CHAPTER 8: CLINICAL MONITORING AND FOLLOW-UP FOR TUBERCULOSIS TREATMENT

INTRODUCTION

All patients receiving treatment for active or suspected tuberculosis (TB) disease on a multidrug regimen are monitored throughout the duration of therapy for response and adherence to treatment, as well as for adverse reactions to their treatment. Comprehensive clinical monitoring and follow-up by a dedicated team of clinical and public health staff supports positive treatment outcomes and ensures adverse reactions are identified and addressed in a timely manner.

MONTHLY CLINICAL MONITORING

As part of the clinical monitoring process, physicians and nurses work collaboratively to evaluate and clinically monitor patients including their response to treatment, development of adverse reactions, and adherence to treatment. In addition, a key component of effective clinical monitoring is use of baseline and follow-up diagnostic tests; these tests are conducted at regular intervals or based on clinical judgment. (See *Figure 8.1: Evaluation and Monitoring Timeline for Tuberculosis Patients with Drug-Susceptible Tuberculosis Disease*.)

PHYSICIAN ASSESSMENT

As part of the monthly clinical evaluation, a medical assessment is conducted and the following items are discussed with the patient. These discussions are conducted in the patient's preferred language and documented in the electronic medical record (EMR):

1. **Signs and symptoms consistent with TB disease and response to treatment:** Patients are evaluated for the presence of signs and symptoms consistent with TB disease during the physical examination. If there is lack of clinical response despite treatment, non-adherence to treatment or drug resistance are considered as potential causes. For patients with a poor response to therapy, sputum specimens are collected for culture and drug-susceptibility tests (DSTs), both molecular and conventional.
2. **Adherence to treatment:** Adherence to treatment regimens, supported by directly observed therapy (DOT), is vital to successful treatment outcomes. While not mandated in New York City (NYC), DOT is strongly recommended and is the standard of care for TB treatment. If patients are not on DOT, they are encouraged to start.
    - For patients on DOT, DOT records are reviewed. When treatment adherence is less than 80%, DOT records are discussed with the patient to identify reasons why and how to improve adherence. If adherence remains low and the patient is infectious, the patient may be referred for regulatory intervention. (See *Chapter 10: Case Management for Patients with Tuberculosis*.)
    - Patients who are prescribed intermittent DOT and who are less than 80% adherent are switched to a daily DOT regimen to ensure treatment success.
    - Patients on self-administered treatment are instructed to bring the last-issued medication bottles to follow-up visits. Pill counts are conducted by the nurse and the information is recorded in the patient's EMR. All patients are asked when and how they take their medications, to describe the appearance of the medications, and the number of pills they take each day.
3. **Medication side effects and adverse reactions:** Anti-TB medications can have varied side effects and adverse reactions ranging from mild to severe. Patients are asked about any side effects or adverse reactions that have occurred during their treatment. (See *Appendix G: Dosages, Adverse Reactions, and Monitoring for First-Line Medications Used to Treat Tuberculosis*.)

4. **Physical examination:** The nature and extent of the physical examination depends on the patient's symptoms, site of disease, and/or medication side effects.
5. **Chest radiograph (CXR) and laboratory tests:** Previous CXR, sputum, and other laboratory test results are reviewed on an ongoing basis. The patient is informed about whether their tests show improvement or deterioration, and the effect on the length of treatment.
6. **Care and treatment plan:** A plan of care is developed for every patient based on evaluation of their current disease status. Because several medical providers may be involved in the care of a patient, it is important to outline a plan of care that details reasons for decisions, names and dosages of medications, and planned length of therapy in order to ensure continuity of care. The plan of care is documented in the EMR and communicated to non-Bureau of TB Control (BTBC) providers when necessary. Changes in treatment plans are communicated to all providers in a timely manner.
7. **Medication orders:** Medication must be ordered through the EMR. Changes in medication orders due to an adverse reaction are noted in the patient's EMR and communicated to other personnel caring for the patient. If medications are stopped for any reason, they are discontinued in the EMR as well.
8. **Review of non-TB medications:** At each monthly follow-up, all current prescribed medications, as well as any vitamins, minerals, and herbal supplements that the patient is taking, are reviewed with the patient and noted in the EMR. If potential drug interactions are identified, a mutually agreed upon plan to resolve them is established and documented.

DIAGNOSTIC ASSESSMENT

CHEST RADIOGRAPH

Repeat CXRs are obtained after two months and at the end of treatment for patients with pulmonary and pleural TB disease to document the radiological response to treatment (see *Reclassification of Patients Being Evaluated for Tuberculosis* later in this section). In patients with culture-negative TB disease, a CXR is obtained at four months if that is the end of treatment. Whenever a patient receives a CXR, the results are reviewed with the patient. Additional CXRs are obtained as clinically indicated.

SPUTUM

Sputum is induced in NYC Health Department TB clinics and sent for acid-fast bacilli (AFB) smear and culture. A positive AFB smear is used as a proxy for infectiousness and is one factor used to determine when airborne infection isolation can be discontinued and/or when patients can be discharged to the community or congregate settings (with some exceptions). **AFB smear conversion is defined as having three consecutive negative AFB sputum smears.** For patients who are initially AFB smear-positive and are being managed as outpatients, specimens are collected every one to two weeks until smears convert to negative. This allows timely decision-making about when patients may be allowed to leave their home, receive visitors, or return to work or school. (See *Chapter 13: Infection Control*.)

Sputum culture conversion within the intensive phase is a strong indicator of successful treatment of pulmonary TB disease. **Culture conversion for drug-susceptible pulmonary TB is defined as documented conversion to a negative culture, without a subsequent positive culture, within 60 days of treatment initiation.** Sputum culture conversion also typically helps identify patients who can complete treatment with six months of therapy.

Sputum should be collected from all patients with pulmonary TB by two months of therapy to document culture conversion. In NYC, sputum should also be collected at the end of treatment to document cure.

- All patients should have a sputum sample taken one to three weeks before the end of the intensive phase if culture conversion has not been documented.
- Sputum is collected from all patients at the end of treatment to document cure. A negative sputum culture at the end of treatment is the only conclusive evidence of cure.
- For patients with isoniazid- (INH) and rifampin- (RIF) susceptible TB disease, it is not necessary to examine sputum monthly once culture conversion is documented for patients with good adherence.
- For patients with RIF-resistant TB disease or INH and RIF-resistant TB, sputum culture results are collected monthly until the end of treatment, and post-treatment evaluations are conducted according to the guidelines under *Post-Treatment Evaluation* in this chapter.
- Sputum specimens are collected more frequently if there has been poor adherence, there are signs of relapse, or the patient is prescribed a regimen that does not include INH and RIF.
- Sputum is collected in NYC Health Department TB clinics via induction. Natural sputum collection for patients obtaining care from the Health Department may be done only in cases where the patient is homebound, has difficulty reaching the NYC Health Department TB clinics, or is unable to produce induced sputum during clinic hours. (See *Appendix E: Instructions for Performing Sputum Induction*.)
- Rarely, a clinically stable patient who is already smear- or culture-negative unexpectedly has a positive AFB smear. If this occurs, two to three specimens are collected within one week (a CXR is obtained if it was not included in the last evaluation), and a new evaluation is conducted. As the patient is already receiving treatment, a nucleic acid amplification (NAA) test is not ordered. Specimens are sent for mycobacterial culture. Patients should be evaluated for relapse or worsening disease and whether additional drugs need to be added to the treatment regimen. The possibility of a nontuberculous mycobacterium or a lab error may be considered while awaiting final culture results.
- If the patient remains culture-positive and/or they fail to improve clinically after four months of adequate treatment, susceptibilities, both conventional and molecular, are requested.

CLINICAL LABS MONITORING

BASELINE BLOOD TESTS

Laboratory tests are obtained for all patients at baseline and appropriate intervals according to the medications used and the presence of side effects. These tests may include:

- Complete blood count (CBC)
- Metabolic chemistry panel (including creatinine and glucose)
- Viral hepatitis screen
- Uric acid values, which are affected by pyrazinamide (PZA) (**NOTE:** An increase in uric acid is not an indication to discontinue PZA, as long as the patient remains asymptomatic)
- Thyroid function tests are performed for patients taking para-aminosalicylic acid (PAS) or ethionamide (ETA) at baseline and periodically
- HIV testing is offered to all patients if their HIV status is unknown or negative

LIVER FUNCTION TESTS

Monthly liver function tests (LFT) are obtained on patients who meet one or more of the following criteria (at the discretion of the treating physician):

- Abnormal baseline LFTs
- HIV infection
- Pre-existing liver disease (i.e., alcoholic hepatitis, cirrhosis)
- Viral hepatitis (i.e., hepatitis B or C)
- History of chronic alcohol ingestion or intravenous drug use
- Pregnant or postpartum (up to two to three months after delivery)
- Taking drugs that may be hepatotoxic or interact with TB treatment

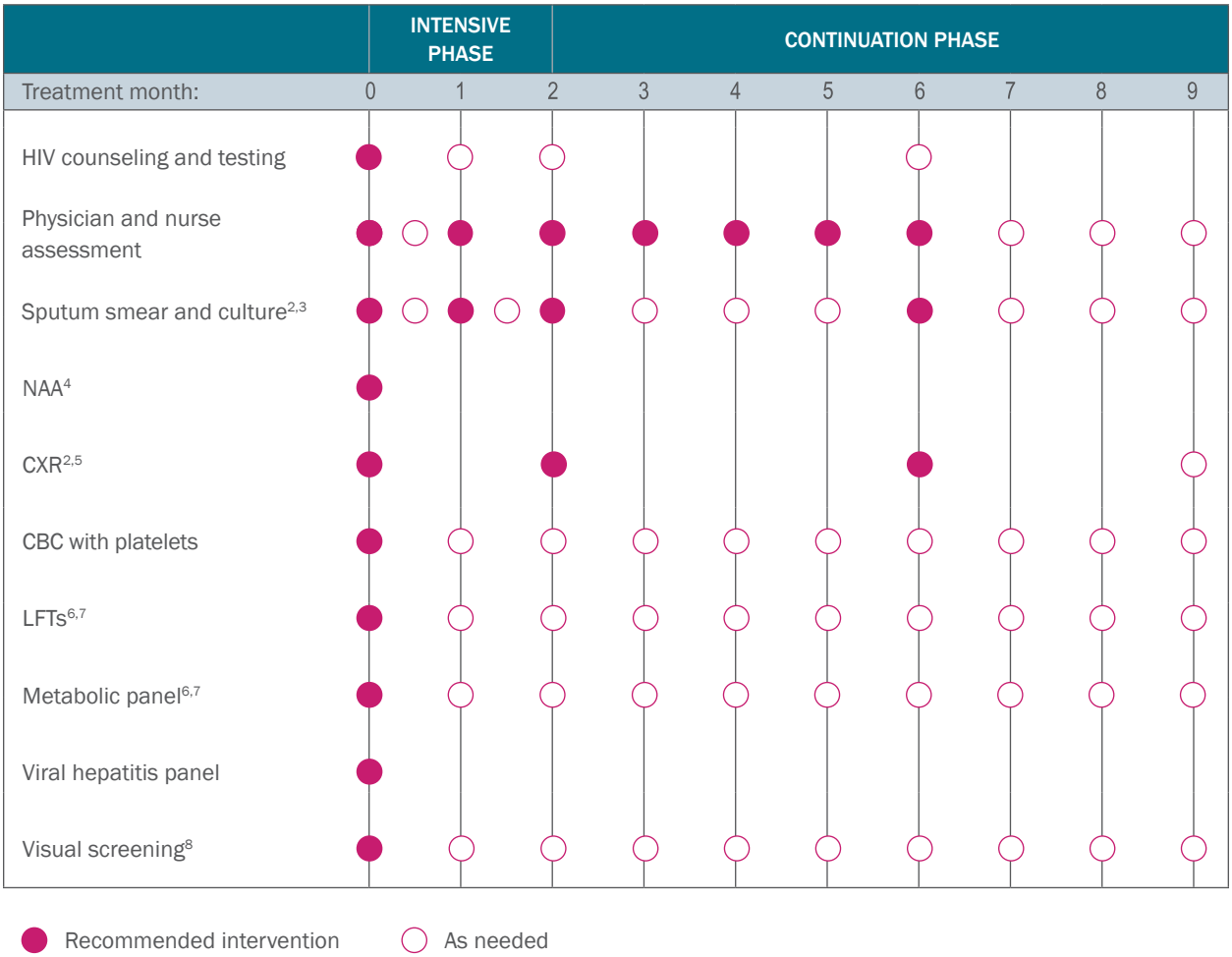
Significantly abnormal laboratory test results must be addressed immediately, independent of the date of the monthly follow-up visit.

NURSE ASSESSMENT

In NYC Health Department TB clinics, the nurse is responsible for performing a monthly assessment of the patient. Nurses document the following information in the EMR:

- Vital signs and patient's weight
- Current signs and symptoms of TB disease and assessment of changes from prior evaluation
- Assessment of treatment adherence

FIGURE 8.1: Evaluation and monitoring timeline for tuberculosis patients with drug-susceptible TB disease[1]



1. This chart applies only to patients whose isolates are found to be drug-susceptible and started on a standard regimen on INH, RIF, PZA, and EMB. If drug resistance is documented, consult an expert in its management. To obtain treatment information and susceptibility results, call the TB HOTLINE at 844-713-0559 during business hours.

2. Sputum smear and culture and CXR apply only to patients with pulmonary TB.

3. Initially at least 3 sputa for AFB smear and culture should be collected in 8 to 24 hour intervals over 48 to 72 hours in order to maximize bacteriologic diagnosis. Most patients (e.g., patients on DOT, patients adherent to the treatment regimen, and patients with INH- and RIF-susceptible TB disease) need monthly sputum tests only until cultures become negative. To document cure, a sputum test should be obtained at the end of treatment. If drug resistance is suspected or documented, expert consultation is sought.

4. NAA testing should be performed on the first AFB-positive smear and on selected smear-negative specimens if the clinical suspicion of TB disease is high.

5. A CXR is obtained for all patients at 2 months. In culture-negative patients, a CXR is obtained at 4 months to document cure. All other patients receive a final CXR at the end of treatment (6 to 9 months) to document cure.

6. Monthly LFTs should be done in patients with the following risk factors: abnormal baseline LFTs; HIV infection; pre-existing liver disease (i.e., alcoholic hepatitis, cirrhosis); viral hepatitis (i.e., hepatitis B or C); history of chronic alcohol ingestion or intravenous drug use; pregnant or postpartum (up to 2 to 3 months after delivery); taking drugs that may be hepatotoxic or interact with TB treatment.

7. Comprehensive basic metabolic panel may include creatinine, LFTs, and uric acid. HgbA1c may be checked in patients who have diabetes.

8. During treatment with EMB and/or LZD, monitor visual acuity and color vision monthly.

Abbreviations Used: AFB=acid-fast bacilli; CBC=complete blood count; CNS=central nervous system; CXR=chest radiograph; DOT=directly observed therapy; DST=drug-susceptibility test; EMB=ethambutol; HIV=human immunodeficiency virus; INH=isoniazid; LFT=liver function test; LZD=linezolid; NAA=nucleic acid amplification; PZA=pyrazinamide; RIF=rifampin; TB=tuberculosis

- Medication side effects and adverse reactions, including:
  - Visual acuity testing and Ishihara's color vision testing for patients taking ethambutol (EMB)/ linezolid (LZD)
  - Hearing tests for patients receiving injectable agents
  - Observation of patient's sclera and nail beds for signs of jaundice

In addition to collecting and documenting the above, nurses engage the patient in a dialogue to ensure the patient has a clear understanding of their medications and next steps in their care. The nurse:

- Reviews patient's knowledge of medication and dosage, potential side effects, and adverse reactions; and instructs the patient about what to report to the physician and nurse
- Reviews the physician's plan of care with the patient
- Reinforces the need for adherence to treatment and follow-up visits
- Reviews any non-TB medications taken by the patient
- Ensures that all physician orders are followed
- Facilitates referrals for follow-up or coordination of care

MANAGEMENT OF ADVERSE REACTIONS

Anti-TB medications can cause a variety of adverse reactions including nausea, vision loss, fatigue, dermatitis, and hepatitis. The development of adverse reactions is influenced by both a specific drug or drug combination and individual patient health factors. In the event that an adverse reaction occurs that cannot be associated with a specific anti-TB medication, all anti-TB medications are discontinued and re-introduced gradually until the cause of the adverse reaction can be identified. If a patient is also taking non-TB medications, close communication with the patient's primary care provider is necessary to coordinate care. Adverse reactions associated with anti-TB medications are summarized in *Table 8.1: Common Adverse Reactions to First- and Second-Line Anti-Tuberculosis Medications*.

DERMATITIS

All first-line anti-TB agents can cause dermatitis (rash); however, the most common cause is PZA, followed by RIF or INH. RIF and the fluoroquinolones (FQNs) can also cause photosensitivity.

HISTORY AND EXAMINATION

When dermatitis occurs, the patient is asked about exposure to other medications or skin preparations, environmental contact, etc., that may be responsible for the reaction. In addition, the patient is examined for evidence of unrelated skin disease (e.g., scabies, contact dermatitis, childhood exanthema, etc.) to ensure they are not the cause.

TABLE 8.1: Common adverse reactions to first- and second-line anti-tuberculosis medications*

REACTION	SYMPTOMS AND SIGNS	USUAL DRUG(S) RESPONSIBLE
Audiovestibular manifestations	Hearing loss, vertigo, new-onset tinnitus	Injectable agents
Blood sugar abnormalities	Dizziness, sweating, fainting, poor response to infections	FQNs, PZA, RIF
Dermatitis	Itching, rash, hives, fever, petechial rash	PZA, RIF, RPT, INH; rarely EMB, RBT, or injectable agents
Gastritis	Anorexia, nausea, vomiting, epigastric pain	RIF, RPT, PZA, RBT
Hematologic manifestations	Leucopenia, thrombocytopenia, anemia, eosinophilia	RIF, RBT, RPT, INH, LZD, CM
Hepatitis	Anorexia, nausea, vomiting, jaundice, abdominal pain	INH, RIF, RPT, PZA, ETA; rarely EMB and RBT
Hypothyroidism	Fatigue, weight gain, sluggish reflexes, depression	PAS, ETA
Joint, muscle, and tendon manifestations	Gout-like manifestations, systemic lupus erythematosus-like manifestations; tendinopathies	PZA, INH, FQNs, RIF
Neurological and psychiatric manifestations	Headaches, depression, agitation, suicidal ideation	INH, FQNs, CS
Peripheral neuropathy	Numbness or paresthesias of feet or hands	INH, LZD, FQNs
Renal manifestations	Hematuria, azotemia	injectable agents, RIF, RPT
Visual manifestations	Vision loss and color blindness, uveitis	EMB, RBT, LZD

*This is not a comprehensive list of adverse reactions. Please consult the drug's package insert, Physicians Desk Reference, or other reference pharmaceutical texts for more information.

Abbreviations Used: CM=capreomycin; CS=cycloserine; EMB=ethambutol; ETA=ethionamide; FQN=fluoroquinolone; LZD=linezolid; PAS=para-aminosalicylic acid; PZA=pyrazinamide; RBT=rifabutin; RIF=rifampin; RPT=rifapentine

Patients with HIV infection have a variety of dermatologic diseases (which may be either directly or indirectly related to HIV infection or its treatment). Consultation with an appropriate infectious disease service or dermatology clinic may be required.

FOLLOW-UP

If the dermatologic reaction is severe and no other cause is found, anti-TB medications are discontinued promptly and the patient is examined at least weekly until the skin reaction disappears. Patients with a severe dermatologic reaction (e.g., exfoliative dermatitis), or with dermatitis associated with severe

systemic reactions are referred for hospital admission for treatment and the establishment of either a new anti-TB regimen or a re-challenge regimen, under daily surveillance as an inpatient.

If the drug reaction is mild, the patient is initially treated with antihistamines and topical steroids while continuing TB treatment. Clinical discretion is recommended on whether TB medications should be stopped.

RESTARTING ANTI-TUBERCULOSIS MEDICATIONS

For patients managed at a NYC Health Department TB clinic, re-challenge is appropriate after the skin reaction clears or subsides. It may not be possible to identify the specific causative agent by the characteristics of the skin reaction. Thus, it is appropriate to first restart the two most important medications, RIF or INH, before next trying EMB and then PZA. PZA has been found to be a major cause of skin reactions; most reactions occur within the first four weeks of treatment.

Single daily doses of INH or RIF are given alone for three days with instructions to discontinue promptly if a reaction recurs. The patient is examined in three to four days and:

- If there is no reaction, an alternate drug (RIF or INH) is added with similar instructions. The patient is again reexamined in three to four days.
- If the skin reaction does not recur or if it is not severe, EMB (if this drug was part of the initial regimen) is added. If there is not a reaction to EMB, the regimen of INH, RIF, EMB can be continued and PZA discontinued on the presumption that this caused the skin reaction.

Treatment is continued with the original regimen minus the causative agent; however, the duration of treatment may need to be lengthened. For patients with HIV infection or patients who have extensive pulmonary or disseminated TB disease, a single new drug, such as a FQN, can be added to regimens that lack INH or RIF. FQNs themselves can cause phototoxicity. The new drug is continued for the duration of therapy. In such instances, the addition of a single agent to a successful regimen does not violate the rule of "do not add a single drug to a failing regimen."

The same principles of management apply to patients who experience dermatologic reactions while taking regimens for multidrug-resistant TB (MDR-TB).

HEPATITIS

Hepatotoxicity caused by anti-TB medications varies from asymptomatic increases in LFTs to liver failure. In addition, concurrent use of hepatotoxic non-TB medications or substances (e.g., alcohol) or chronic viral hepatitis increases the risk of developing drug-induced liver damage.

Certain drugs provoke various physiologic adaptive responses in the liver (i.e., INH), which may lead to asymptomatic transient elevations of alanine aminotransferase (ALT) (serum glutamate pyruvate transaminase [SGPT]) or induction of microsomal enzymes; these rarely lead to hepatic damage. However, certain toxins such as alcohol can interfere with the adaptive process and augment liver injury. Concurrent

use of other known hepatotoxic agents is avoided if possible during anti-TB treatment, especially in patients with underlying liver disease.

An increase in serum ALT is more specific for hepatocellular injury than an increase in aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT]), which can also signal abnormalities in muscle, heart, or kidney. Transaminases tend to be higher in men and in people with greater body mass index. Levels may vary as much as 45% on a single day, with the highest levels occurring in the afternoon. ALT and AST elevation may occur after exercise, hemolysis, or muscle injury.

There are two patterns of LFT abnormalities that may be seen during TB treatment: hepatocellular and cholestatic. A hepatocellular pattern is usually caused by INH or PZA; a cholestatic pattern is caused by RIF. See sections *Hepatocellular Pattern* and *Cholestatic Pattern* for more information. EMB rarely causes hepatitis.

HISTORY AND EXAMINATION

Individuals taking anti-TB medication who develop symptoms consistent with hepatitis (anorexia, nausea, vomiting, abdominal pain, jaundice, etc.) are instructed to discontinue all medications immediately and prompt evaluation by a provider is necessary. When seeing the patient, symptoms are reviewed, a directed examination is performed, and LFTs and a viral hepatitis screen are obtained. In some patients, RIF or PZA may cause gastritis with symptoms similar to those of hepatitis. If there is strong evidence that the symptoms are not related to hepatitis or anti-TB medications and the LFTs remain stable, the entire regimen may be reinstituted promptly, and the individual is followed closely for the recurrence of symptoms. (See *Chapter 5: Treatment of Drug-Susceptible Tuberculosis Disease in Adults*.)

FOLLOW-UP

If symptoms disappear promptly and LFTs are normal, drug-induced hepatitis is unlikely. Another cause for symptoms is considered. Depending upon the nature, duration, and severity of symptoms, a decision about further diagnostic study is made.

If the LFTs are abnormal (AST or ALT is three times the upper limit of normal [ULN] with symptoms and five times ULN without symptoms) or if serum bilirubin is elevated, drug-related hepatitis is strongly suspected, and all anti-TB medication(s) are discontinued.

While holding medications, the patient is examined, repeat LFTs are obtained and symptoms are reviewed at least weekly. If symptoms persist for more than two weeks without anti-TB medication(s), or if LFTs continue to worsen, progressive drug-related hepatitis or an unrelated cause of hepatitis may be the cause. Depending upon the severity of the hepatitis, as indicated by clinical findings and LFTs, referral to a gastroenterologist or hospitalization may be necessary.

RESTARTING ANTI-TUBERCULOSIS MEDICATIONS

The recommendations for restarting anti-TB medications in patients with drug-induced hepatitis are summarized in *Figure 8.2: Restarting Anti-Tuberculosis Medications in Patients with Drug-Induced Hepatitis*. In an outpatient setting, individual reintroduction of medications is no longer preferred, unless otherwise clinically indicated. BTBC providers usually start with two medications depending on presumed toxicity and add drugs sequentially based on clinical response. LFTS are monitored monthly throughout the course of treatment.

Although the specific cause of hepatitis cannot be identified by the pattern of LFT abnormality, RIF is usually implicated if the pattern is cholestatic (bilirubin and alkaline phosphatase [AP] elevated and out of proportion, with little or no changes in ALT/AST). In contrast, INH, RIF, or PZA may be the cause if the pattern is hepatocellular, with enzymes elevated and out of proportion to bilirubin or alkaline phosphatase.

In some cases, in order to avoid discontinuing a rifamycin in the treatment regimen, rifabutin (RBT) re-challenge may be acceptable with close follow-up of patients.

If the patient has extensive pulmonary, meningeal, or disseminated TB disease, has HIV infection, or is critically ill, the institution of a new regimen with a lesser potential for hepatotoxicity (e.g., injectable agent, EMB, FQN), also known as a "liver-sparing regimen," may be indicated even before liver enzymes return to normal.

For all other patients, anti-TB treatment is withheld until symptoms disappear and LFTs are normal, have declined to two times the upper limit of normal, or plateaued. In general, medications are reintroduced at their standard daily dosage. Patients should be examined weekly until LFTs have stabilized.

If hepatitis is caused by any of the drugs in the anti-TB regimen, INH is most likely responsible, followed by PZA, RIF, and EMB (in this order). A longer duration of therapy may be required if the causative agent was INH, RIF, or PZA during the intensive phase of treatment.

The exclusion of a rifamycin mandates extension of treatment length. The substitution of RBT for RIF may be an option when RIF cannot be used in order to avoid an extended treatment duration.

Depending on the drug that is presumed to be the cause of the hepatotoxicity, treatment may need to be extended. Individuals who cannot take INH and RIF are treated for 18 months. Similar principles of management apply to cases of hepatitis induced by "reserve drugs," as drugs are added depending on the isolate's susceptibility (e.g., PAS, ETA, and, rarely, FQNs).

Hepatocellular Pattern

Laboratory tests of patients with hepatocellular patterns are marked by isolated or predominant elevations of serum transaminases, specifically ALT and AST. If the pattern is hepatocellular, it is appropriate to re-challenge first with the agent(s) least likely to have been responsible after LFTs return to normal or decline and plateau. The patient is instructed to stop the medication immediately if symptoms of hepatitis

re-occur. The patient is examined weekly, with LFTs repeated at each visit. (See *Figure 8.2: Restarting Anti-Tuberculosis Medications in Patients with Drug-Induced Hepatitis*.)

There are two ways to re-challenge a patient who has a hepatocellular pattern in LFTs. The preferred way is to restart RIF/EMB for one week and repeat LFTs.

- If PZA is suspected to be the cause of the hepatitis:
  - INH is added for one week and LFTs are repeated
  - If LFTs are stable, patient is treated with INH, RIF, and EMB until susceptibilities are available (assume PZA-induced hepatitis)

Re-challenging with PZA may be hazardous in patients who tolerate the reintroduction of RIF and INH. In this circumstance, PZA may be permanently discontinued, with treatment extended to 9 months. Although PZA can be reintroduced in some milder cases of hepatotoxicity, the benefit of a shorter treatment course likely does not outweigh the risk of severe hepatotoxicity from PZA re-challenge when the initial hepatitis is moderate to severe.

- If INH is suspected to be the cause of the hepatitis:
  - PZA is added for one week and LFTs are repeated
  - If LFTs are stable, patient is treated with RIF, EMB, and PZA; a FQN may be added (assume INH-induced hepatitis)
- If INH and PZA are felt to be the cause of the hepatitis:
  - RIF, EMB, and a FQN may be given for six to nine months based on clinical judgment (and depending on the length of treatment with PZA)

The exclusion of a rifamycin mandates extension of treatment length. The substitution of RBT for RIF may be an option when RIF cannot be used in order to avoid an extended treatment duration. Whereas the treatment length of an INH, EMB, and PZA (or FQN) regimen is 18 months, successful introduction of RBT (which is less likely than RIF to cause hepatitis) permits treatment completion in six months. If RBT is introduced, LFTs are repeated after one week. If normal, RBT is continued and the patient is monitored weekly for the next several weeks, then monthly until treatment completion.

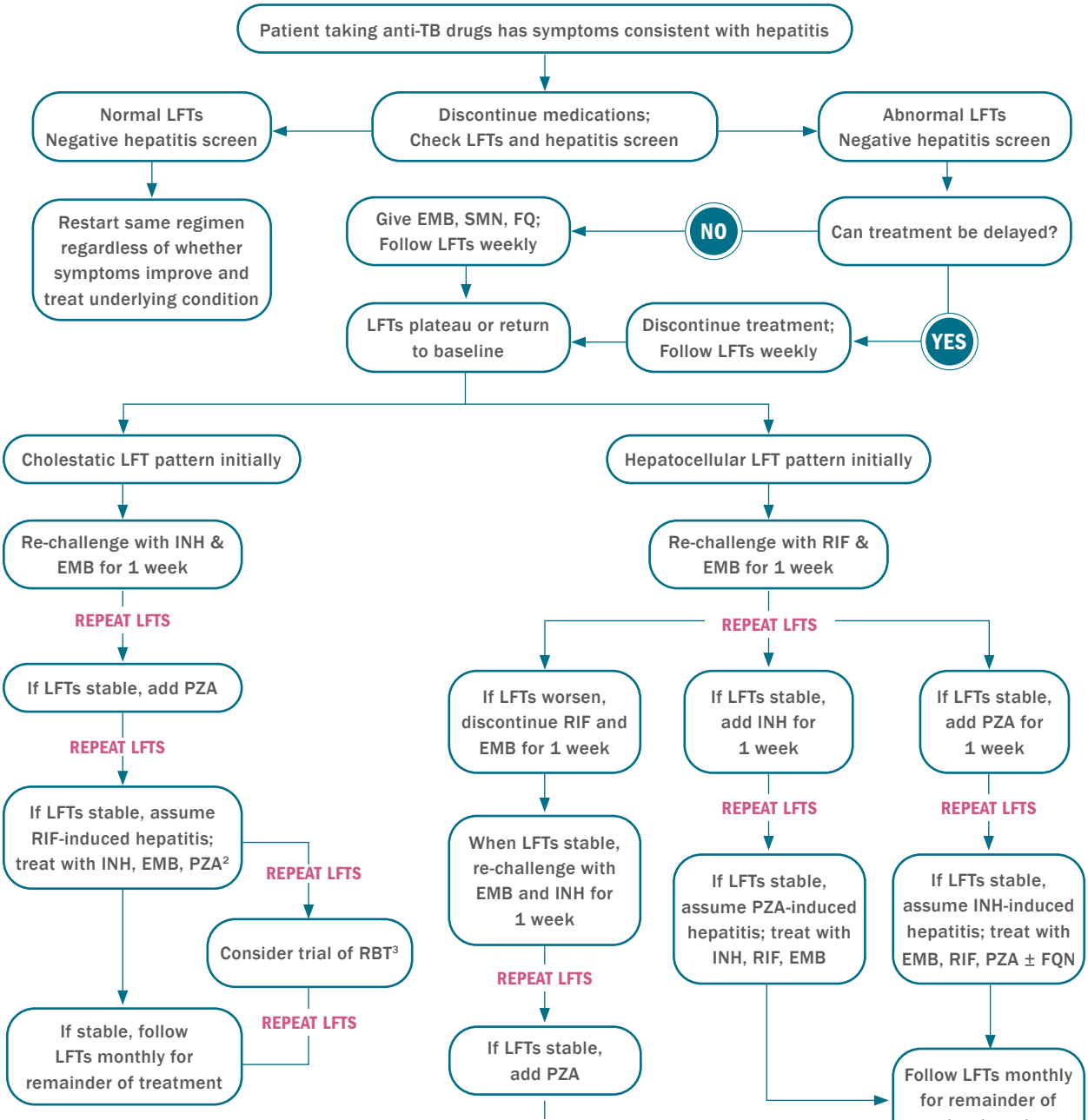
If a rifamycin cannot be used, an additional alternative is adding a FQN to a regimen of INH, EMB, and PZA.

LFTs are monitored monthly for the remainder of therapy.

Cholestatic Pattern

Although the specific cause of hepatitis cannot be identified by the pattern of LFT abnormality, RIF is usually implicated if the pattern is cholestatic (bilirubin and AP elevated and out of proportion, with little or no changes in ALT and AST levels).

FIGURE 8.2: Restarting anti-tuberculosis medications in patients with drug-induced hepatitis



1. Abnormal LFTs are > 3 times the upper limit of normal with symptoms or > 5 times the upper limit of normal without symptoms.
2. A FQN should be considered for the regimen. Treatment needs to last for 18 months unless RBT is added successfully.
3. There may be times when RBT is tried in an attempt to decrease duration of treatment from 18 months to 6-9 months.
4. Some clinicians may prefer to challenge with EMB and RIF sequentially rather than simultaneously.

Abbreviations Used: EMB=ethambutol; FQN=fluoroquinolone; INH=isoniazid; LFTs=liver function tests; PZA=pyrazinamide; RIF=rifampin; RBT=rifabutin; SM=streptomycin

If the initial pattern of hepatitis is cholestatic, the patient is re-challenged with INH and EMB for one week after LFTs return to normal or decline to two times the upper limit or normal, or plateau. LFTs are repeated; if stable and the patient is asymptomatic:

- PZA is added to the regimen for one week. LFTs are repeated.
- If LFTs remain stable, the patient is treated with INH, EMB, PZA (assume RIF-induced hepatitis). A FQN may be added.

The exclusion of a rifamycin mandates extension of treatment length. The substitution of RBT for RIF may be an option when RIF cannot be used in order to avoid an extended treatment duration. Whereas the treatment length of an INH, EMB, and PZA (or FQN) regimen is 18 months, successful introduction of RBT (which is less likely than RIF to cause hepatitis) permits treatment completion in six months. If RBT is introduced, LFTs are repeated after one week. If normal, RBT is continued and the patient is monitored weekly for the next several weeks, then monthly until treatment completion.

If a rifamycin cannot be used, an additional alternative is adding a FQN to a regimen of INH, EMB, and PZA.

LFTs are monitored monthly for the remainder of therapy.

GASTRITIS

Almost any medication can cause gastric irritation in susceptible individuals. Of the first-line anti-TB medications, RIF most often causes gastritis, although PZA is responsible in some instances. Because RIF is the most important member of combined chemotherapy, every effort is made to reintroduce this drug once gastric symptoms resolve. RBT may be substituted for RIF as it causes less gastritis.

HISTORY AND EXAMINATION

Because the symptoms of gastritis (anorexia, nausea, vomiting, and epigastric distress) may be due to drug-related hepatitis, LFTs are obtained for all individuals who present with such symptoms.

FOLLOW-UP

Anti-TB medications are discontinued in symptomatic patients. If LFTs are normal or unchanged from baseline and symptoms persist for four to five days without medication, unrelated gastrointestinal (GI) disease (e.g., peptic ulcer disease, gastritis due to another cause, etc.) is suspected and the patient is referred for appropriate diagnostic study.

RESTARTING ANTI-TUBERCULOSIS MEDICATIONS

After symptoms subside, medications are reintroduced in a step-wise process. Despite the fact that most gastritis is caused by INH and RIF, they are the two most important medications in an effective TB

treatment regimen. RIF and EMB are restarted for one week. If tolerated, INH is added to the regimen. If INH is well-tolerated, PZA is assumed to be the cause. The treatment duration is extended according to the final regimen successfully reintroduced.

When reintroducing RIF, more success may occur by modifying the pattern of administration. RIF is either administered before bedtime, or the patient is instructed to eat a small meal before taking the medication. If RIF is identified as a cause of gastritis, RBT can be considered as an alternative.

Although antacids may help to alleviate the symptoms of gastritis, they may also interfere with the absorption of INH and FQNs. If used, the patient is instructed to take antacids two hours after taking either INH or a FQN; prolonged use of antacids is avoided. Alternatives to antacids are an H2-blocker or a proton pump inhibitor. However, if these are used and the patient is taking PAS granules, the patient is instructed to take PAS with acidic foods such as yogurt, applesauce, or orange juice, rather than with neutral foods such as milk, because PAS needs to be absorbed in an acidic environment.

If gastritis is caused by PZA, it can be omitted from the regimen with less risk than omitting RIF. If the patient has TB susceptible to INH and RIF, these two medications can be used for a total of nine months.

PERIPHERAL NEUROPATHY

INH may cause peripheral neuropathy, especially in individuals with a predisposing cause, such as alcoholism, diabetes, HIV infection, or malnutrition. Pyridoxine usually, but not invariably, prevents the emergence of INH-induced peripheral neuropathy. Linezolid (LZD) can also cause an irreversible peripheral neuropathy. If symptoms of peripheral neuropathy arise while the patient is taking these drugs, they are discontinued and replaced with an appropriate regimen. Rarely, EMB, and also the FQNs, can be a cause of peripheral neuropathy.

HISTORY AND EXAMINATION

INH is assumed to be the primary cause for paresthesias and numbness of the feet and hands (with or without peripheral motor weakness) in INH-treated patients, even if other predisposing causes are present.

FOLLOW-UP

INH is discontinued in patients with peripheral neuropathy and pyridoxine (25 mg per day) is given (or continued) until symptoms abate. The neuropathy usually subsides over weeks to months, when it is diagnosed early and INH is promptly discontinued. However, neurologic injury may be irreversible if diagnosis is delayed and manifestations become severe; neurologic consultation is obtained if the diagnosis is not clear. In patients with LZD-induced peripheral neuropathy, LZD is discontinued. LZD is reintroduced into the regimen only if symptoms of peripheral neuropathy have resolved and no other reasonable alternatives for the regimen are available.

JOINT MANIFESTATIONS

INH (and rarely, RIF) can induce active systemic lupus erythematosus (SLE), especially in patients with sub-clinical disease. The patient may have only arthralgias or alopecia, or may present with a full-blown pattern of SLE, with arthritis and other systemic manifestations. If INH-induced SLE is suspected, INH is discontinued, and these patients are referred to an appropriate provider. Blood tests should be sent for antinuclear antibodies, anti-double stranded DNA antibody, and anti-histone antibody. Anti-histone antibody, which is usually found in drug-induced lupus, can also be found in SLE; however, it is not specific enough to SLE to make the diagnosis.

PZA invariably causes an asymptomatic increase of serum uric acid because it impairs renal excretion of uric acid; this finding can be used as a measure of PZA adherence. Patients with asymptomatic elevations of uric acid are not treated; however, patients with a history of gout are at increased risk for PZA-related gout attacks. PZA is discontinued in patients with a gouty attack. Allopurinol can lower the baseline serum uric acid level, but not elevations due to PZA.

Hyperuricemia without symptoms of gout is not a reason for discontinuing PZA.

RENAL MANIFESTATIONS

With first line drugs, acute kidney injury (AKI) is a rare and severe complication that can interrupt treatment and cause permanent kidney damage. Although INH and EMB have rarely been associated with AKI, RIF is the most common first-line drug responsible for AKI. RIF can cause acute or chronic nephritis (with or without symptoms), evidenced by proteinuria, hematuria, and sterile pyuria. Renal injury in patients treated for TB disease can also occur due to injectable agents. Acute or chronic renal failure can also occur. The blood levels of EMB, cycloserine (CS), and injectable agents may become markedly elevated in patients with renal function impairment. PZA is metabolized by the liver, but its metabolites may accumulate in patients with renal insufficiency. Potassium and magnesium losing nephropathy is common with the injectable agents, particularly capreomycin (CM), and can usually be managed with oral supplements.

HISTORY AND EXAMINATION

Blood urea nitrogen, serum creatinine, and electrolytes, including magnesium, are monitored serially in patients with underlying renal disease who are receiving EMB, CS, or injectable agents. Urinalysis can be obtained when clinically indicated. Similar studies are done promptly in any patient who has symptoms consistent with acute or chronic nephritis.

FOLLOW-UP

For information on treatment and follow-up in patients with chronic renal failure, see *Chapter 5: Treatment of Drug-Susceptible Tuberculosis Disease in Adults*.

HEMATOLOGIC MANIFESTATIONS

All first-line anti-TB agents can, in rare cases, lead to hematologic abnormalities. Leukopenia can be caused by RIF (most commonly), INH, PZA, and, rarely, EMB. RIF is the most common cause of thrombocytopenia, although the other first-line drugs may depress platelets as well. A "flu-like syndrome" has been reported with all rifamycins, especially when used intermittently; it consists of an acute episode with fever, chills, and muscle pain that may be associated with severe anemia, thrombocytopenia, and leukopenia. Hemolytic syndromes and other types of anemia rarely occur. Eosinophilia can be seen with CM. LZD can cause pancytopenia and a hemolytic anemia. (See *Figure 8.1: Evaluation and Monitoring Timeline for Tuberculosis Patients with Drug-Susceptible TB Disease* and *Appendix H: Dosages, Adverse Reactions, and Monitoring for Additional Medications Used to Treat Tuberculosis*.)

EXAMINATION AND FOLLOW-UP

If a patient taking anti-TB drugs develops symptoms, signs, or laboratory evidence of significant anemia, leukopenia, or thrombocytopenia that cannot otherwise be explained, all anti-TB drugs are discontinued. The patient is promptly referred to a hematologist for consultation. Blood counts are allowed to recover with sequential reinstitution of the TB medications least likely to have caused the hematologic abnormality.

Each medication is reintroduced gradually (within three to four days) based on clinical judgment, with close follow-up of the CBC and differential. If the medication is absolutely necessary for the patient's regimen and the patient does not have evidence of hemolysis, growth factors to increase blood counts, if available, may be used in consultation with a hematologist. In the case of RIF-induced thrombocytopenia and leukopenia, RBT may be tried while following CBC every one to two weeks.

VISUAL MANIFESTATIONS

Visual adverse effects are a concern with EMB, RBT, and LZD. Both EMB and LZD can cause optic neuritis. Routine vision screenings (visual acuity and color vision) are recommended when patients are on regimens containing either EMB or LZD. Toxic levels of RBT are associated with an increased risk of uveitis that is manifested by visual disturbances.

Elevated serum levels of EMB are associated with the risk of optic neuritis; however, this condition usually resolves completely when EMB is discontinued. When diagnosed late, optic neuritis may progress to severe visual loss. As EMB is cleared largely by renal excretion, individuals with impaired renal function, especially the elderly, are most susceptible, as are adult patients who receive doses of EMB greater than 15 mg/kilogram (kg) body weight per day.

HISTORY AND EXAMINATION

The usual symptoms of optic neuritis are loss of visual acuity for small objects (newsprint, sewing, etc.) and/or impairment of red-green color discrimination.

All patients started on EMB and LZD have baseline visual acuity and red-green color discrimination established at the initiation of therapy.

All patients at risk for renal disease have serum blood urea nitrogen and creatinine tested before treatment with EMB. EMB is used with caution and frequent monitoring of vision and renal function in patients with:

- Renal function abnormalities
- Risk for renal function abnormalities (e.g., elderly patients and patients with diabetes or hypertension)
- Patients with pre-existing, non-correctable loss of vision

Patients are asked about visual changes, and serial tests of visual acuity and color vision are performed to detect early signs of optic neuritis at each follow-up visit.

If the patient already has red-green colorblindness at baseline and the use of EMB is necessary, the patient is referred for specialized ophthalmologic evaluation to assess the degree of colorblindness; treatment decisions are made in conjunction with the ophthalmologist.

FOLLOW-UP

EMB is discontinued immediately if optic neuritis is suspected; the patient is referred for ophthalmology consultation if the visual impairment does not reverse promptly. In some patients, visual impairment due to EMB may take months to resolve.

Patients on LZD also receive monthly vision testing. LZD is discontinued immediately if optic neuritis is suspected; the patient is referred to a specialist if the optic neuritis does not reverse promptly.

AUDIOVESTIBULAR MANIFESTATIONS

HISTORY AND EXAMINATION

Patients receiving an injectable agent have a baseline audiogram and a follow-up audiogram every month. An audiogram is repeated promptly if hearing loss is suspected.

At each monthly examination, patients receiving an injectable agent are asked about changes in hearing, tinnitus, or dizziness.

FOLLOW-UP

The injectable agent is discontinued if hearing loss, vertigo, or new-onset tinnitus occurs. An ear examination is conducted to exclude other sources of these symptoms, such as cerumen or otitis media. An audiogram is performed, and the results are compared with the baseline in order to detect hearing loss. If symptoms or any other evidence of hearing loss is suspected to be unrelated to the injectable agent, the patient is referred to an appropriate provider for consultation.

RESTARTING ANTI-TUBERCULOSIS MEDICATIONS

If significant hearing loss, new-onset tinnitus, or vertigo is demonstrated and any of these reactions cannot be explained otherwise, the injectable agent is eliminated from the regimen.

QTc PROLONGATION

Several drugs used in the treatment of TB can cause QTc prolongation. These include FQNs, clofazimine (CFZ), delamanid (DLM), and bedaquiline (BDQ). Levofloxacin (LFX) prolongs the QTc interval less than moxifloxacin (MFX). With respect to QTc prolongation, BDQ is the most concerning. Patients receiving BDQ should receive an electrocardiogram (EKG) at baseline, and at minimum at two, 12, and 24 weeks of treatment. BDQ is discontinued if the QTc is greater than 500 milliseconds, as the most common ventricular arrhythmias such as torsade de pointes have been associated with this value. (See *Chapter 6: Treatment of Drug-Resistant Tuberculosis in Adults*.)

DRUG DESENSITIZATION

Drug desensitization following a severe adverse reaction has been tried with most of the first-line agents with varying degrees of success. RIF has been the drug most commonly tried. Desensitization is done in a manner similar to penicillin desensitization, with incrementally increasing amounts of RIF given to the patient until a full dose is tolerated. This is only done in a highly monitored setting, such as the intensive care unit.

PARADOXICAL REACTIONS/IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

Paradoxical response, commonly known as immune reconstitution inflammatory syndrome (IRIS), is defined as the clinical or radiological worsening of pre-existing TB lesions or the development of new lesions after initial clinical improvement on effective anti-TB therapy.

Although IRIS may occur at any time during treatment, it usually occurs within weeks of beginning treatment (especially after initiation of antiretroviral therapy [ART]). Although IRIS occurs more commonly in patients with concomitant HIV, IRIS can also occur in patients without HIV.

ETIOLOGY

The etiology of IRIS may be related to reversal of the immunosuppression caused by TB disease once anti-TB therapy has been initiated. The rapid killing of bacilli may cause increased cytokine release, which subsequently causes a severe inflammatory response.

DIAGNOSIS

The paradoxical response occurs most commonly at the initial site of disease. When the paradoxical response occurs in another anatomical site, it frequently involves the central nervous system (CNS). Other

sites of disease include pulmonary, pleural, lymph node, abdominal, and osteoarticular. The diagnosis may only be made after secondary infection, non-adherence with therapy, drug resistance, and adverse effects to medication have been excluded.

TREATMENT

The use of corticosteroids may be considered in the case of prolonged or severe paradoxical reactions. There is not a consensus on the preferred dosage of steroids; however, many experts recommend prednisone (or a prednisone equivalent) be prescribed at 1 mg/kilogram (kg) per day, usually up to 60 mg/day, gradually tapered over several weeks. Some experts prescribe up to 80 mg/kg/day based on clinical judgment. Recurrence with tapering is not common.

- Surgical drainage is considered in the case of tense, painful lymphadenopathy with impending sinus tract formation. Any drainage is sent for AFB smear and culture
- The anti-TB regimen rarely needs to be changed once the diagnosis of paradoxical reaction has been established

REPORTING ADVERSE EVENTS

All severe or life-threatening adverse reactions to medications in patients followed in an NYC Health Department TB clinic must be reported on the Health Department Reportable Occurrences Form. A severe or life-threatening adverse reaction is any Grade 3 or 4 adverse event that leads to temporary or permanent discontinuation of a drug. Below are general definitions of grades of toxicity.

The reportable occurrence form is completed and the patient is followed until the adverse reaction is resolved or until transfer to another medical provider or facility has been confirmed.

TABLE 8.2: Grades of toxicity

GRADE	DESCRIPTION
GRADE 1 (Mild)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required
GRADE 2 (Moderate)	Mild to moderate limitation in activity — some assistance may be needed; no or minimal medical intervention or therapy required
GRADE 3 (Severe)	Marked limitation in activity, some assistance usually required; medical intervention or therapy required, hospitalization possible
GRADE 4 (Life-threatening)	Extreme limitation in activity, significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

BTBC providers must complete a New York City Health Department REPORTABLE OCCURRENCES FORM online for any severe or life-threatening adverse events (e.g., liver injury, anaphylaxis, seizure, or severe dermatitis) leading to hospitalization or death of a patient receiving TB treatment. Forms can be found at https://airs.health.dohmh.nycnet/IntelexLogin/Intelex.

RE-CLASSIFICATION OF PATIENTS BEING EVALUATED FOR TUBERCULOSIS DISEASE

For programmatic purposes, all patients are assigned a TB classification based on the International Classification of TB. (See *Appendix B: Tuberculosis Risk Assessment Tool*.) All patients initially classified as TB Class V, currently being evaluated for active TB disease, are reclassified to the appropriate TB class within four months of the initiation of evaluation.

For example:

- Patients initially classified as TB Class V are reclassified as TB Class III if they have a positive *M. tuberculosis* culture.
- Patients initially classified as TB Class V who do not produce a positive culture for *M. tuberculosis* are re-classified as TB Class III if they are on treatment and improve in a time-course consistent with TB:
  - Resolution of TB symptoms on TB treatment (e.g., cough, fever, sweats, weight loss, chest pains)
  - Improvement of CXR (e.g., improvement or resolution of infiltrates, cavities, and effusions) or in findings of extrapulmonary sites of disease when extrapulmonary TB is present
- Patients initially classified as TB Class V (high or low) who are found to have a negative culture for *M. tuberculosis* are reclassified as TB Class IV if their CXR is stable after two and four months of treatment, and is consistent with "old TB disease." A positive test for TB strengthens this diagnosis. A non-TB diagnosis is also considered.

CASE-CLOSING AND END-OF-TREATMENT EVALUATION

›› At the end of treatment for pulmonary TB disease, a sputum culture and a CXR is obtained.

›› A notation is made in the EMR that the patient has completed treatment and this disposition is also entered into Maven.

›› All patients who complete treatment, except those requiring post-treatment evaluation (see below), are discharged from the clinic.

›› Each patient is given a document stating that they have completed a course of treatment for TB disease.

POST-TREATMENT EVALUATION

The risk of relapse is low in patients with TB susceptible to INH, RIF, and PZA who complete an optimal treatment regimen. Post-treatment evaluation of these patients is rarely productive and is not cost-effective. These patients are advised to return to the NYC Health Department TB clinic for re-evaluation if, in the future, they develop symptoms suggestive of active pulmonary TB disease (e.g., fever, night sweats, weight loss, malaise, or prolonged cough greater than two weeks with or without sputum).

Post-treatment evaluation is also not required for most patients who:

- Have *M. tuberculosis* isolates resistant or intolerant to INH only but susceptible to RIF, PZA, and EMB
- Have completed six months of treatment with all three medications, with or without a FQN

Patients with TB resistant to INH and RIF and patients not treated with a rifamycin-containing regimen because of adverse reaction are at greater risk for post-treatment relapse. Patients are scheduled for surveillance follow-up after completing treatment. The post-treatment follow-up schedule is: four, eight, 12, 18, and 24 months. At each visit:

- A medical history review is conducted to assess symptoms of active TB
- A CXR is obtained for comparison to the CXR obtained at the end of therapy
- A single sputum specimen is obtained for smear and culture

Patients with any positive result for TB are contacted for additional follow-up. If the smear is positive for AFB, three additional sputa specimens are collected.

›› If any specimen is culture-positive for *M. tuberculosis*, the patient is contacted immediately for a complete clinical re-evaluation and the reinstitution of appropriate therapy.

Additional follow-up evaluation is also based on clinical judgment.

MONITORING SERUM DRUG LEVELS

Therapeutic drug monitoring should be done when there is a clear indication for it. New York State (NYS) Clinical Laboratory Evaluation Program approval must be obtained. Routine monitoring of anti-TB drug levels is not recommended in clinical practice. The significance of low serum levels of anti-TB drugs in relation to clinical response has not been demonstrated. Studies have shown that as many as 60% of TB patients had low serum levels of INH or RIF. However, the clinical response to TB therapy did not differ in those with low drug levels when compared to those with normal levels. (See *Appendix K: Procedures for Therapeutic Drug Monitoring*.)

Monitoring serum drug levels can be used in patients with the following medical conditions:

- HIV infection
- Diabetes

- Malabsorption syndromes
- Renal failure
- Failure to improve on treatment/relapse
- MDR-TB
- Suspected non-adherence

LATE COMPLICATIONS OF TREATED PULMONARY TUBERCULOSIS DISEASE

Some patients who have been successfully treated for pulmonary TB disease in the past develop symptoms or have abnormalities on a CXR that raise the possibility of a recurrence of active TB disease. However, other late complications are considered in the differential diagnosis for such patients.

BRONCHIECTASIS AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Bronchiectasis is a well-recognized sequela of pulmonary tuberculosis. Globally, TB is one of the leading causes of bronchiectasis. Bronchiectasis is characterized by irreversible dilatation of bronchi with destruction of elastic and muscular elements of bronchial walls. These changes can lead to recurrent infections and shortness of breath.

Pulmonary TB is also recognized as a cause of chronic airway obstruction. Parenchymal lung destruction can affect pulmonary compliance, resulting in peripheral airway collapse and air trapping. Patients develop cough, wheezing, and breathlessness. Obstructive lung disease can develop during therapy or even after successful therapy.

HEMOPTYSIS

Bleeding from ruptured bronchial veins. Some individuals with fibrotic residuals of pulmonary TB, such as contracted lobes or segments, residual "open healed" cavities, or localized fibrosis, develop hemoptysis due to bleeding from the old, inactive post-tuberculous lesion. In most cases, the origin of the blood is a ruptured bronchial vein that occurs in rich plexuses in the endobronchial mucosa in such lesions. Hemoptysis often begins during an acute viral respiratory infection. It is usually self-limited, but may be so severe as to require emergency surgical resection.

This cause of hemoptysis can be diagnosed only by ruling out the other causes outlined here, as well as active TB (by obtaining multiple sputum cultures). If sputum cultures are negative, and no other criteria prove active TB, patients with hemoptysis should not be re-treated for active TB.

Mycetoma. Healed TB cavities can be colonized by fungi, usually *Aspergillis* species, and evolve into a mass of matted mycelia — a movable, intracavitary "fungus ball." This process is accompanied by the development of vascular granulation tissue in the internal wall of the cavity, which appears on serial

CXRs as a progressive thickening of the cavity wall. In some cases, this thickening is evident even before a mycetoma can be visualized. The granulation tissue is the site of bleeding in some individuals with *Aspergillis*-colonized cavities, usually with mycetoma. Some patients experience massive hemoptysis and require an emergency surgical resection of involved tissue or radiological intervention. Others experience chronic or recurrent hemoptysis of lesser amounts.

The diagnosis can be suspected on the basis of characteristic radiological signs, cultural isolation of *Aspergillis* from sputum, and the presence of serum antibodies, usually against *Aspergillis fumigatus*.

Other causes of hemoptysis. Many conditions unrelated to TB may lead to hemoptysis in patients who were treated for TB in the past. Among these are pneumonia, pulmonary emboli, bronchiectasis, lung abscess, and tumors.

Patients with hemoptysis may need further evaluation such as computed tomography (CT) scan of the chest, and pulmonary/surgical consultation.

CHEST PAIN

Some patients with successfully treated tuberculous pleural effusions experience chest pain over a period of months or years. Some describe pleuritic pain; others, chronic aching or a burning sensation. Often the cause is not clear. Unless there is a demonstrable recurrence of a pleural effusion on the CXR, treatment for active TB is not indicated. Infrequently, chest pain may be due to a spontaneous pneumothorax caused by the rupture of a bleb, which can evolve in an area of pulmonary scarring related to TB.

DYSPNEA

Patients with extensive pulmonary or pleural fibrosis due to healed TB may experience exertional dyspnea. Pulmonary function tests demonstrate a restrictive defect. Except for this cause, the development of dyspnea after successful therapy for TB usually reflects the presence of another, unrelated cause (e.g., chronic obstructive pulmonary disease, asthma, heart disease, and anemia).

RECURRENCE OF COUGH, SPUTUM, FEVER OR WEIGHT LOSS

Such symptoms are nonspecific and may occur from a wide variety of respiratory diseases other than TB. Among these are viral, mycoplasmal, bacterial, fungal, and other respiratory infections; exacerbations of bronchiectasis or chronic bronchitis; and tumors. In such cases, the reinstitution of anti-TB treatment is not indicated unless cultures are positive for *Mycobacterium tuberculosis* or the CXR suggests recurrent TB.

CLUBBED FINGERS

Clubbed fingers may be found in individuals with very advanced pulmonary TB and chronic respiratory insufficiency. However, if a patient who has been previously treated for pulmonary TB subsequently

develops clubbed fingers, another cause—especially a tumor—should be strongly suspected, even if the CXR has not changed.

CHANGES IN THE APPEARANCE OF THE CHEST RADIOGRAPH

In an individual who has been treated for TB, these changes may reflect a recurrence of active TB, even in the absence of symptoms. However, they could be due to completely different causes, including the following:

- **Mycetoma.** A mycetoma is usually characterized by a thickening of the cavity wall or the presence of an intracavitary mass, often manifesting a "crescent" sign.
- **Endobronchial lesions.** Endobronchial lesions that obstruct lobar or segmental bronchi usually lead to an airless, "collapsed" lobe or segment or to chronic organizing pneumonia in the parenchyma distal to the obstruction. Such lobar or segmental lesions should be suspected to be due to a tumor, malignant or benign, or to a foreign body. Appropriate diagnostic investigation should be undertaken.
- **Fluid level in an emphysematous bleb.** Although "open healed" TB cavities are rarely secondarily infected or the site of fluid levels, emphysematous bullae in the area of healed TB may develop fluid levels, especially after lower respiratory infections. These rarely represent reactivated TB.
- **Pleural effusion.** Recurrent TB infection may present as a pleural effusion in a previously treated patient, but many nontuberculous causes must be considered as well. Among these are pneumonia, pulmonary emboli, trauma, tumor, pleurodynia, connective tissue disease, and others.

SUMMARY

Monthly evaluation with periodic ancillary testing as indicated ensures the treatment team promptly detects potential relapse, clinically worsening disease, adherence problems, and medication-related adverse reactions. Together, this coordinated approach to clinical monitoring during TB treatment increases the likelihood of optimal patient outcomes.

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