagia and dyspnea can occur as well.
4. The vocal folds represent the most frequent site encountered on direct laryngoscopy examination, followed by the vestibular folds, epiglottis, subglottic region and posterior commissure.
5. Treatment of pleural TB is the same (drug composition and duration) as recommended for pulmonary disease. Particular attention should be given to infection precautions/respiratory isolation before and early in therapy.

D. Central nervous system (CNS) TB
1. Has been identified in approximately 1% of extra-pulmonary cases.
2. TB meningitis
   a. Neurologic presentations for TB meningitis range widely from lethargy and agitation to coma.
   b. Arachnoiditis of the spinal column may develop and may be associated with radicular pain, paresthesia, paralysis, and bladder or rectal dysfunction.

c. Head CT or MRI findings often show basilar meningeal enhancement combined with any degree of hydrocephalus.

d. CSF analysis typically shows a moderate lymphocytic pleocytosis, elevated protein levels, and low glucose (hypoglycorrachia). Opening pressure may be elevated. Neutrophils may predominate early in disease.

e. AFB staining of CSF commonly is negative (5-30% positivity from simple examination); higher yield with repeated CSF evaluations. Culture positivity is quite variable (25-70%). Repeated CSF evaluations may be needed.

f. NAA test and use of ADA testing may increase diagnostic yield but should not replace culture.

3. CNS tuberculomas and abscesses

   a. Clinical manifestations of a tuberculoma or tuberculous brain abscess depend largely on their location. Patients often present with headache, seizures, papilledema, or other signs of increased intracranial pressure.

   b. Tuberculomas may occur as solitary or multiple nodules and are often found in the frontal and parietal lobes.

   c. TB brain abscesses seen on CT or MRI cannot be reliably differentiated from pyogenic abscesses and usually require a biopsy for confirmation.

4. Treatment of CNS tuberculosis

   a. Early recognition and treatment of CNS TB imperative to optimize favorable outcomes.

   b. Treatment of CNS TB utilizes the same drug composition as recommended for pulmonary disease with the following caveats:

      i. Treatment should be extended for a total of 9-12 months (7-10 months continuation phase).

      ii. Use of higher-dose rifampin and adjunctive fluoroquinolones may improve outcomes.

      iii. Ethambutol has minimal penetration across the blood brain barrier and its relative contribution in the treatment of CNS TB remains unclear.

      iv. Repeated CSF evaluations are recommended to assess response to treatment. Ventricular drain placement is considered for refractory hydrocephalus.

      v. Paradoxical worsening is common after starting anti-TB therapy (not limited to patients with HIV). Presentation can be variable and include new onset of fever, headache, mentation changes, seizures, etc.

vi. Use of corticosteroids decreases mortality in patients with TB meningitis and are, therefore, recommended in combination with anti-TB drug therapy (e.g. prednisone or dexamethasone taper over 6-8 weeks; longer courses are often needed).

c. In patients with HIV and CNS TB who are not currently taking antiretroviral therapy (ART), it is recommended to delay starting ART up to 8 weeks after starting anti-TB therapy.

E. Bone and Joint TB

1. Has been identified in approximately 10-15% of extra-pulmonary cases.

2. TB vertebral osteomyelitis (Pott's Disease):

   a. Most common locations are in the lower thoracic and upper lumbar vertebrae, skip lesions are common.

   b. Unlike bacterial/pyogenic vertebral osteomyelitis, vertebral TB disease may initially spare the disc space in up to 50% cases (with adjacent vertebral body disease); however discitis usually subsequently develops .

   c. Anterior kyphosis (“Gibbus”) deformity common.

   d. Paravertebral abscess can develop and impinge the spinal cord.

   e. Spinal x-rays may be normal early in disease; CT or MRI imaging more sensitive.

3. TB osteomyelitis (other sites)

   a. Can develop in virtually any bone structure.

   b. Slow onset; usually solitary location.

4. TB synovitis

   a. Monoarticular, weight bearing (hip and knee) joints are the most common locations of infection.

   b. Sacroiliac, shoulder, clavicle, rib, elbow, ankle, carpal and tarsal joints may also be involved but less commonly.

   c. Synovial fluid typically with WBC pleocytosis; AFB stain positive in only 20-40% of cases; increase diagnostic yield with NAA test, culture and synovial tissue biopsy.

   d. With chronic synovial inflammation, “rice bodies” consisting of fibrin, collagen, and mononuclear cells may form within the synovial fluid.

5. Treatment of bone and joint TB

   a. Six to nine months of combination anti-TB drug therapy.

b. Surgical consultation may be needed for neurologic compromise (e.g. vertebral disease), other bone and joint instability and to maintain joint function.

F. Pericardial TB

1. Clinical findings can be variable and nonspecific with cough, shortness of breath, chest pain, and orthopnea.

   a. Chest x-ray may show enlarged cardiac silhouette. Pleural effusions present in 40-60% cases.

   b. ECG typically with low voltage findings and nonspecific T-wave changes.

   c. Echocardiography, CT and/or MRI imaging may show pericardial thickening and pericardial effusions.

2. Complications include constrictive pericarditis with cardiac tamponade.

3. Diagnosis is made by clinical and corresponding radiologic features along with pericardiocentesis.

   a. Exudative pericardial fluid with high protein, WBC pleocytosis (typically lymphocyte predominant).

   b. AFB staining of fluid commonly negative; culture, NAA testing and ADA testing increase diagnostic yield.

   c. Pericardial biopsy may increase diagnostic yield.

4. Treatment of pericardial TB is generally the same (drug composition and duration) as recommended for pulmonary disease.

   a. Adjuvant use of corticosteroids no longer recommended (randomized control trail demonstrated no benefit shown among mortality, cardiac tamponade, or constrictive pericarditis).

   b. Selective use of glucocorticoids can be considered for patients at highest risk of developing complications of pericardial inflammation (those with large pericardial effusions, those with high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction).

G. Abdominal TB

1. TB Peritonitis – most common form of abdominal TB

   a. Typically presents with gradual onset of ascites, abdominal pain and recurring fever.

   b. Paracentesis typically shows exudative, lymphocytic predominant fluid. CT scan may show thickening of peritorium and/or abdominal wall thickening.

      i. Sensitivity of AFB staining on peritoneal fluid is low; culture, NAA testing and ADA testing can increase diagnostic yield.

ii. Repeat paracentesis and/or peritoneal biopsy may be needed to confirm diagnosis.

2. Gastrointestinal TB

   a. *M. bovis* (which is a member of *M. tuberculosis* complex) should be a consideration when GI tract disease is diagnosed. *M. bovis* may also cause pulmonary disease.

   b. Ileocecal region is most commonly involved, although multiple locations may be affected. The stomach and esophagus are rarely involved. Bowel wall thickening can be observed by CT scan.

   c. May resemble inflammatory bowel disease.

   d. Stool should be sent for NAA test and mycobacterial culture.

   e. Obstruction and perforation are occasional complications.

3. Hepatobiliary disease is a common manifestation of disseminated TB. Hepatosplenomegaly with ascites and abnormal serum liver function tests (LFT) is often present.

4. Treatment of abdominal TB is the same (drug composition and duration) as recommended for pulmonary disease.

H. Genitourinary TB (GUTB)

1. Clinical findings

   a. Unilateral renal disease is more common

   b. Renal dysfunction via renal parenchymal fibrosis and calcification is not uncommon

   c. Ureterostricture formation (most common in ureteropelvic junction) with secondary hydronephrosis can be seen

   d. Bladder wall thickening with calcification can occur; bladder wall stricture is a late manifestation

   e. TB epididymitis is more common than prostate or testicular involvement

2. Diagnostic considerations

   a. Consider GUTB in appropriate setting with “sterile” pyuria or hematuria (without a bacterial pathogen identified).

   b. First morning urine sample submitted for AFB staining, NAA testing, and culture may help with diagnosis; more specimens increase diagnostic yield.

   c. Assess patient history for prior therapy with *M. bovis* BCG.

   d. Cervical and ovarian TB should be considered in women, especially if associated with infertility.

I. Ocular TB

1. Often a disease of exclusion; opthalmologic evaluation typically required.
2. Wide spectrum of clinical presentations
   a. Posterior uveitis is the most common presentation of intraocular TB with clinical findings including chorioretinitis, multiple choroidal nodules (tubercles), choroidal granuloma (tuberculoma), optic neuritis, and subretinal abscess.
   b. Anterior uveitis can present as unilateral or bilateral chronic granulomatous disease.
3. Clinical diagnosis is usually difficult to confirm and often made presumptively via a combination of clinical findings, patient risk factors for TB infection and positive TST or IGRA. Intravitreal sampling with NAA testing and culture could be helpful, but is often negative.
4. Treatment is generally the same as for pulmonary TB disease. At times, topical steroid drops are used in combination with oral prednisone to control sight-threatening inflammation. Improvement with treatment of TB allows successful weaning of steroid therapy.

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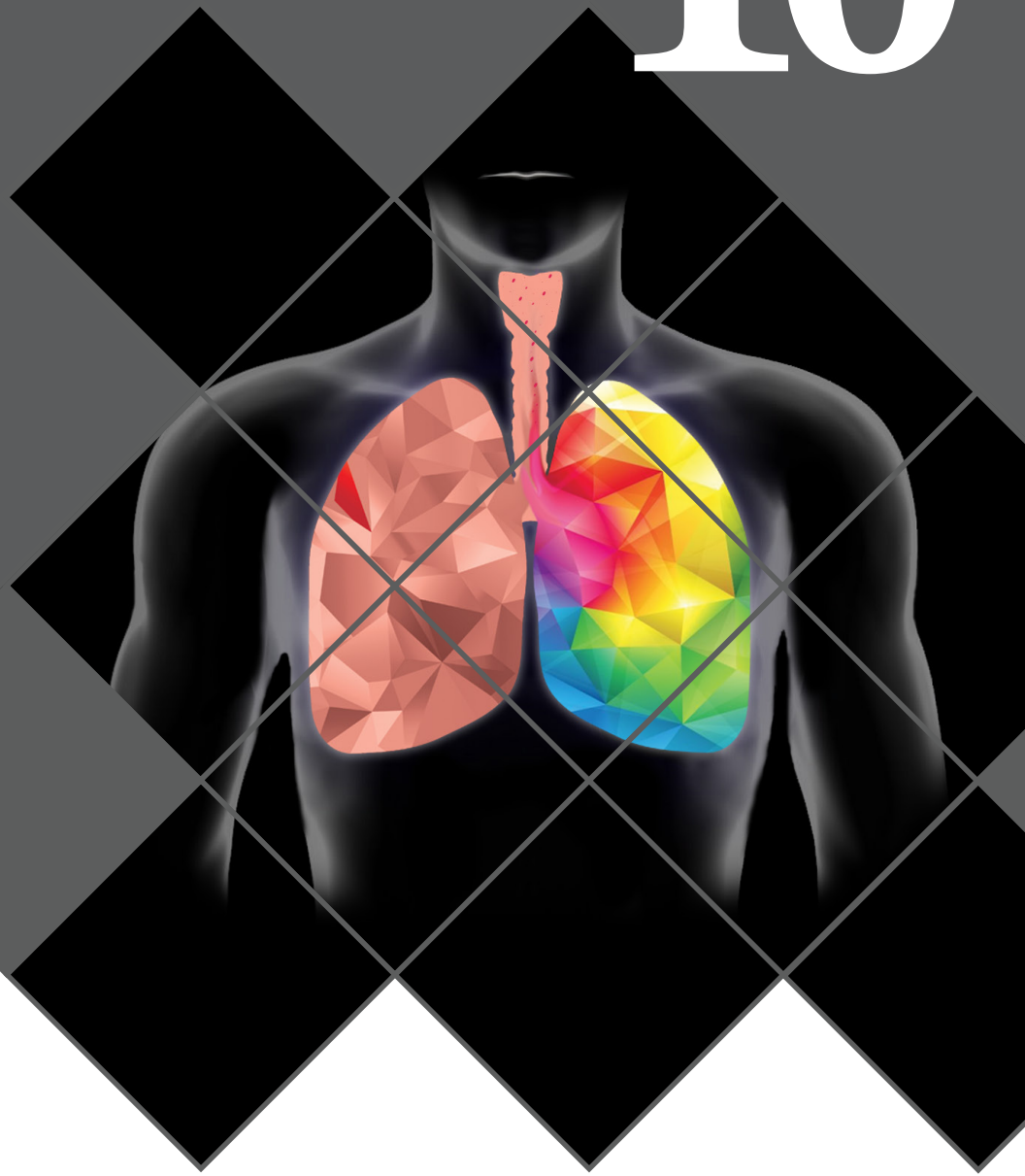
Chapter 10



Drug Therapy for TB

Chapter 10

Drug Therapy for Tuberculosis

John Zeuli, PharmD, BCPS-AQ ID, AAHIVP

I. Adult TB Drug Formulation

A. Standard dosing and dose adjustments for renal/hepatic impairment in adults can be found in **Table 20**. For pediatric dosing see Chapter 7: TB in Children.

Table 20. Dosages and Adjustments to Anti-TB Drugs for Adults

First Line Anti-TB Drugs			
Drug	**Standard Dose**	**Renal Dose Adjustment**	**Hepatic Dose Adjustment**
Isoniazid[4,6]	Daily dose: 5 mg/kg (max 300 mg) LTBI dosing (w/RPT x 12wk): 15 mg/kg (max 900mg) once weekly	No dose adjustment	Acute liver disease: Avoid use Stable hepatic disease: Avoid if possible Close monitoring and periodic liver function testing
Ethambutol[1]	15-20 mg/kg once daily	Est crcl < 30ml/min: 20-25 mg/kg 3x/weekly	No adjustment
Pyrazinamide[2]	25-35 mg/kg once daily	Est crcl <30ml/min: 25-35 mg/kg (maximum 3000mg) three times weekly	Moderate impairment: Consider use with close monitoring, TDM, and periodic liver function testing
Rifampin	10 mg/kg daily 20 mg/kg or greater with TB meningitis	No dose adjustment	Moderate impairment: Consider use with close monitoring, TDM, and periodic liver function testing

1. Ethambutol standard adult dosing table:

	40-55 kg	**56-75 kg**	**76-90 kg**
Daily	800 mg	1200 mg	1600 mg
2x/wk	2000 mg	2800 mg	4000 mg
3x/wk	1200 mg	2000 mg	2400 mg

2. Pyrazinamide standard adult dosing table:

	40-55 kg	**56-75 kg**	**76-90 kg**
Daily	1000 mg	1500 mg	2000 mg
2x/wk	2000 mg	3000 mg	4000 mg
3x/wk	1500 mg	2500 mg	3000 mg

Table 20. Dosages and Adjustments to Anti-TB Drugs for Adults

Second Line Anti-TB Drugs[10]			
Drug	**Standard Dose**	**Renal Dose Adjustment**	**Hepatic Dose Adjustment**
Amikacin[5]	15 mg/kg daily 5 days/week	Est crcl <30 ml/min: Avoid	No adjustment
Bedaquiline	**Week 1-2:** 400 mg once daily **Week 3-24:** 200 mg 3x/wk *Give with food*	No adjustment	Mild/moderate impairment: No adjustment
Clofazimine	100 mg daily	No adjustment	Mild-moderate impairment: No adjustment
Cycloserine[3,4]	500-750 mg daily May divide dose (2 x 1 day) to improve tolerability	Est crcl < 30 ml/min: 1) 250 mg daily -OR- 2) 500 mg 3x/weekly *monitor for peak level	No adjustment
Ethionamide[3,4]	500-750 mg daily May divide dose (2-3 x day) to improve tolerability	No dose adjustment	No published recommendations
Imipenem	Imipenem 1000 mg IV 2-3 times daily Always give 125 mg clavulanic acid with each dose	Est crcl 20-40 ml/min: 750mg every 12 hours Est crcl < 20 ml/min: 500mg every 12 hours	No adjustment
Levofloxacin	71kg or >: 1000 mg daily 50-70kg: 750-1000 mg daily 35-49kg: 750 mg daily	Est crcl <30 ml/min: Standard dose given 3x/weekly	No adjustment
Linezolid[4]	600 mg daily Monitor trough level to keep < 2 mcg/ml Monitor peak level	No adjustment. Metabolite accumulation may increase toxicity	Mild-moderate impairment: No adjustment
Moxifloxacin	400 mg daily (600-800 mg daily if moxi MIC = 1)	No adjustment	Mild-moderate impairment: No adjustment
Para-aminosalicyclic acid[3,7]	4 gm orally 2-3 times daily	Est crcl <30ml/min: 4 gm orally twice daily	Mild-moderate impairment: 4 gm orally twice daily

Table 20. Dosages and Adjustments to Anti-TB Drugs for Adults

Second Line Anti-TB Drugs[10]			
Drug	**Standard Dose**	**Renal Dose Adjustment**	**Hepatic Dose Adjustment**
Rifabutin	300 mg daily	Est crcl <30ml/min: Consider standard dose[8] Hemodialysis: Standard dosing	Moderate impairment: Consider use with close monitoring, TDM, and periodic liver function testing
Rifapentine[11]	LTBI dosing (w/INH x 12wk): >50kg = 900 mg weekly	No dose adjustment	Moderate impairment: Consider use with close monitoring, TDM, and periodic liver function testing
Streptomycin[5]	15 mg/kg daily 5 days/week	Est crcl <30 ml/min: Avoid	No adjustment

3. Gradual up-titration of dose aids with tolerability:
   a. Cycloserine and ethionamide: Days 1-3 = 250 mg daily. Days 4-6 = 250 mg twice daily. Day 7 forward: 250 mg(AM) and 500 mg(PM). Therapeutic Drug Monitoring (TDM) to optimize dosing of cycloserine; especially with dose > 500 mg daily
   b. PAS: Day 1-3 = 2 gm twice daily. Day 4-6 = 2 gm(AM) + 4 gm (PM); Day 7 forward: 4 gm twice daily. Four grams 3x daily is the usual dose, though 4 gm 2x daily can attain adequate concentrations with less risk for adverse effect. Many patients are not able to tolerate high doses.
4. Vitamin B6 augmentation: Vitamin B6 augmentation is recommended to decrease adverse effect when on the following agents:
   a. INH: Vitamin B6 25-50mg daily (high risk of neuropathy: pregnant, breastfeeding infants, HIV, Diabetes, malnourished, alcoholism, age ≥65 years)
   b. Cycloserine: Vitamin B6 50-100 mg daily for all patients
   c. Ethionamide: Vitamin B6 50-100 mg daily
   d. Linezolid: Vitamin B6 daily 25-100 mg daily
5. Use adjusted body weight for dosing obese patients. Adj BW = IBW + 0.4(ABW – IBW). Serum levels (peak and trough) should be followed. Continuation therapy dosing may include frequency decrease to 3x weekly.
6. When given 2-3x weekly, INH dose is 15 mg/kg (max 900mg). High dose INH therapy, 13-18 mg/kg once daily, has been utilized in the setting of low-level INH resistance (or resistance other than the Kat G gene mutation).
7. Take with meals/food to mitigate GI side effects. Sprinkle granules on applesauce (or yogurt) or suspend in tomato, orange juice, grapefruit, grape, cranberry, apple, or fruit-juice containing punches for administration. Do not chew the granules, as this will destroy the delayed release coating
8. Standard rifabutin dosing can be used with est crcl <30 ml/min. However, patients may be at increased risk of adverse effects related to renally-cleared metabolite accumulation. May use 50% of standard dose and monitoring serum drug levels. Standard dosing should be appropriate in patients on dialysis.
9. Rifapentine LTBI weekly dosing for weight <50 kg:

10-14 kg	14.1-25 kg	25.1-32 kg	32.1-49.9 kg
300mg	450mg	600mg	750mg

10. Expert medical consultation is recommended when treating with second-line anti-TB drugs.

II. Mechanism of Action

A. The mechanism of action, metabolism/excretion, and drug-drug interaction potential of first-line anti-TB drugs can be found in Table 21.

Table 21. Mechanism of Action

Drug	Mechanism of Action	Metabolism/ Excretion	Interaction Potential
Ethambutol	Inhibits the synthesis of metabolites in mycobacterial cell wall synthesis	Some hepatic metabolism; major excretion pathway is renal	Aluminum containing antacids decrease ethambutol absorption; space accordingly
Isoniazid	Inhibition of mycolic acid synthesis	Extensive liver acetylation with renal excretion of parent drug and metabolite	Weak CYP3A4 inhibition; limited data for clinically relevant CYP drug interactions
Pyrazinamide	Unknown, thought to disrupt membrane energetics	Primary liver metabolism via hydrolysis with metabolite excretion renally	Potential additive effect with other hepatoxic agents; counters effect of uric acid lowering agents
Rifampin	Stops bacterial RNA transcription by inhibiting bacterial DNA-dependent RNA polymerase	Intestinal and hepatic metabolism with notable enterohepatic circulation; majority excreted in feces	Extensive enzyme inducer (notably CYP3A4/PgP) Dramatic drug exposure decrease possible; close monitoring/dose adjustments required

III. Aminoglycoside Therapeutic Drug Monitoring

A. When using the injectable aminoglycosides/cyclic polypeptide drug agents in the treatment of tuberculosis (TB), therapeutic drug monitoring (TDM) is recommended (when feasible and resources allow) to optimize the pharmacokinetics/pharmacodynamics of the drug while minimizing risk for toxicity in patients.

B. Serum aminoglycoside monitoring

1. TDM of AG should include a single serum level drawn at 1 hour after the END of infusion. The goal would be 25-35 mcg/ml for the level 1 hour after the END of infusion.

2. A weekly serum trough level should be taken at approximately 24 hours after a daily dose and drawn prior to administration of the next dose. The goal for the trough should be undetectable (or less than the limit of detection of the assay), which confirms that the drug is not accumulating.

IV. Therapeutic Drug Monitoring

A. Optimizing drug therapy for TB ensures successful outcomes for individual patients and public health.

B. TDM can help to optimize drug therapy and ensure standard doses are yielding appropriate drug exposure in specific patients. Given that each individual patient has different pharmacokinetic profiles, while noting the extended duration of TB therapy, consideration should be given to the use of TDM for select patients.

C. Use of TDM should be considered for the following:

1. Patients at risk of malabsorption; history of gastric bypass, history of intestinal resection, or conditions that would lead to suspected decreased drug absorption.
2. Decreased hepatic function or renal function that could lead to accumulation and toxicity of drug agents.
3. Known or potential drug interactions that could affect TB drug exposure and lead to sub-therapeutic levels or toxicity.
4. Lack of early clinical or microbiologic response to appropriately dosed TB drug therapy.
5. Use of second line therapeutic agents.

D. In general, the approach for TDM of most oral agents used in the treatment of TB is to assess two serum levels (generally at 2 hours and 6 hours after the oral dose of TB drug therapy).

1. The initial 2 hour level will often indicate whether drug absorption is appropriate and the desired peak level is attained.
   a. If the 2 hour level is normal, the 6 hour level will help provide some insight on the extent and rate of drug clearance.
   b. However, if the 2 hour level is low, then the 6 hour level can help determine if malabsorption vs delayed absorption is occurring (which would have different management strategies).

E. **Table 22** discusses typical associated C_{max} values for commonly used dosing of TB medications.

Table 22. Typical Associated C_{max} Values

TB Drug	Normal C_{max} (mcg/ml) Range	TB Drug	Normal C_{max} (mcg/ml) Range
Isoniazid	3-6	**Linezolid**	12-26 (8-26 with 600 mg dose)
Clofazimine	0.5 – 2.0	**Moxifloxacin**	3-5
Cycloserine	20-35	**PAS****	20-60
Ethambutol	2-6	**Pyrazinamide**	20-60
Ethionamide*	2-5	**Rifabutin*****	0.45-0.90
Levofloxacin	8-13	**Rifampin**	8-24

*Often will see delayed absorption due to gastric irritation
**Due to delayed release formulation with enteric coating, C_{max} is reached notably later than with other agents. C_{max} is usually attained between 4 and 8 hours; draw serum level at 6 hours after the dose
***Rifabutin peak level should be drawn at 3 hours after the dose

V. Performing Serum Assays

A. Any CLIA approved laboratory that has experience performing the assay should be acceptable, but oftentimes finding a lab to perform the serum assays can be challenging.

B. Two reference laboratories that routinely perform serum drug assays on most agents used to treat TB are:

1. University of Florida Infectious Disease Pharmacokinetics laboratory: http://idpl.pharmacy.ufl.edu/.
2. National Jewish Health Advanced Diagnostics Laboratory: https://www.nationaljewish.org/for-professionals/diagnostic-testing/adx/our-laboratories/therapeutic-drug-monitoring.

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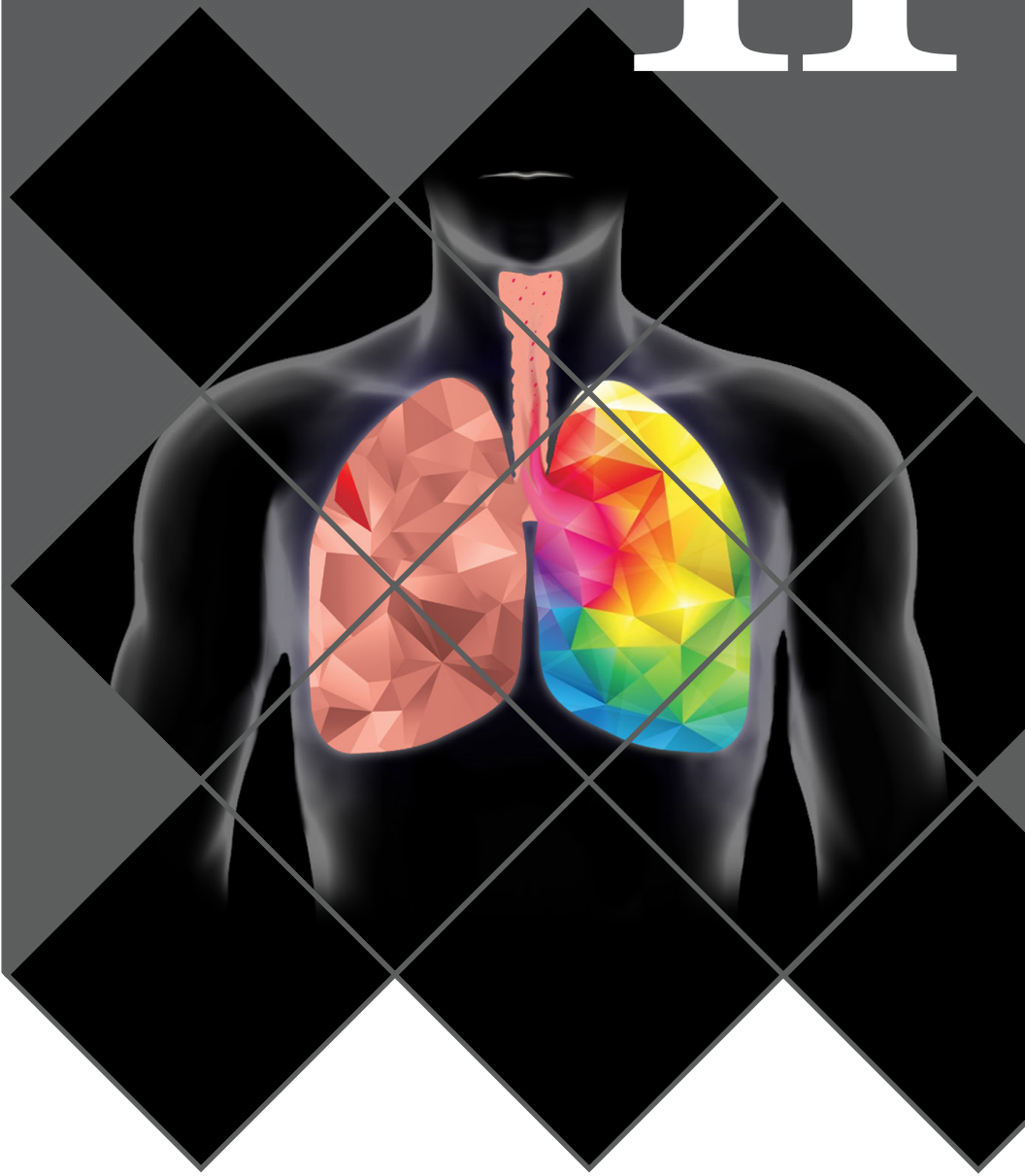
Chapter 11



Clinical Monitoring and Toxicity Management

Chapter 11

Clinical Monitoring and Toxicity Management

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I. Initial Evaluation Prior to Starting Standard Four Drug Therapy

A. Laboratory testing: Liver function tests (LFTs) including ALT and bilirubin at minimum, glucose, BUN/creatinine, CBC with platelets, and HIV serology; additional testing depending upon patient co-morbidities including hepatitis B/C serologies are optional.

B. Evaluation of baseline visual acuity (Snellen chart) and color discrimination (Ishihara test).

C. Review of concurrent medications for drug interactions.

D. Establish a baseline for signs and symptoms related to co-morbid disease and any toxicity to current drug therapy.

E. Review of microbiology data including sputum samples (for pulmonary disease) submitted for acid-fast bacilli (AFB) staining, mycobacteria cultures and antimicrobial drug susceptibility testing (DST) results, if available.

II. Ongoing Clinical and Laboratory Monitoring

A. Brief assessment for any symptoms of disease progression (including IRIS) and drug toxicity by outreach worker with each directly-observed therapy (DOT) dose.

B. Monthly clinical evaluation by physician or nurse case manager

1. Review of any active symptoms, new medical diagnoses/co-morbidities, or new medication changes or additions (including over the counter medications).

2. Visual acuity and color discrimination assessment if on ethambutol (EMB) or linezolid (LZD).

C. Laboratory monitoring during standard drug susceptible TB

1. Follow monthly LFTs for the following risk factors:

a. Abnormal baseline testing, development of symptoms consistent with hepatotoxicity, chronic alcohol use, potentially hepatotoxic medications, viral hepatitis, history of liver disease, HIV infection, prior drug-induced liver injury, pregnancy and the immediate postpartum period (2-3 months).

2. Some TB clinical experts suggest intermittent monitoring during therapy.

D. First line TB drug adverse reactions and monitoring for drug susceptible TB can be found in **Table 23.**

The following tables/recommendations are a general guide and should not substitute for clinical judgement in individual patient case scenarios. Concomitant medications, drug interactions, co-morbidities, and unique patient scenarios may warrant closer, more frequent assessment and closer attention for more rarely seen side effects.

Table 23. First Line TB Drug Adverse Reactions and Monitoring

Adverse Reactions	Clinical Monitoring	Lab Monitoring
Ethambutol		
Ocular toxicity-optic neuritis (often manifested as decreased visual acuity or decreased red-green color discrimination) **Rare:** Peripheral neuropathy	Visual acuity/color-discrimination (Ishihara) assessment, baseline and monthly. Ask about vision changes with each DOT dose	**Serum creatinine:** baseline and monthly if CKD or risk factors for kidney injury
Isoniazid		
Elevated liver enzymes (predominantly ALT and AST; may be asymptomatic or symptomatic), hepatitis, peripheral neurotoxicity, rash, arthralgia, drug induced lupus **Rare:** Hypersensitivity reactions	Monitor for clinical signs of hepatotoxicity (nausea, abdominal pain, jaundice, etc.) and neuropathy	**AST/ALT, alkaline phosphatase, bilirubin:** baseline and monthly if risk factors present
Pyrazinamide		
Polyarthralgia (non-gouty), asymptomatic hyperuricemia, hepatotoxicity, GI upset, self-limited transient morbilliform rash, photosensitive dermatitis **Rare:** Acute gout, usually in patients with pre-existing gout	Monitor for joint pain, GI adverse effects, and rash Monitor for clinical signs of hepatotoxicity (nausea, abdominal pain, jaundice, etc.)	**AST/ALT, alkaline phosphatase, bilirubin:** baseline, and then monthly if risk factors present **Serum creatinine:** baseline and monthly if CKD or risk factors for kidney injury
Rifampin		
Rash/pruritis, GI upset/nausea, hepatotoxicity (cholestatic picture), Hematologic: thrombocytopenia, hemolytic anemia, flu-like syndrome/ arthralgias **Note:** Rifampin will produce an expected orange discoloration of body fluids (sweat, tears, urine, saliva) – this is NOT a toxicity, it will resolve after treatment completion, and can be a marker of patient drug adherence	Monitor for GI adverse effects and rash Monitor closely for drug-drug interactions	**AST/ALT, alkaline phosphatase, bilirubin:** baseline, one month, and then monthly if risk factors **CBC w/differential:** baseline, and monthly if symptoms or risk factors for hematological toxicity; many clinicians check monthly.

E. Other TB drug adverse reactions and monitoring for second line drugs can be found in Table 24.

Table 24. Other TB Drug Adverse Reactions and Monitoring

Adverse Reactions	Clinical Monitoring	Lab Monitoring
Amikacin		
Ototoxicity (vestibular and auditory), nephrotoxicity, electrolyte abnormalities (K, Mg, Ca)	Audiometry + vestibular assessment at baseline and monthly for extended courses. Inquire on balance status or ringing in ears with each DOT dose.	**Serum creatinine, potassium, calcium, magnesium:** monthly; some providers favor laboratory monitoring weekly or every 2 weeks, especially if risk factors of nephrotoxicity present Serum level monitoring for durations >1 week
Bedaquiline		
Nausea Arthralgia Headache Chest pain QT prolongation	ECG: baseline, 2 weeks, 12 weeks, and 24 weeks into therapy; monthly if used with other Qtc prolonging drugs.	**AST/ALT/bilirubin/alkaline phosphatase, potassium, calcium, magnesium:** baseline, then monthly or as indicated
Clofazimine		
Orange/red/brown hyperpigmentation and discoloration (skin, conjunctiva, body fluids, hair, sweat, sputum, urine, feces), dry skin, rash, GI disturbance (nausea, vomiting, diarrhea) **Rare:** QT prolongation, hepatitis, jaundice	Monitor for GI effects, skin effects, and psychological disturbances (depression/ anxiety) related to skin discoloration ECG: monthly if used with other Qtc prolonging medications	**Serum creatinine**: baseline and monthly **AST/ALT, alkaline phosphatase, bilirubin:** baseline and monthly
Cycloserine		
CNS effects (inability to concentrate, confusion, lethargy, headache, restlessness), severe CNS effects (psychosis, seizures, depression, suicidal ideation), peripheral neuropathy **Rare:** Stevens-Johnson syndrome; Lichenoid skin eruptions	Monitor for neurologic/ psychiatric effects, change in behavior Monthly clinical assessment of depressive symptoms (PHQ9, Beck Depression inventory)	**Serum creatinine:** baseline and monthly Consider TDM with a goal 2 hour post dose level < 35 mcg/ml
Ethionamide		
GI disturbance (nausea, vomiting, diarrhea), metallic taste, endocrine effects (gynecomastia, hair loss, acne, impotence, menstrual irregularity, hypothyroidism), hepatotoxicity, neurotoxicity (peripheral neuropathy, optic neuritis, depression, and psychosis)	Monitor for gastrointestinal, neurotoxic, and endocrine adverse effects	**AST/ALT, alkaline phosphatase, bilirubin:** baseline and monthly **TSH:** baseline and every 3 months

Table 24. Other TB Drug Adverse Reactions and Monitoring

Adverse Reactions	Clinical Monitoring	Lab Monitoring
Imipenem		
Low risk of gastrointestinal effects: nausea, vomiting, diarrhea **Rare:** seizure (noted with CNS infection), especially in children	Monitor for gastrointestinal adverse effects	**CBC w/differential and serum creatinine:** baseline, then weekly
Levofloxacin		
Gastrointestinal effects (nausea, bloating, diarrhea), CNS effects (headache, dizziness, insomnia, tremulousness, agitation), QTc prolongation **Rare:** tendon rupture, arthralgias, peripheral neuropathy, seizures, aortic dissection	Monitor for gastrointestinal and other clinical adverse effects	**Serum creatinine:** baseline and monthly if underlying CKD or risk factors for kidney injury Consider ECG monitoring if used with other potentially QTc-prolonging medications
Linezolid		
GI effects (nausea, vomiting, diarrhea), headache, myelosuppression (low platelets, white blood cells, and/or anemia), Peripheral neuropathy **Rare:** optic neuritis, lactic acidosis, seizure, serotonin syndrome	Monitor for GI adverse effects, clinical thrombocytopenia (unusual bleeding, bruising), and peripheral neuropathy Monthly visual acuity (Snellen) and red/green color discrimination (Ishihara)	**CBC w/differential:** baseline, weekly x 2 weeks, then at least monthly **AST/ALT, alkaline phosphatase, bilirubin:** baseline and monthly if underlying liver compromise
Moxifloxacin		
Gastrointestinal effects (Nausea, bloating, diarrhea), CNS effects (Headache, dizziness, insomnia, tremulousness, agitation), QTc prolongation **Rare:** tendon rupture, arthralgias, peripheral neuropathy, seizures, aortic dissection	Monitor for GI adverse effects, neuropsychiatric effects and joint pain	**AST/ALT, alkaline phosphatase, bilirubin:** baseline and monthly Consider ECG monitoring if used with other potentially QTc-prolonging medications
Para-aminosalicyclic acid		
Gastrointestinal intolerance (less with granules), hypothyroidism (increased with ethionamide), Malabsorption syndrome (characterized by steatorrhea and low serum folate) **Rare:** hepatotoxicity and coagulopathy (increased prothrombin time)	Monitor for GI adverse effects and hypothyroidism	**AST/ALT, alkaline phosphatase, bilirubin:** baseline and monthly **TSH:** baseline and every 3 months

Table 24. Other TB Drug Adverse Reactions and Monitoring

Adverse Reactions	Clinical Monitoring	Lab Monitoring
Rifabutin		
Rash/pruritis (generally self-limited), orange discoloration/staining of body fluids, GI upset, hepatotoxicity (cholestatic picture), hematologic (leukopenia, neutropenia, thrombocytopenia), uveitis, arthralgias, fever **Note:** rifabutin may produce an orange discoloration of body fluids (sweat, tears, urine, saliva) – this is NOT a toxicity, resolves after treatment completion	Monitor for GI adverse effects, rash, and uveitis Monitor closely for drug-drug interactions	**AST/ALT, alkaline phosphatase, bilirubin:** baseline, one month, and then monthly if risk factors **CBC w/differential:** baseline, one month, and every 1-3 months
Rifapentine		
Rash/pruritis, orange discoloration/staining of body fluids (sweat, tears, urine, stool, saliva), GI upset/nausea, hepatotoxicity, hematologic (thrombocytopenia, neutropenia, anemia) hypersensitivity reaction **Note:** rifapentine may produce an orange discoloration of body fluids (sweat, tears, urine, saliva) – this is NOT a toxicity; resolves after treatment completion	Monitor for GI adverse effects and rash Monitor closely for drug-drug interactions	**AST/ALT, alkaline phosphatase**, baseline and monthly if risk factors **CBC w/differential:** baseline, one month, and every 3 months
Streptomycin		
Ototoxicity (vestibular and auditory), nephrotoxicity, electrolyte abnormalities (K, Mg, Ca)	Baseline and monthly audiometry and vestibular assessment for extended courses. Inquire about hearing/balance status with each dose	**CBC w/differential:** weekly **Serum creatinine:** weekly x 4 weeks, then weekly to every 2 weeks (if stable) Serum level monitoring for durations > 1 week

F. Management of select toxicities associated with TB drug therapy can be found in **Table 25.**

Table 25. Management of Toxicities

Causes	Assessment	Mangement
Diarrhea		
Clofazimine Ethionamide PAS Fluoroquinolone Linezolid	Rule out other causes (infection, parasites, lactose intolerance, C. difficile infection)	1) Address other causes as appropriate 2) Maintain hydration and electrolyte balance 3) If drug-induced, consider anti-diarrheal[1]
Hepatotoxicity		
INH PZA Rifamycins Ethionamide	1) AST/ALT > 3x ULN (with symptoms[2]), AST/ALT > 5x ULN or total bilirubin > 2.0	1) Hold medications. Reintroduce[3] in monitored fashion after symptoms resolved and AST/ALT are <2x ULN
	2) AST/ALT < 3x ULN without symptoms	2) Continue medications. Eliminate other contributors as able (alcohol, other hepatotoxic drugs, e.g. statins/supplements). Continue to monitor for symptoms and check LFTs weekly at least weekly x 4 weeks. 3) Check serum serologies to HAV, HBV and HCV
Nausea/Vomiting		
Clofazimine Ethionamide PAS Rifampin FQ PZA **Note:** All TB drugs have the potential for nausea and vomiting	1) Rule out drug induced liver disease with physical exam/LFTs 2) Rule out other causes/ contributors	1) Cease all medications if acute liver failure 2) Address non-drug causes as appropriate 3) Consider anti-emetic pre-medication and drug therapy interventions for tolerability 4) If necessary, can cease meds with sequential reintroduction or provide medications at different times to identify causative agents
Peripheral Neuropathy		
Cycloserine Ethambutol Ethionamide Fluoroquinolones INH Linezolid	1) Document baseline abnormalities if present, especially important in those with diabetes mellitus or HIV. 2) Determine clinical symptoms, location (toes, fingers) and stage: **Early:** tingling, burning in distal extremities **Progressing:** loss of deep tendon reflexes, gait unsteadiness	1) Treat with pyridoxine 50 – 100 mg daily 2) Address other contributing factors 3) Consider drug therapy (tricyclic antidepressant, gabapentin) for symptoms 4) Stop linezolid, if possible, if symptoms are progressing 5) Moderate to severe: stop or hold suspected offending drug and consider substituting with another if possible.

Table 25. Management of Toxicities

Causes	Assessment	Mangement
Rash		
Ethambutol Ethionamide Isoniazid FQ Pyrazinamide Rifampin Fluoroquinolones *Any TB drug can cause a rash	1) **Severe:** anaphylaxis, fever, rapid progression, skin blistering, mucous membrane involvement, lip/eye swelling, SOB/wheezing, airway compromise, any appearance of DRESS, TEN, SJS	1a) Cease medications 1b) Emergently address with epinephrine (if evidence of anaphylaxis), activate emergency response as appropriate
	2) **Non-Severe:** mild –moderate maculopapular rash/itching lacking systemic symptoms	2a) May require hospital admission 2b) Emergently administer epinephrine if any evidence of anaphylaxis; give antihistamine therapy/oral or topical corticosteroid depending on extent of reaction; consider cessation/reintroduction as needed
	3) Petechial rash	3) Assess CBC for eosinophilia, thrombocytopenia, generally if < 50,000 cease rifamycin; check liver and renal function if DRESS is possible diagnosis.
Visual Changes		
Optic neuritis: Ethambutol (most common) Ethionamide INH Linezolid **Uveitis:** Rifabutin **Polychromatic crystal deposition:** Clofazimine	1) Document visual acuity and Ishihara at least monthly, sooner if change in vision. 2) Assess clinically for uveitis if on rifabutin	1) Cease ethambutol and/or other likely causative agents and refer to ophthalmology for assessment 2) Hold rifabutin if uveitis identified; may consider lower dose 3) Stop linezolid, if possible, if symptoms are progressing

1. Antidiarrheals: Loperamide 4 mg after 1st loose stool, then 2mg-4mg after each subsequent loose stool (up to 16 mg daily). Can also titrate to a daily maintenance regimen for symptom control (e.g. 4 mg twice daily to maintain 2-3 semi-formed stools daily). Lomotil (diphenoxylate 2.5 mg /atropine 0.025 mg) 2 tablets up to four times daily can be used for symptom control.
2. Symptoms of hepatoxicity can include: nausea, vomiting, RUQ pain, abdominal swelling/tenderness, jaundice, scleral icterus, confusion/altered mental status, fatigue/malaise
3. Graded sequential reintroduction of hepatotoxic agents one at a time can enhance regimen tolerability and help identify likely drug contributor. We recommend the following approach after ceasing drug therapy:
   a. Cease all drugs in regimen until LFTs are WNL (or at least <2x ULN) and patient is symptom free.
   b. Query patient for all herbal supplements, natural product use. Eliminate all non-medically necessary supplements/products for duration of therapy.
   c. Review medication list and eliminate or find alternative therapy for any potentially likely hepatotoxic agents (e.g. substituting alternative therapy for acetaminophen products; hold statin therapy if able).
   d. Query the patient regarding alcohol use and ensure patient avoids alcohol
   e. Reintroduce suspect hepatotoxic drugs in sequential, graded fashion with one to two (depending on clinical status and fragility of patient) assessments of LFTs in a one week period prior to further sequential drug agent addition. Rifampin, along with ethambutol (to prevent mono-therapy), is usually the first drug to be challenged, as it is the most important drug in the regimen, with regimen composition and duration dependent on rifampin. Drugs unlikely to contribute to hepatotoxicity can be started with the 1st hepatotoxic agent.

III. Other Contributing Factors

A. Nausea/vomiting:

1. Pregnancy (in woman of child bearing potential), gastrointestinal TB, pancreatitis, lactose intolerance, acute kidney injury, gastric reflux disease, H. pylori gastritis, inflammatory bowel disease, gastritis due to other medication therapy or supplements (e.g. NSAIDS).
2. Consider addressing symptoms with optimization with hydration/ nutrition, antiemetic use, acid suppression, and medication timing/ administration factors
   a. Hydration/nutrition: Ensuring patients (if no fluid restrictions) are getting ~30 ml/kg of water intake daily and a well-balanced nutritional diet to maintain hydration status and appropriate caloric intake. Dehydration/malnourishment can worsen symptoms.
   b. Antiemetic considerations: ondansetron 4-8 mg, metoclopramide 10-20 mg, prochlorperazine 5-10 mg, promethazine 12.5-25 mg. These can be given 30-45 minutes prior to TB medication administration and then at appropriate intervals as needed throughout the day to assist with nausea/vomiting symptoms and TB medication tolerability. Drug-drug interactions with rifampin and ondansetron may decrease the effectiveness of the antiemetic.
   c. Acid suppression (with H2RA and PPI therapy) can aid with gastritis symptoms and medication tolerability. Antacids should be given 12 hours after TB medications to avoid interactions.
   d. Timing/administration options: (1) adjusting to evening administration can enable patients to sleep through most symptoms, as opposed to being bothered during waking hours; (2) encourage patient to take a nap after DOT, especially after the medications presumed to be causing the nausea. This often works well, as early in treatment many patients struggle with fatigue; (3) spacing out the individual medications throughout the day can help mitigate symptoms or determine causative drug (though generally not feasible with DOT); (4) administering with a light meal or snack can aid with tolerability. While the absorption of some medications can be mildly decreased (e.g. rifamycins), the enhanced adherence through medication tolerance makes this appropriate if necessary. TDM can be assessed if needed.

B. Peripheral Neuropathy

1. Malnourishment
2. Diabetes
3. Alcoholism

4. HIV infection
5. Hypothyroidism
6. Pregnancy
7. Dialysis
8. Other drugs

C. Severe reactions

1. Warrant close assessment of the reaction, likely drug cause, and consultation with a TB expert, dermatologist, and/or allergist for appropriate determination of TB agent selection.
2. If causating agent cannot be discontinued, desensitization/ reintroduction approach should occur in a monitored setting.

D. Mild maculopapular rashes

1. Often do not require cessation of therapy, can usually be treated and can be symptomatically addressed with antihistamine therapy and/or topical corticosteroid creams/ointments.
2. You may consider long-acting antihistamine therapy (cetirizine 10 mg daily, fexofenadine 180 mg daily, loratadine 10 mg daily), short acting antihistamine (diphenhydramine 25-50 mg or hydroxyzine 25-50 mg) given 30 minutes prior to administration and up to 3-4 times daily, or a combination of both short-acting and long-acting. Please note the sedating effects of short-acting antihistamine therapy.
3. Low dose oral corticosteroids (10-20 mg prednisone daily) for several weeks may also allow drugs associated with minor rashes to continue.

E. Cessation of all drug therapy

1. Use to enable symptom control may be reasonable. Sequential reintroduction with therapy to prevent symptoms can enhance regimen tolerability and help identify culprit agent. We recommend initiation of a basal long-acting antihistamine and premedication with a short acting antihistamine 30 minutes prior to administration as a reasonable approach with graded, sequential drug introduction every 2-3 days. Example: Reintroduction of medications after resolution of moderate maculopapular rash on chest.
2. Sample drug reintroduction regimen: Start cetirizine 10 mg daily. Provide diphenhydramine 25 mg, 30 minutes before medication doses. Prednisone 20 mg can be added 30 minutes prior to addition of each drug if reaction was moderate to severe. Full dose can be considered in place of partial dose especially if reaction is not severe or if prednisone is given prior to addition of medication. In general, new medications should be added Monday – Thursday so public health staff are available to respond to or support patient's efforts to seek medical intervention for adverse effects. New medications

should generally be added after 2 – 3 days on prior treatment and when medication is tolerated for at least one dose without need for pre-medication.

IV. Other Toxicity/Management Pearls

A. Rash

1. Itching and maculopapular rash are quite common during early course of TB therapy and can usually be managed with drug continuation and symptomatic treatment.
2. Any TB drug can be the cause of a rash, many of which are self-limiting and resolve with continued drug therapy.
3. Be sure to evaluate differential causes of rash (phototoxicity, insect bites/scabies, dry skin, psoriasis, atopic dermatitis, etc.).
4. Notable flushing can occur from high tyramine content food ingestion while on INH. Address by avoiding high tyramine containing food (aged wines, cured/processed meats, sauerkraut, fermented beer, etc.).

B. Hepatotoxicity

1. Asymptomatic elevations in transaminases are common in patients on standard rifampin, isoniazid (INH), pyrazinamide (PZA), EMB therapy.
2. These often resolve with continued treatment and typically do not require drug cessation.
3. Holding treatment with later sequential reintroduction should be considered if symptoms of liver toxicity are present with transaminases > 3x ULN or > 5x ULN even without symptoms.
4. Treatment should also generally be held if total bilirubin is > 2.0.
5. Assess and monitor for all other contributors (alcohol—increased AST/ALT ratio, gallstones, supplement/natural products with hepatotoxic potential, other hepatotoxic drugs e.g statins, azoles, acetaminophen, etc.).
6. Patterns of abnormal elevated LFTs can provide clues to etiology – examples:
   a. Elevated transaminases – suspect INH, PZA more so than rifamycin.
   b. Elevated bilirubin and alkaline phosphatase (more so than transaminases) –suspect rifamycin-based toxicity.
7. If patient has high *M. tuberculosis* disease burden where it would be problematic to temporarily hold combination TB drugs in the setting of hepatotoxicity, consider a “liver sparing program” until hepatotoxicity is resolved (e.g. EMB and a fluoroquinolone with LZD,

cycloserine or an injectable). This would be a temporary measure in order to address the TB while enabling hepatic recovery.

C. Visual changes

1. Ocular toxicity is rare with TB therapy. EMB is the most likely causative factor.
2. Optic neuritis attributable to EMB is dose-dependent, requires discontinuation of EMB, and requires urgent ophthalmologic evaluation. Decreased visual acuity due to ethambutol is usually reversible if the drug is stopped early.
3. LZD is also associated with visual toxicity; loss of visual acuity due to optic neuritis or decreased color vision can occur. Changes are reversible in nearly all patients if toxicity is detected early and LZD is stopped. Visual toxicity usually occurs after >12 weeks of treatment.
4. When patients have vision toxicity both EMB and LZD should be stopped; patients can be rechallenged with LZD, but EMB should not be restarted.
5. Ethionamide and INH are also rarely implicated as causes of optic neuritis.
6. Uveitis due to rifabutin can affect vision. This can be dose/exposure related and should be assessed if visual disturbance or eye discomfort on rifabutin. Vision changes are reversible after rifabutin is stopped.
7. Clofazimine has been associated with polychromatic crystalline deposition in the cornea and conjunctiva. Rare cases of bull's eye retinopathy have also been described with clofazimine.

D. Nausea/vomiting

1. Nausea/vomiting can be a symptom of acute liver failure related to drug associated hepatotoxicity and should be promptly evaluated by LFT assessment and physical exam. If drug induced liver disease is considered, all potentially liver toxic medications should be held until results of liver enzymes are available.
2. Nausea/vomiting is not uncommon with TB medications, especially early after starting combination therapy.
3. Nausea/vomiting usually improves notably as nutritional status improves, hydration status improves, and therapy continues.
4. Drug cessation/substitution is typically a last option with first line therapy. All reasonable attempts should be made to address nausea/vomiting to optimize tolerability. Consultation with a TB expert should be undertaken before regimen substitution.

E. Flu-like syndrome (fever, chills, headache, body aches)

1. Rare syndrome that can occur with rifamycin therapy, more likely with intermittent dosing.

2. May resolve with transitioning to daily therapy.
3. Syndrome alone may not require drug cessation but requires close evaluation and drug cessation if associated with other hypersensitivity phenomena: thrombocytopenia, leukopenia, agranulocytosis, vasculitis, red blood cell aplasia, disseminated intravascular coagulation, hemolytic anemia, acute renal failure, elevated liver enzymes or CPK.
4. Check CBC w/differential, LFTs, serum creatinine and evaluate for hypersensitivity, if noted.

V. General Principles in the Management of Drug Toxicity

A. Assessment

1. Be sure to evaluate other non-TB drugs, supplements, and additional co-morbid conditions as potential contributors to toxicity.
2. Review medication profile for assessment of drug interactions that could lead to toxicity.
3. Consider treating through mild/moderate symptoms and continuing the medications when able and appropriate.
4. Consider assessment of serum drug levels (See Chapter 10: Drug Therapy for TB) if concentration dependent toxicity is a consideration.

B. Reintroduction

1. In many cases, TB medications can be held until moderate-severe toxicity symptoms resolve and then re-introduced one at a time. In more severe forms of TB and earlier in therapy, treatment may need to be continued with an alternative regimen (e.g. "hepatic sparing" regimen such as ethambutol, levofloxacin and either linezolid or cycloserine in cases of hepatotoxicity) temporarily until toxicity symptoms are resolved and etiology clarified.
2. Graded reintroduction may aid with tolerability; using a lower dose of drug and gradually increasing dose to full strength before adding next drug.
3. Consider allergy consultation for severe reactions that may require desensitization in a monitored setting during medication rechallenge.

C. Involve TB experts

1. Always consult a TB specialist if unable to use standard therapy or considering therapy modification.
2. If patient has extensive TB burden, is extremely ill, or is highly contagious, suspected drugs causing specific toxicities can be held and a TB expert should be consulted for use of an appropriate alternative regimen to address TB that temporizes the current toxicity.

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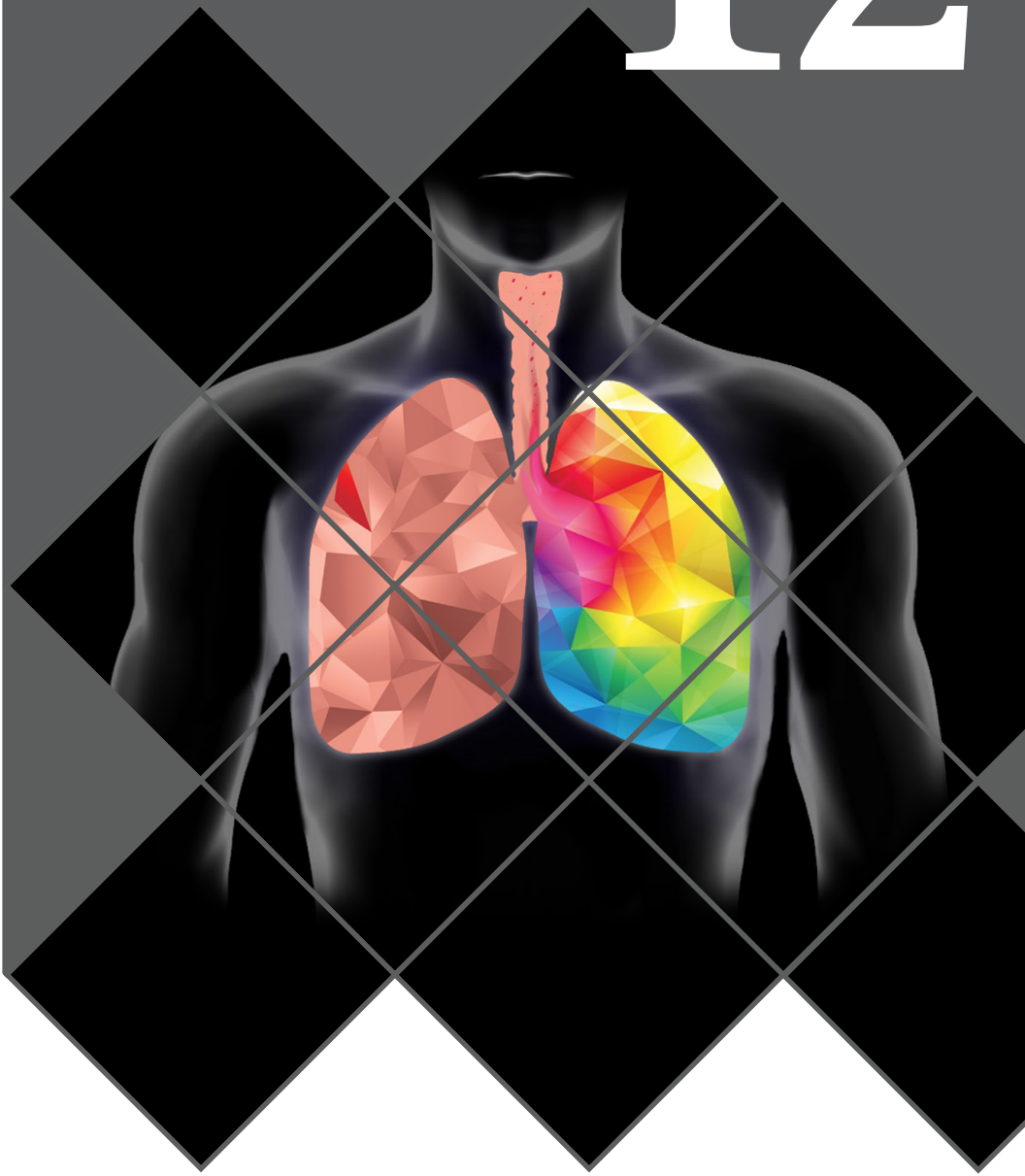
Chapter 12



TB in Special Populations

Chapter 12

Tuberculosis in Special Populations

Lisa Y. Armitige, MD, PhD; Claudia C. Dobler, MD, PhD; Robert (Rob) J. Morgan III, MD, PhD

Section 1: TB and Pregnancy

I. Evaluation

A. A pregnant woman suspected of latent tuberculosis infection (LTBI) or active tuberculosis (TB) should be tested with a tuberculin skin test (TST) or an interferon gamma release assay (IGRA). As with the general population, testing of pregnant women should be targeted with only individuals at high risk of LTBI or TB disease progression being tested.

B. Testing in this population should be done with the intent to treat during pregnancy if the patient is at high risk for progression to active disease and the TST or IGRA is positive. This group includes (see Chapter 1: Testing for Tuberculosis Infection) those with:

1. Recent infection (e.g. within the past 2 years)
2. Immunosuppressive conditions including, hematologic malignancies and other cancers treated with antineoplastic chemotherapy, hematopoietic and solid organ transplant recipients, diabetes – especially if poorly controlled, recipients of tumor necrosis factor alphas antagonists and other immunosuppressant biologic therapies, other immunosuppressive therapies equivalent to prednisone ≥ 15 mg/day for 1 month or longer.
3. Fibrotic chest x-ray (CXR) lesions of old untreated/inactive TB
4. Injection drug use
5. Chronic kidney disease
6. Pulmonary silicosis
7. Malnourishment

C. Pregnant women (without evidence of active disease) who are at low risk for progression to active disease and test positive by a TST or IGRA may have treatment delayed until after the post-partum period.

II. Treatment of Latent TB Infection

A. Cases of congenital TB requiring treatment of both mother and child with concomitant risks of disease progression and requirement for multi-drug regimens can be avoided by careful screening and treatment of at-risk pregnant women with LTBI.

B. For women at high risk for progression from LTBI to active TB (see Section I.B. above), treatment should be given, even during the first trimester. Treatment with first line TB drugs is considered safe in pregnancy and all TB infection regimens may be used in this population with the exception of 3HP. Use of 3HP in pregnancy has not been studied and should not be offered in this population.

C. While treatment with both INH and rifampin is generally safe, all pregnant and peripartum (e.g. within 2-3 months of delivery) women undergoing TB infection treatment should have monthly clinical monitoring with LFTs (and a CBC if taking rifampin). A slight increase in hepatotoxicity has been noted with treatment using isoniazid (INH) during the peripartum period and pregnant women should be closely monitored while on this drug.

D. For women whose risk of progression to disease is low, some experts recommend waiting until 2-3 months after delivery to start LTBI treatment. In this case, the woman should be monitored regularly and educated about the signs and symptoms of active disease.

E. Standard recommendations for LTBI treatment should be followed when treating pregnant women. Rifampin is preferred by many experts but INH is also an option although the risk of liver toxicity is greater.

F. Women who are HIV positive and pregnant should not receive INH during pregnancy. Rifampin daily for 4 months may be given safely during pregnancy to HIV positive women. Pregnant women receiving either INH or rifampin should be followed carefully during pregnancy and the postpartum period. Liver enzymes should be checked at least monthly.

III. Treatment of TB Disease

A. Pregnant women in whom active tuberculosis is strongly suspected or confirmed, should start treatment without delay. Outcomes for both pregnant women and their infants are worse when treatment is delayed.

1. All first line TB medications have a category C rating. While inclusion of pyrazinamide (PZA) in the treatment regimen of fully drug susceptible TB in pregnant women in the United States (U.S.) has been controversial, it is important to recognize that PZA has been used extensively in high-TB burden countries for many years. Use of PZA is recommended by the World Health Organization (WHO) for TB in pregnancy. Clinicians should evaluate the risks and benefits of prescribing PZA, acknowledging that the exclusion of PZA in a standard regimen for drug susceptible TB requires extending the treatment duration from 6 to 9 months.

2. Use of PZA during pregnancy in the U.S. is recommended for the treatment of INH and/or rifampin resistant TB, in cases of drug intolerance, and in women with HIV.

3. If PZA is not used, INH and rifampin should be continued for a total duration of 9 months.
4. Pyridoxine (Vitamin B-6) supplementation is recommended for all pregnant women taking INH.

B. All pregnant and peripartum women should have monthly clinical and laboratory monitoring.

IV. Breastfeeding

A. The low concentrations of antituberculous drugs in breast milk are not adequate to cause toxicity in the nursing newborn. Therefore, breastfeeding should not be discouraged in women being treated for tuberculosis.

B. Drugs in breast milk are ineffective to treat or prevent tuberculosis in a nursing infant.

C. Pyridoxine (vitamin B6) is recommended for both nursing mothers and for exclusively breastfed infants receiving INH.

Section 2: TB and Mental Health

A. The relationship between mental health and TB is complex and bidirectional. Up to 70% of patients with TB may also have a co-morbid mental illness. The most common co-morbidity is depression but disproportionately high rates of anxiety, psychosis, and substance use disorders co-occur as well.

B. A number of shared risk factors have been identified that may predispose those with TB to a mental health diagnosis and vice versa. These include:

1. Homelessness
2. Substance use disorders
3. Poverty
4. Migrant status
5. HIV-positive serology

C. Mental health co-morbidities in patients with TB results in higher rates of:

1. Poor healthcare utilization
2. Difficulties with treatment adherence
3. Progression from LTBI to active disease
4. Multi-drug resistant tuberculosis
5. Physical and social disability
6. Negative stigma
7. Social isolation

D. Due to the prevalence of depression in patients with tuberculosis, screening for depression using the PHQ-2 (Table 26) can be useful in identifying patients who may benefit from further mental health assessment and treatment. The PHQ-2 has a high sensitivity and moderately high specificity for identifying patients with a depressive illness. Two questions are scored from 0-3 (total range: 0-6) with a cutoff of 3 suggesting a need for further investigation.

Table 26. PHQ-2

In the last two weeks, how often have you been bothered by either of the following problems?	Score
1. Feeling down, depressed, or hopeless 2. Little interest or pleasure in doing things	0 Not at all 1 Several days 2 More than half the days 3 Nearly every day

E. Management of a positive PHQ-2 screen for depression may include a combination of:

1. Further discussion of symptoms with patient
2. Discussion with TB case manager
3. Referral to primary care or psychiatry specialist
4. Referral to a psychotherapist
5. Initiation of pharmacotherapy (e.g. SSRI)

F. Frequently, patients who are treated for tuberculosis will already be on medications for a mental health diagnosis. There are numerous interactions between psychotropic medications and anti-tuberculous agents, and these interactions can have clinical significance. Most interactions occur due to the effects of anti-tuberculous agents on the cytochrome p450 (CYP450) enzymes involved in metabolism of the psychotropic drugs. Table 27 displays the clinically relevant effects of anti-tuberculous agents on various CYP450 enzymes.

Table 27. Impact of Anti-Tuberculous Agents on CYP450 Enzymes

Drug	1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
Rifampin		↑	↑	↑	↑			↑
Isoniazid					↓			↓
Erythromycin								↓

↑ : Induction of CYP enzyme; ↓:Inhibition of CYP enzyme

G. The CYP450 interactions in Table 27 result in alterations in plasma levels of many psychotropic agents which can impact these agents' efficacies. Table 28 shows a selection of clinically relevant interactions between anti-tuberculous agents and psychotropics. When using medication combinations from this table, consider obtaining baseline plasma levels when possible and tracking levels during the course of treatment, adjusting doses accordingly. Patients should also be monitored closely for emergence of symptoms that suggest decreased therapeutic efficacy or toxicity. Dose adjustments may also be necessary when discontinuing anti-tuberculous treatment. Close collaboration with a patient's psychiatrist or primary care provider is recommended. Substitution of rifabutin for rifampin usually decreases the effect of the psychotropic medications.

Table 28. Anti-Tuberculous Agents and Psychotropic Medication Interactions

Drug	Increased Level	Decreased Level
Rifampin		Alprazolam (B) Amitriptyline (D) Aripiprazole (P) Buspirone (A) Carbamazepine (C) Citalopram (D) Clozapine (P) Diazepam (B) Eszopiclone (H) Haloperidol (P) Imipramine (D) Methadone (O) Midazolam (B) Nortriptyline (D) Pimozide (P) Risperidone (P) Sertraline (D) Trazodone (D) Triazolam (B) Valproic acid (C) Zolpidem (H)
Isoniazid	Carbamazepine (C) Diazepam (B) Haloperidol (P) Lamotrigine (C) Methadone (O) Valproic acid (C)	
Erythromycin	Buspirone (A)	

A: Non-benzodiazempine anxiolytic; B: Benzodiazepine; C: Anticonvulsant mood stabilizer; D: Antidepressant: H: Sedative-hypnotic; O: Opiate; P: Antipsychotic

H. Other relevant drug-drug interactions to be aware of include:

1. Linezolid (a monoamine oxidase inhibitor (MAOI)) increases risk of serotonin syndrome in combination with many antidepressants.
2. Fluoroquinolones can increase risk of QTc prolongation in combination with other QTc-prolonging medications such as most antipsychotics and some antidepressants.
3. Isoniazid is a weak MAOI but there are no reports of serotonin syndrome in combination with antidepressants.

I. Anti-tuberculous agents not only interact with treatments for psychiatric illnesses, they also have the potential to cause adverse psychiatric effects. Table 29 provides a summary of the psychiatric adverse effects associated with anti-tuberculous agents. Approximate frequencies are provided where available.

Table 29. Psychiatric Adverse Effects

Drug	Adverse Effect
Cycloserine	Anxiety Insomnia Mania Psychosis ** Total rate of psychiatric events: 20-33% ** Contraindicated with seizure disorders or agitation
Ethambutol	Psychosis (rare)
Fluoroquinolones	Delirium (rare)
Isoniazid	Depression Psychosis
Rifampin	Delirium/confusion (rare)

J. While co-morbidities between mental illness and tuberculosis can result in increased risks of negative outcomes, awareness and treatment of mental illness can improve patient well-being and outcomes.

1. Actions that have been shown to improve to positively impact outcomes for patients with mental illness and TB include:
   a. Tuberculosis support groups
   b. Individual psychotherapy
   c. Group psychotherapy
   d. Supportive home visits
   e. Combination of directly-observed therapy for tuberculosis and opiate use
2. A culturally sensitive approach, utilizing locally available resources and bearing in mind the role of stigma and discrimination toward patients with both tuberculosis and mental illness, is recommended for optimal results when treating this vulnerable population.

Section 3: Tuberculosis, TNF Antagonists and Other Biologics

I. TB Risk Associated with Treatment with a Biologic

A. Different types of biologics are associated with variable risks of TB. For example, anti-TNF-alpha monoclonal antibodies (adalimumab and infliximab) are associated with a significantly higher risk of TB compared to soluble TNF-alpha receptor therapy (etanercept). The newer TNF-alpha inhibitors certolizumab pegol and golimumab have not been associated with an increased risk of TB to date.

B. Consideration should be given to differences in TB risk between different biologics when determining the optimal treatment for individual patients. In situations where patients have an ongoing risk of TB exposure (for example travel to TB-endemic areas) or could not complete a course of LTBI treatment (for example due to an adverse reaction), choosing a biologic associated with a lower risk of TB should be considered.

II. Screening for Latent TB Infection

A. Before patients commence treatment with a biologic they should be screened for latent TB infection with a TST or IGRA or a combination of the two.

B. Compared with the TST, IGRAs can better identify BCG vaccinated persons who have LTBI (true positive). They also appear to be slightly better at correctly identifying patients with immune-mediated inflammatory disease such as rheumatoid arthritis or Crohn's disease who truly have infection with TB (true positive). Immunosuppressive due to underlying disease or immune suppressive therapy can be associated with false negative and indeterminate IGRA results, as well as false negative TST results.

C. In patients with a high pre-test probability of latent TB infection (history of contact to a case of active TB, birth or extended stay in a TB-endemic setting) it is prudent to use IGRA and TST sequentially —in any order— if the first test for TB infection is negative. If any test result from either the TST or IGRA is positive, the result should then be interpreted as indicative of TB infection.

D. The recommended cut-off for a positive TST is 5 mm in patients with an immune-mediated inflammatory disease who are considered for treatment with a biologic.

E. A CXR to exclude active TB is indicated if the patient has any of the following:

1. Positive TST or IGRA
2. History of TB disease
3. Recent exposure to a person with known active TB
4. Physical examination consistent with active TB or past TB

III. Treatment of Latent TB Infection

A. Treatment of latent TB infection is effective in reducing the risk of TB reactivation in patients treated with a biologic.

B. Treatment regimens for latent TB infection are:

1. 12 weeks of once-weekly isoniazid and rifapentine
2. 4 months of daily rifampin
3. 3 months of daily isoniazid and rifampin
4. 6-9 months of daily isoniazid (generally reserved for when 3HP or daily rifampin cannot be given)

C. Ideally, it is desirable to delay treatment with a biologic for at least one month after starting treatment for LTBI. In some patients, however, the need for urgent immunomodulatory therapy may justify the risk of starting treatment with a biologic at the same time as treatment for LTBI.

IV. Monitoring During Treatment with Biologics

A. Patients should be monitored for signs and symptoms of TB at least until 6 months after cessation of biologic treatment.

B. There is no need to perform routine chest x-rays.

C. For patients who had an abnormal chest x-ray but stable findings at the time of initial screening (i.e. previously appropriately investigated and treated) and patients with a past history of TB treatment, a repeat chest x-ray 3 months after commencing TNF-alpha blocker therapy is recommended. A chest CT and/or additional testing and evaluation are warranted if the initial screening chest x-ray shows new findings or the patient is symptomatic.

D. Annual testing for TB infection with IGRA or TST is only recommended in patients with no prior positive test results and an ongoing or new risk of TB infection (for example after travel to a TB endemic setting). Other patients should not have routine repeat testing with TST and/or IGRA.

E. Patients with an ongoing or new risk of TB infection, who had a positive TST or IGRA at baseline and received prior therapy for either latent TB infection or active disease, should be monitored for clinical signs and symptoms of TB. Repeating a TST or IGRA is not helpful, as these tests typically remain positive, even after a full course of treatment for latent TB infection.

V. Treatment of TB Disease

A. Patients on treatment with a biologic who develop active TB have an increased risk of poor outcomes (meningitis, disseminated disease, fulminant disease, death).

B. As soon as a clinical diagnosis of TB is suspected, anti-TB treatment should be promptly started, even if patients previously tested negative for latent TB infection or have a history of treatment for latent TB infection.

C. Discontinuation of biologic therapy, at least temporarily, should be considered at the time of TB diagnosis.

D. Re-initiation of biologic therapy can be considered once the patient has demonstrated improvement on effective combination TB drug therapy.

E. Prolonging anti-TB treatment to 9 months may be prudent, but the evidence is insufficient to make any definite recommendations about this.

VI. Immune Reconstitution Inflammatory Response

A. TB can paradoxically worsen when treatment with a biologic is discontinued. This reaction is also called immune reconstitution inflammatory syndrome (IRIS).

B. The optimal treatment of TB-IRIS is unclear. Re-initiation of biologic therapy, treatment with non-steroidal anti-inflammatory drugs, as well as prolonging anti-TB treatment to 9 months may be beneficial in biologic-associated TB-IRIS. Some patients may require steroid therapy.

C. A TB expert should be consulted in cases of TB in patients on treatment with a biologic.

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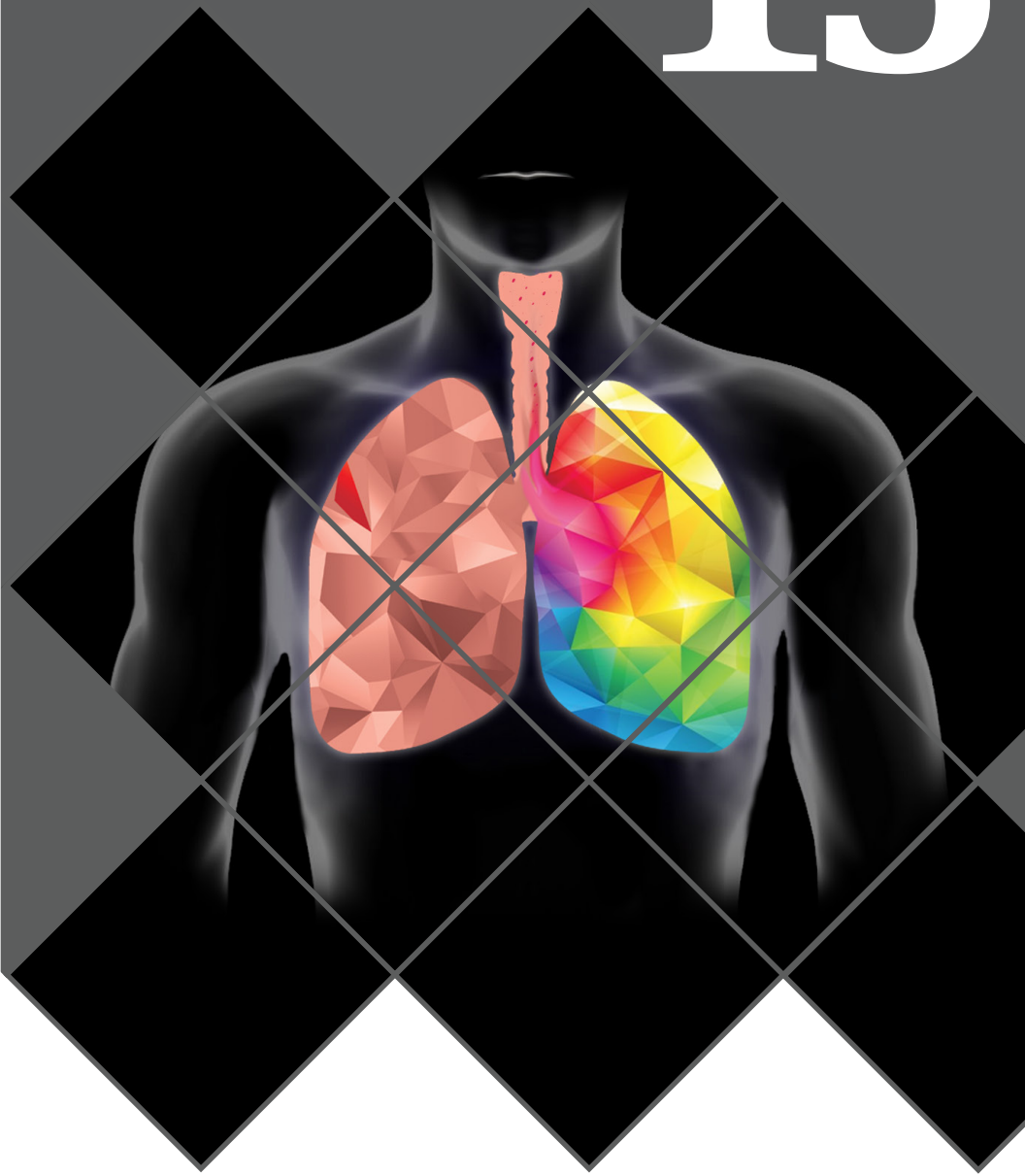
Chapter 13



Hospitalization, Isolation, Public Health Case Management

Chapter 13

Hospitalization, Isolation, Public Health Case Management

Shu-Hua Wang, MD, MPH&TM, PharmD, FIDSA;
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I. General Principles

A. Pulmonary tuberculosis (TB) can be infectious to others via inhalation of infected particles.

B. Extra-pulmonary TB generally is not communicable to others unless:

1. Concurrent pulmonary TB is present.
2. Surgical debridement using a water pick or other methods that produce aerosolization of *Mycobacterium tuberculosis (M. tuberculosis)* from the wound is used.

C. These criteria are general guidelines. State Public Health programs may have specific criteria for programs to follow. Expert consultation may be needed.

II. Hospitalization

A. TB patients can be treated as outpatients when they are:

1. Clinically stable
2. Likely to adhere to therapy, and
3. Live in stable household settings without immunosuppressed persons and/or small children present

B. Hospitalization is advised for patients with active pulmonary TB who are:

1. Clinically unstable with severe disease, medical co-morbidities and/or surgical complications.
2. Unable to adhere to TB treatment (consult state and local public health department for specific regulations).
3. Living in the same household with highly susceptible contacts, i.e., small children or immunocompromised persons.
4. Living in congregate settings or situations that will expose new contacts to infection (e.g. nursing homes or homeless shelters); visiting foreign nationals or patients staying in hotels.

III. Hospital Airborne Infection Isolation

A. Patients to be evaluated for TB or with confirmed infectious pulmonary TB should be placed in individual airborne infection isolation (AII) rooms to prevent the spread of infection to others.

B. Isolation rooms should have:

1. A minimum of 6 room air exchanges/hour
2. Negative air flow which does not recirculate into the system
3. Air vented to the outside at least 25 feet from intake vents
4. Ultraviolet lights and/or HEPA filters are useful adjunct
5. Isolation room should have specific precautions posted and the doors should remain closed as much as possible

C. Duration of time that the TB patient spends outside the AII room should be minimized. During transfer, the patient should wear a surgical mask.

D. Staff who enter the isolation room must wear an N-95 mask or powered air purifying respirator (PAPR).

1. The N-95 mask should provide a tight facial seal and filter particles 1 to 5 microns in size.
2. Healthcare personnel should be annually fit tested for N-95 masks or trained on the use of a PAPR.

E. During procedures that induce aerosols (sputum induction, gastric aspiration or bronchoscopy):

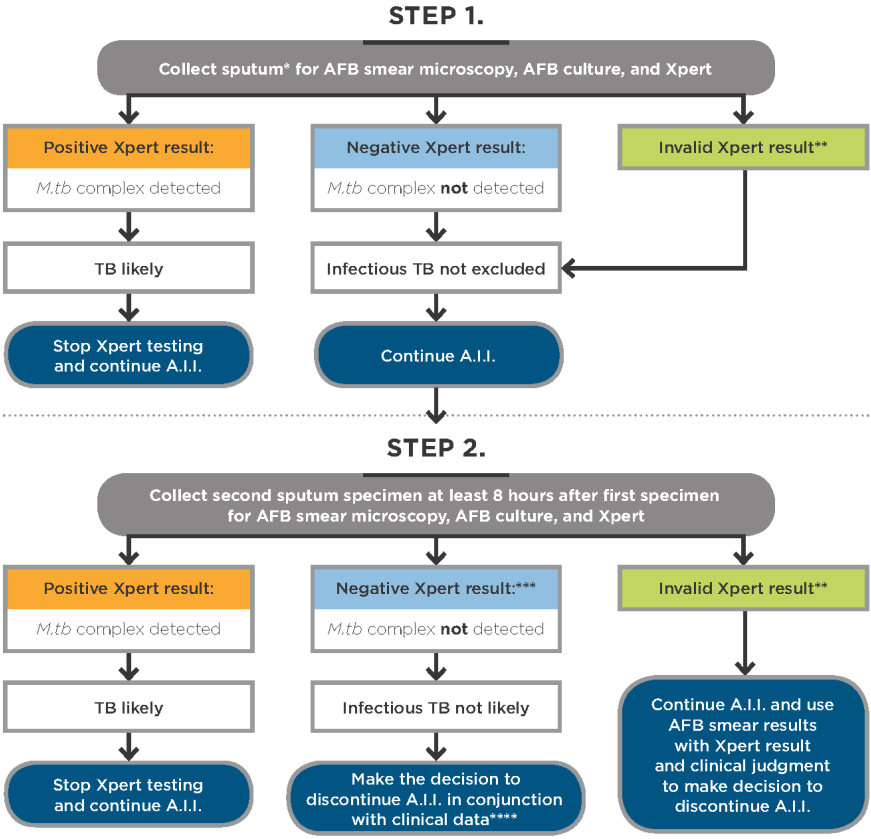
1. Negative air flow ventilation is mandatory and healthcare personnel should wear N-95 or HEPA filter masks.
2. Infectious patients should be scheduled as the last case of the day if negative airflow isolation rooms are not available. Early morning is usually recommended for collecting gastric aspirations.

IV. Duration of Airborne Infection Isolation

A. Patients with low suspicion for pulmonary TB can be removed from AII after obtaining:

1. Three consecutive AFB-negative smear sputum results of adequate quality, separated by at least 8 hours (adequate sputum is defined as a sample that is felt not to be saliva by the healthcare provider taking the sample).
2. Molecular tests such as the Cepheid GeneXpert® (Xpert®) MTB/RIF assay (Cepheid, Sunnyvale, USA) may be used to discontinue AII in hospital settings after obtaining two adequate quality sputum AFB smears and two Xpert® MTB/RIF results that are negative. (**Figures 4 & 5**).

Figure 4. Use of GeneXpert in Discontinuing Airborne Infection Isolation



*First morning specifimen preferred to maximize diagnostic yield of AFB sputum smear, culture, and Xpert

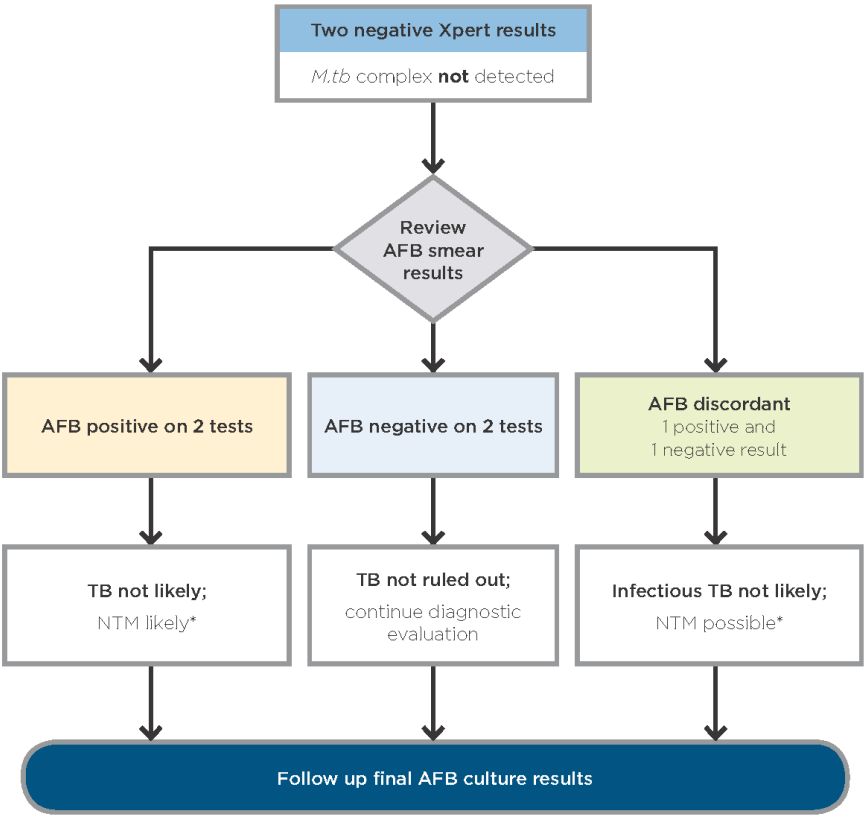
**Most laboratories/protocols will automatically retest leftover sample if an initial invalid (failed) result is obtained; in such cases, a reported invalid result reflects repeat testing of a single specimen

***If this result is negative following an initial invalid result in Step 1 and infectious TB still is clinically suspected, a repeat test (repeat Step 2) using a new specimen, if available, is recommended in order to improve sensitivity. Alternatively, the clinician may use the single negative Xpert result from Step 2 with smear results and clinical information to make the decision to discontinue or maintain AII.

**** **Note:** This process does not rule out tuberculosis with 100% certainty. Refer to Appendix IIIb Application of AFB Smear Microscopy to Negative Xpert Results to assist in diagnostic evaluation.

Appendix IIIa. NTCA/APHL Consensus statement on the use of Cepheid Xpert MTB/RIF® assay in making decisions to discontinue airborne infection isolation in healthcare settings. Used with permission from NTCA.

Figure 5. Application of AFB Sputum Smear Microscopy To Negative GeneXpert Results



*Negative Xpert Results with positive or discordant AFB sputum smears: Two negative Xpert results with positive AFB sputum smears likely indicate presence of nontuberculous mycobacteria (NTM); One negative Xpert result in a patient with positive AFB sputum smears is suspicious for NTM, and collection of sputum for a second Xpert test is recommended. If the second Xpert result is still negative, infectious TB is not likely. If smears are discordant (i.e., 1 AFB positive, 1 AFB negative), decisions should be based on clinical suspicion.

Appendix IIIb. NTCA/APHL Consensus statement on the use of Cepheid Xpert MTB/RIF® assay in making decisions to discontinue airborne infection isolation in healthcare settings. Used with permission from NTCA.

B. If clinical suspicion for pulmonary TB is high: For patients with high suspicion for pulmonary TB, AII should be maintained until the patient is considered no longer infectious to others, the diagnosis of TB is excluded, or the patient can be discharged to a home or other safe environment.

   1. While hospitalized, patients with pulmonary TB should remain in AII until criteria below are met and approved by hospital epidemiology/ infection control, and/or (if available) infectious diseases or pulmonary health provider. Consultation with a local or State Public Health official is recommended.

2. Criteria for removal of AII from inpatient setting (all three required):
    a. Have three consecutive acid-fast bacilli (AFB) negative smear sputum results of adequate quality separated by at least 8 hours (adequate sputum is defined as sample that is felt not to be saliva by the healthcare provider taking the sample).
    b. Patient is receiving effective combination multi-drug anti-tuberculous drug therapy.
        i. For baseline sputum AFB smear positive: at least 2 weeks of treatment.
        ii. For baseline sputum AFB smear negative: at least 5 to 7 days of treatment.
    c. Patient has demonstrated clinical improvement while on therapy.
3. Molecular tests such as Xpert® MTB/RIF assay (Cepheid, Sunnyvale, USA), may increase sensitivity of detecting *M. tuberculosis* on respiratory samples, as well as determine whether resistance to rifampin may be present. Note the Xpert® MTB/RIF assay should not be used to monitor response to TB therapy nor determine infection risk for confirmed or highly suspected cases of pulmonary TB.

C. Patients being discharged to a congregate setting, (e.g., nursing home, skilled care facility, prison, etc.) should meet the same criteria as for hospitalized patients to discontinue AII.
    1. Additional considerations for dismissing patients home include: Patient demonstrates complete adherence to treatment (patient is on Directly Observed Therapy [DOT]), clinical improvement.
    2. Assessment of close contacts of the index patient with TB, along with a plan for prompt evaluation and treatment of TB infection and disease if diagnosed.
    3. Contacts who are children under 5 years of age or immunosuppressed require prompt assessment for TB infection and consideration for prevention treatment.

D. If pulmonary multi-drug resistant TB (MDR-TB) has been diagnosed or suspected, the patient should generally remain in AII until respiratory cultures are negative for *M. tuberculosis* and in consultation made with local/state public health as well as a CDC supported regional TB Centers of Excellence (https://www.cdc.gov/tb/education/tb_coe/). Definitive recommendations for release from AII do not exist. Guidelines vary by state and country. Many states and TB experts require 3 negative cultures. The World Health Organization (WHO) requires 2 negative cultures to allow an individual to fly, but other states and experts discontinue isolation after 3 negative smears and clinical improvement.

E. Other considerations:

1. Patients who are infectious can be discharged from the hospital to home after the public health department has completed a home, assessment, ensures isolation can be maintained at home and household contacts have been evaluated.

2. State Public Health should be consulted to further address isolation precautions for patients with MDR-TB and time away from work for healthcare personnel with pulmonary TB in contact with vulnerable populations (including children under 5 years, HIV and other immunosuppressed patients).

V. Public Health Roles and Responsibilities

A. State public health agencies are mandated by law with the responsibility for oversight of all persons diagnosed or being evaluated for TB. The roles and responsibilities of the state public health agency are:

1. Assessment of the health of the state

2. Surveillance/reporting of cases

3. Policy development

4. Assurance of essential services for persons with TB

B. Persons with or to be evaluated for TB are referred to the local public health agency for provision of essential services which includes:

1. Public health case management, including oversight of clinical and diagnostic services

2. Directly observed therapy

3. Contact identification

VI. Basic Principles of Case Management

A. Case management is an intervention utilized to ensure patients complete an appropriate and effective course of treatment in the shortest possible time. Case management includes a number of activities listed below under the direction of public health and education of persons with TB infection/disease and family members.

B. Case assessment – Initial and continued during therapy

1. Gather patient-specific information, including medical history, demographics, and potential contacts with other people.

2. Identify the “infectious period” (period of time prior to isolation when the person confirmed or being evaluated for TB may have exposed and transmitted TB to others. Consult public health as this period depends on several factors such as clinical symptoms, radiologic findings including cavitary disease, sputum AFB smear status, duration of illness, etc.).

3. Complete public health medical record documentation, which should include the diagnostic evaluation results, medical evaluation and longitudinal clinical status and response to therapy.
4. Identify existing medical co-morbidities of the patient and potential mental health issues. Such concurrent health concerns should be addressed, including drug-drug interactions up front before starting treatment for TB.
5. Developing a plan of care
    a. Establish a plan of care to address the potential barriers to care identified in the initial assessment.
    b. Establish a plan for administration of treatment via DOT, including options of virtual/electronic DOT if available (see below).
    c. The plan of care will often require continued adjustments. Adverse events, including drug intolerance and toxicities, IRIS, poor adherence to treatment and unforeseen medical, psychological and social concerns may require modifications of the plan.

C. Implementation of the plan of care
1. Monitor response to treatment (e.g. change/improvement in symptoms, respiratory culture results, follow up imaging, etc.), interventions, and patient adherence.
2. Make referrals for additional services as needed such as unmet medical needs, housing, social services, transportation, etc.
3. Implement the DOT method plan by directly observing the patient take medications or observing the patient through technological methods.
4. Educate the patient, family, significant other, community.
5. Evaluation of the plan - The plan of care is periodically evaluated to determine if the patient's care needs and goals are met.
    a. Review the established plan of care and regularly update the plan as goals are met, problems are resolved or new problems are identified. Evaluate identified barriers regularly to ensure successful completion of treatment.
    b. Review patient status with clinician on a regular basis.
    c. Review the contact identification list to assure completion of evaluation and analysis; adjust the infectious period as needed and identify additional persons exposed to TB are identified.
    d. Assure reports are submitted.

D. Documentation of all activities is critical for quality care of the patient. It allows other health providers to review the patient record and facilitate care through understanding of patient-specific case management information.

1. Recording the interventions, activities and outcomes for the patient documents, in the health record, the progress of the patient toward the goal of treatment completion.
2. Record all case management activities within the patient's health record.
3. Record surveillance/reporting activities when completed.
4. Show adherence to laws, regulations, policies, procedures and standards of care.

E. Directly observed therapy: using a healthcare personnel or their designee to directly watching a patient swallow each dose of medication

1. Most strongly recommended for use in the treatment of patients with active or suspected TB (with both daily and intermittent regimens).
2. DOT is not mandatory for the treatment of LTBI, including once weekly isoniazid-rifapentine regimen (3HP) for 12 weeks.
3. Consider the use of incentives and/or enablers (e.g. food tokens, bus passes) to promote adherence when using DOT.
4. DOT can lead to reductions in disease relapse and acquired drug resistance.
5. Use electronic technologies to remotely monitor TB patients self-ingesting their medication, either in real-time or recorded. These methodologies may include the use of a smartphone, tablet or computer with webcam to observe the self-administration of TB medications. The video DOT (vDOT) can be performed in real-time with public health personnel observing at the same time or it can be asynchronous, where the individual submits the recording for later viewing by healthcare personnel.

F. Contact identification: the responsibility for contact identification is assigned by law to the public health departments in each state.

1. Objectives of contact identification: Identify and assess persons most at risk of being infected with *M. tuberculosis.*
2. Ensure individuals identified with either LTBI or active TB disease are referred into care for appropriate management.
3. Prevent progression to TB disease in certain individuals with presumptive infection by using window-period prophylaxis.
4. Definitions used with contact investigations

a. Index person with TB disease: the initial person diagnosed with pulmonary TB that prompts contact identification within a group, family or community.

b. Person to be evaluated for TB: a person for whom the diagnosis of TB disease is being considered possible or likely and before microbial or clinical confirmation.

c. Source person with TB: The original person with TB disease who may have transmitted *M. tuberculosis* to another person(s).

d. TB contacts: persons at highest risk of acquiring TB infection due to a close or substantial airborne exposure to index case.

G. TB contacts prioritized as high, medium or low priority based on:

1. The infectiousness of the index person with TB disease depends on several factors such as cavitary lung disease, active coughing, quantity of positive AFB smear (i.e., 4+ smear vs. negative AFB smear on sputum sample).

2. Amount of time spent in close exposure (few minutes vs. hours).

3. Environment that the exposure occurred in (small, crowded room vs. large well-ventilated room, or outdoors).

4. Medical co-morbidities of the exposed person increasing the risk of future disease development (e.g. HIV infection and other immunosuppressive conditions).

H. Types of contact identifications

1. Source Case or Associate: to identify the source of recent infection in a pediatric patient or when a healthcare setting detects an unexplained cluster of TST/IGRA conversions among healthcare personnel.

2. New or Presumptive Case: conducted surrounding newly diagnosed or Presumptive Case.

I. Initiate a contact identification for a patient with confirmed or presumed pulmonary or laryngeal TB based on clinical, radiologic and/or microbiologic testing results.

J. Steps in a contact identification

1. Field investigation to identify home, work and social environments to assess for transmission risk and additional contacts.

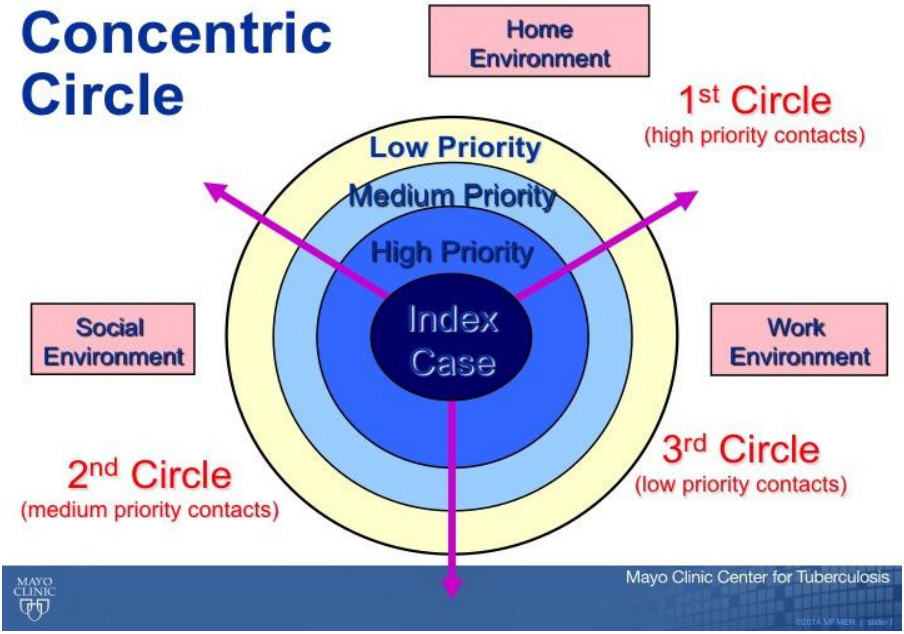
2. Assessment of transmission risk (See section VI.G.#1.).

3. Prioritization of contacts using the concentric circle method (See **Figure 6**).

4. Medical evaluation of contacts (symptom assessment, TST or IGRA, CXR if positive).

5. Decision concerning expansion of investigation based on evaluation of findings for active TB and contacts, and infection rate.

Figure 6. Concentric Circle for Prioritization of Identified Contacts



K. Index case medical information. Gather medical information to assist clinician's evaluation including:

1. TST or IGRA result - to determine prior exposure and infection (note that patients with active TB disease may not always have a positive TST or IGRA result, especially in small children and in immunosuppressed patients)
2. History of prior TB disease, infection or exposure
3. History of prior treatment for TB disease or latent TB infection -would increase suspicion for possible drug resistant TB
4. Signs/Symptoms of TB disease –Evaluate for possible disseminated TB
5. Date of onset of signs/symptoms – To assist with determination of infectious period
6. CXR results and other radiological images performed
7. Sputum bacteriology (including AFB stain, molecular genotyping or nucleic acid amplification test, cultures and antimicrobial drug susceptibility testing results)
8. Other mycobacterial testing such as AFB cultures from other than pulmonary sites or histopathology report if biopsy was performed to look for necrotizing granulomas
9. Other baseline testing, such as CBC with differential, liver function test, chemistry (HIV serology, chronic hepatitis panel, hemoglobin A1C, etc.)

L. Determine the infectious period. The infectious period establishes time frames during which the patient is capable of transmitting tubercle bacilli as well as the time frames for conducting the contact identification.

1. Beginning of Infectious Period:

   a. For AFB smear positive patients: Go back approximately 3 months from the onset of symptoms and consider site of disease, onset of symptoms, smear results and CXR results.

   b. For AFB smear negative patients: Go back approximately 1 month from the onset of symptoms and consider site of disease, onset of symptoms, smear results and CXR results.

2. End of Infectious Period:

   a. When most likely no longer capable of transmitting tubercle bacilli and considering adherence to treatment, microbiologic response (e.g. timing of smear and culture), and clinical improvement.

M. Required examinations for evaluation of contacts:

1. TST or IGRA

2. Obtain a CXR if either the TST or IGRA is positive, the patient has symptoms of active TB disease, is immunocompromised or under the age of 5 years

3. Assessment of signs/symptoms. Obtain sputum if symptomatic.

N. Infection Rate:

1. Know the infection rate for the community in which the investigation is being conducted.

2. Determine the infection rate of the investigation:

O. Completion of contact identification:

1. Repeat TST/IGRA 8-10 weeks after the date of last exposure for those who initially tested negative by TST or IGRA.

$$\frac{\text{\# Contacts with New TB Infection= \%}}{\text{Total \# of Contacts Tested and Read}}$$

2. Recalculate infection rate if new TB infection is identified.

3. If the infection rate exceeds that of the community, proceed to the next circle of contacts.

P. Genotyping: Whole Genome Sequencing (WGS): Since 2018, all culture confirmed M. tuberculosis isolates in the U.S. are genotyped by the Centers for Disease Control and Prevention (CDC)'s Division of TB Elimination. TB genotyping when combined with epidemiological investigation can help identify clusters of persons with TB disease due to recent transmission compared to those individuals with reactivation due to past infection.

1. CDC reports identification of linked genotype clusters to the local and/or state health department for additional follow-up.
2. State TB Contact Information can be found:
   a. https://www.cdc.gov/tb/links/tboffices.htm
   b. http://www.tbcontrollers.org/community/statecityterritory/#.Wnnc%20UmbMz-Y

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