CHAPTER 6:

TREATMENT OF DRUG-RESISTANT TUBERCULOSIS DISEASE IN ADULTS

INTRODUCTION

Treatment regimens for drug-resistant tuberculosis (DR-TB) are individualized and based on results of susceptibility testing. Guidelines help in establishing an optimal regimen but other factors such as physician and patient preferences, the extent of disease, and procurement of medications are used in choosing the components and length of a therapy. Treatment options with a preference for all-oral regimens are presented in this chapter based on new guidelines. New treatment options offer hope for the possibility of shorter duration therapy for DR-TB.

In addition to standard case management, the New York City (NYC) Bureau of TB Control (BTBC) provides comprehensive clinical oversight to every case of

DR-TB. Multidrug-resistant tuberculosis (MDR-TB) is tuberculosis with resistance to at least isoniazid and rifampin and requires prolonged therapy. Expert medical consultation should be sought for individuals with a confirmed diagnosis of MDR-TB.

PRINCIPLES OF TREATING DRUG-RESISTANT TUBERCULOSIS DISEASE

Drug resistance patterns are categorized based on the drugs to which a TB isolate is resistant, most importantly to isoniazid (INH) or rifampin (RIF) alone or in combination with other medications. MDR-TB refers to a TB isolate resistant to at least INH and RIF. Extensively drug-resistant (XDR-TB) traditionally referred to a TB isolate resistant to INH and RIF, plus a fluoroquinolone (FQN) and at least one of the injectable second-line drugs. This definition was recently revised to include resistance to INH and RIF, resistance to any FQN, and resistance to either bedaquiline (BDQ) or linezolid (LZD), or both. Access to timely drug-susceptibility test (DST) results, both conventional and molecular, is vital to successful treatment outcomes, as these tools aid in the determination and initiation of an effective treatment regimen.

Traditionally, TB medications are categorized based upon their effectiveness and use in a TB regimen and are designated as first-line, second-line, and third-line medications. (See *Table 6.1: Standard United States Classification for Anti-Tuberculosis Medications*.) First-line medications, while most effective in the treatment of TB disease, are the most frequent to be identified as resistant. When possible, any first-line medications found to be susceptible are included in the treatment regimen. Second-line medications are TB drugs used to treat TB disease when first-line medications are no longer available. These are often the medications used in MDR-TB regimens; they are less potent and may have more serious side effects than first-line medications. Finally, third-line medications are used when other TB medications are no longer available. These medications are most commonly used for treatment of XDR-TB, and often have the potential for more adverse reactions. Adverse effects of second- and third-line medications, often serious and intolerable, may preclude the use of these drugs for the full length of therapy. Use of anti-TB medications should not be stopped unless the reaction is severe or cannot be ameliorated by supportive treatment. Recently, additional research and new guidelines have reprioritized the use of these medications in drug-resistant TB as will be discussed later in the chapter. As additional research is published, the classification of these drugs will change and updated accordingly.

Unlike treatment for drug-susceptible TB, there is no “standardized” treatment regimen for DR-TB. Instead, treatment regimens are individualized based upon the patient’s TB isolate DST results as much as is possible. Use of both molecular DST and conventional culture DST are vital to successful patient outcomes and treatment success. The use of molecular methods including whole genome sequencing (WGS) allows for faster susceptibility results and more timely initiation of appropriate therapy. (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.) Any treatment recommendations for DR-TB consider both the DST results of the individual TB isolate as well as the history of any prior TB treatment. If molecular DST results are pending and the patient is clinically stable, a treatment regimen can be delayed until DST results are available. If there is a need to start treatment for the patient, an empiric regimen can be started with at

least three anti-TB medications to which the isolate is likely to be susceptible. Empiric treatment regimens may be determined based on:

- Drug-susceptibilities of close contacts with MDR-TB
- Medications used to treat prior TB disease episodes in the patient
- Epidemiology of drug resistance based on patient's country of birth

Once first- and second-line DST results are known the initial MDR-TB regimen is revised.

In general, the following principles apply to initiation of treatment for MDR-TB:

1. First-line drugs to which the isolate is still susceptible are started or continued
2. A FQN is added (if not already begun) and the organism is susceptible
3. Second-line and third-line drugs are added until there are at least five drugs to which the isolate is susceptible
4. All-oral regimens are preferred
5. Length of treatment is usually at least 15 months (range: 15 to 21 months) after culture conversion. In some instances treatment may be extended due to cavitary disease, delayed culture conversion or if the patient has immunosuppression

In general, any level of resistance to an anti-TB medication indicates that the drug is unlikely to be effective. However, susceptibility testing for pyrazinamide (PZA), ethionamide (ETA), and CM is often inconsistent among laboratories or even within the same laboratory. In the case of partial resistance or inconsistent results, physicians follow the general dictum, "use the medication, but do not depend on it for success."

At times, a patient's regimen may show signs that it is "failing" (e.g., the patient is not clinically improving or cultures are still positive four months after the start of therapy). When this occurs in a patient who has DR-TB, a single new anti-TB medication is never added to the regimen alone; instead, at least two, and preferably three, new anti-TB medications to which the isolate is susceptible are added. Adding multiple new medications to a failing regimen decreases the likelihood that a patient will develop acquired resistance to a single anti-TB medication and improves treatment outcomes overall.

Treatment regimens prescribed for patients with DR-TB are administered by directly observed therapy (DOT), which is the standard of care for treatment of TB disease. (See *Chapter 10: Case Management for Patients with Tuberculosis*.) DOT supports successful treatment outcomes, especially for patients with DR-TB and MDR-TB, as the patient is engaged in a dialogue to foster optimum adherence to reduce the risk of the development of additional drug-resistance or treatment failure. Some patients with DR-TB may require DOT more than once per day depending on the frequency and types of medication; new modalities including video-based DOT are useful for patients requiring observation multiple times a day.

There are no fully intermittent regimens for MDR-TB treatment. Injectable agents, if used, can be given intermittently after the initial phase of treatment. BDQ is given three times per week after the initial two weeks of daily administration. Certain drugs may be given intermittently in patients with chronic renal failure.

Most of the medications used to treat MDR-TB are known to cause fetal abnormalities, or have not been studied adequately regarding their safety in pregnancy. Therefore, persons of childbearing age who have MDR-TB and their partners are strongly encouraged to use birth control if sexually active. Children with MDR-TB are treated with drugs to which their TB, or that of the known source patient, is susceptible. Some FQNs and some third-line medications are not Food and Drug Administration- (FDA) approved in children and must be used after careful consideration of the potential risks and benefits. (See *Appendix H: Dosages, Adverse Reactions, and Monitoring for Additional Medications Used to Treat Tuberculosis*.)

TABLE 6.1: Standard United States classification for anti-tuberculosis medications

FIRST-LINE MEDICATIONS	SECOND-LINE MEDICATIONS		THIRD-LINE MEDICATIONS
Isoniazid	Amikacin	Kanamycin[2]	Bedaquiline
Rifampin	Capreomycin[2]	Streptomycin	Clofazimine
Ethambutol	Moxifloxacin	Levofloxacin	Delamanid[2]
Pyrazinamide	Ethionamide	Linezolid[1]	Imipenem/cilastin[3]
Rifabutin	Cycloserine		Meropenem[3]
Rifapentine	Para-aminosalicylic acid		Amoxicillin/ clavulanate[3]
			High-dose isoniazid[4]
			Pretomanid[5]

Adapted from: Curry International Tuberculosis Center, & California Department of Public Health. (2016). Drug-resistant tuberculosis: a survival guide for clinicians, third edition.

1. Linezolid, while historically considered a third-line drug in the United States, is now more commonly used as a second-line medication.
2. Capreomycin, delamanid, and kanamycin are not currently available in the United States.
3. Amoxicillin/clavulanate is recommended as an adjunctive agent to both imipenem/cilastatin and meropenem; it is not recommended for use alone.
4. NYC BTBC does not use high-dose isoniazid for MDR-TB, unless the patient has W strain. High-dose isoniazid is usually given as 900 mg three times per week.
5. Pretomanid is used as part of a regimen that includes linezolid and bedaquiline.

Abbreviations Used: BTBC=Bureau of Tuberculosis Control; MDR-TB=multidrug-resistant tuberculosis; NYC=New York City

SPECIFIC MEDICATIONS USED TO TREAT DRUG-RESISTANT TUBERCULOSIS

When arranging a regimen for DR-TB disease, medications are chosen based on DST results. Theoretically, any TB medication can be used, unless there is known resistance. Select medications are described in more detail below. For specific medications and dosages for the treatment of DR-TB, see *Appendix H: Dosages, Adverse Reactions, and Monitoring for Additional Medications Used to Treat Tuberculosis*.

FIRST-LINE MEDICATIONS

ISONIAZID

In general, once there is known resistance to INH at any tested concentration, use of INH is not recommended in that treatment regimen. The only exception to this rule is when the patient is diagnosed with MDR-TB due to the W strain and W variants. In this instance, high-dose INH can be prescribed. High-dose INH is usually given as 900 mg three times per week. High-dose INH has also been used in nine-month regimens that include injectable agents. (See section *Shorter Regimens Using Injectable Agents*.)

RIFAMYCINS

Most, but not all, TB isolates that are resistant to RIF are also resistant to rifabutin (RBT). Occasionally, a RIF-resistant organism will be reported as sensitive to RBT. This situation is associated with certain genetic mutations. When there is in vitro sensitivity to RBT, it can be added to the regimen along with other oral agents as outlined. However, the effectiveness of RBT in this situation cannot be relied upon. The treatment length is usually 12 to 18 months, depending on the regimen used. With newer drugs such as BDQ and LZD, shorter treatment may be possible. However, data is lacking at this time.

ETHAMBUTOL

If EMB is used in an MDR-TB regimen, the recommended dose is 25 mg/kg/day. A baseline and monthly visual acuity exam and Ishihara's test for color blindness is performed.

PYRAZINAMIDE

If there is mono-resistance to PZA, *M. bovis*, another member of the *M. tuberculosis* complex, is suspected. Repeat testing for PZA resistance may be inconsistent; as such the genetic mutation in the pncA gene may be helpful in determining susceptibility. It is not the practice of the BTBC to use PZA in MDR-TB patients if there is known drug-resistance to PZA.

INJECTABLE AGENTS

Historically, BTBC has used CM as the preferred injectable agent until DST results were known, due to the widespread incidence of W strain and W strain variants seen in NYC in the 1990s that are commonly resistant to streptomycin (SM) and AK/KM. NYC has excellent outcomes using CM. However, recent American Thoracic Society (ATS)/Centers for Disease Control and Prevention (CDC)/European Respiratory

Society (ERS)/Infectious Disease Society of America (IDSA) and World Health Organization (WHO) guidelines for the treatment of MDR-TB recommend against use of CM and instead recommend AK if an injectable agent is used. AK is commonly used for hospitalized patients due to accessibility of the drug, ease of administration intravenously, and the ability to easily monitor drug levels. Administration of intramuscular AK to an outpatient is challenging due to the volume of drug that needs to be administered and level of pain associated with the injection. Laboratories usually test for either AK or KM susceptibility, as there is cross-resistance between these two agents, and resistance to one generally predicts resistance to the other. KM is not available for use in the United States (U.S.).

With the availability of new, safer, and more effective medications, the injectable medications are rarely used today in the outpatient setting. Patients may be started on injectable agents as part of a holding regimen while hospitalized. If an injectable agent is continued, it could be given for six months after culture conversion unless ototoxicity or nephrotoxicity develops. The continuation of the injectable agent for longer than six months after culture conversion is only appropriate if there are no other reasonable treatment options and there is extensive disease, extensive resistance, intolerance to second-line or newer drugs, or when conversion of sputum cultures did not occur within the first two months of treatment.

If an injectable agent is used in a DR-TB regimen, a baseline and monthly audiogram is performed.

FLUOROQUINOLONES

FQNs are the backbone of a successful MDR-TB regimen because they are bactericidal, well-tolerated, and can be given orally. The later generation FQNs, levofloxacin (LFX) and moxifloxacin (MFX), are preferred in the treatment of DR- TB disease. In general, FQNs are not considered for first-line treatment in patients with drug-susceptible organisms unless the patient is intolerant to other first-line drugs. If a FQN is used, molecular and conventional DSTs are requested to confirm isolate sensitivity, as this drug class is typically not included in first-line molecular and conventional DSTs and rates of FQN resistance are increasing. The NYS lab can test for FQN susceptibility using pyrosequencing.

LFX is cleared by the kidney and is the preferred agent for patients with hepatic insufficiency; however, it is used with caution. In patients with renal failure, the interval between doses of LFX is increased. MFX is mostly cleared by the liver and therefore may be the preferred FQN in a patient with renal insufficiency.

- The dose of LFX is 500 to 1000 milligrams (mg) once daily. Doses of 750 or 1000 mg per day are preferable. The higher end of the dose range may be bactericidal. In children older than five years of age, the dose is 8 to 10 mg/kilograms (kg)/day. In children younger than five years of age, the dose is eight to 10 mg/kg/12 hours.
- MFX is usually dosed in adults at 400 mg once per day. Children receive 10 mg/kg/day. Some experts recommend higher doses of MFX in children.
- When used in children, the potential benefit must justify the potential risk. Disclosure of potential risks to the patient is done by the clinician and is documented in the electronic medical record (EMR).

›› LFX and MFX are a category C drug in pregnancy. They are only used if the potential benefit to the mother justifies the potential risk to the fetus. Disclosure of this risk to the patient is done by the clinician and is documented in the EMR.

SIDE EFFECTS:

FQNs are generally considered to be well-tolerated in both adults and children; however, some side effects include:

- Nausea/vomiting/abdominal pain
- Diarrhea (can be due to *C. difficile*, especially MFX)
- Reversible transaminase elevation
- Cholestasis, hepatitis, and hepatic failure (infrequently reported)
- Photosensitivity (except MFX)
- Cardiotoxicity (see *QTc Prolongation*)
  - Prolongation of the QTc interval and possible arrhythmia including Torsade de Pointes
  - Most notably associated with the use of the later generation FQNs (MFX greater than LFX)
  - This side effect is uncommon
    - Baseline and follow-up electrocardiogram (EKG) are not indicated unless otherwise clinically indicated, i.e., if the patient is receiving other QTc prolonging medications
- Central nervous system [CNS] effects
- Peripheral neuropathy
- Worsening muscle weakness in patients with myasthenia gravis
- Tendinopathy/tendinitis (may be more prevalent in the elderly [65 and older], patients on corticosteroids, and patients with organ transplants)
  - May cause tendon rupture
  - Tendinopathy and rupture may be reported even months after drug discontinuation
  - Main site affected is rupture of the Achilles tendon; however, it has also been reported in the shoulder, knee, hand, and plantar aponeuroeses
  - Treatment includes discontinuing the FQN and resting the affected tendon; physical therapy may be needed early in treatment and may be prolonged
- Hypoglycemia and hyperglycemia (All FQNs; may be more prevalent in the elderly or patients with diabetes)
- Hypersensitivity reaction either after a single dose or multiple doses
  - Treatment is discontinued at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity
- Ruptures or tears in the aorta, rarely

In addition, FQNs cause a number of other notable drug interactions:

- Medications with divalent cations, such as aluminum-, magnesium-, or calcium-containing antacids, can decrease the absorption of FQNs
- FQNs can inhibit the metabolism of methylxanthines

LINEZOLID

LZD belongs to the oxazolidinones class of antibiotics and is active against TB, including isolates resistant to many first-line anti-TB drugs. LZD may be used as part of a regimen for treating patients with MDR-TB who have extensive second-line drug resistance or are intolerant to many second-line drugs. LZD is being used more frequently as a second-line drug by BTBC. There is excellent data showing positive outcomes using LZD for patients with pre-XDR-TB and XDR-TB. LZD is usually included as part of the newer all-oral regimens used for MDR-TB.

LZD is available for oral use as well as for intravenous administration and a dose of 600 mg per day is recommended when used for TB. Food may cause delays in LZD absorption, but does not lower peak plasma concentrations. The drug is partly metabolized in the liver and does not affect the cytochrome P450 enzyme system; it is excreted in the urine. The LZD oral suspension contains phenylalanine, and therefore is not given to patients with phenylketonuria. The oral suspension is non-formulary and needs approval by BTBC. LZD can be used in children. Complete blood count (CBC) and SMA-18 profile need to be monitored monthly; if there is evidence of myelosuppression the CBC should be monitored more frequently. Vision is monitored monthly.

LZD is a reversible, non-selective inhibitor of monoamine oxidase and therefore may interact with adrenergic and serotonergic agents. Patients should avoid eating diets high in tyramine (e.g., strong or aged cheese, cured or smoked meats, beers on tap or home-brewed, soy products, and fava or broad beans). Co-administration of drugs containing pseudoephedrine, phenylpropanolamine, selective serotonin reuptake inhibitors, and possibly other antidepressants, is undertaken with caution, as serotonin syndrome may occur. This syndrome manifests as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination, and such patients may need referral to a neurologist or other specialist. The benefit of taking LZD with these drugs must be weighed against these risks.

SIDE EFFECTS:

The following are side effects reported with LZD:

- Optic neuritis (may be reversible)
- Peripheral neuropathy (may be irreversible)
- Myelosuppression including anemia, leukopenia, pancytopenia, and thrombocytopenia (reversible upon discontinuation of the drug)
- Hemolytic anemia
- Diarrhea

- Nausea/vomiting (patients who have recurrent nausea and vomiting, unexplained acidosis, or a low bicarbonate level should receive immediate medical attention to rule out lactic acidosis)
- Liver function test (LFT) elevations
- Tongue discoloration
- Severe hypertension (if taken concomitantly with large amounts of tyramine)

CLOFAZIMINE

CFZ has been used for many years to treat MDR-TB. Since it has in vitro activity against TB, *M. avium-intracellulare* (MAI), and leprosy, this drug has been used in both the treatment of MDR-TB and nontuberculous mycobacteria (NTM). According to the new WHO and ATS/CDC/ERS/IDSA guidelines, CFZ is being recommended in the treatment of MDR-TB and XDR-TB. CFZ is given at a dose of 100 mg per day for most patients.

CFZ for MDR-TB patients is only available from Novartis via an IND application from the FDA. Approval from the institution's IRB and patient consent is required. Contact FDA and Novartis for more information at clofazimine.managedaccess@novartis.com

Obtaining CFZ is a complicated process; the Bureau of TB Control (BTBC) can provide support in obtaining CFZ for MDR-TB patients. As of October 2018, CFZ is only available from the drug supplier Novartis, where a Letter of Agreement needs to be established with the institution. Prior to requesting the drug, a unique patient Investigational New Drug (IND) application approval letter from the FDA must be acquired. This process includes attesting that the institution has an Institutional Review Board (IRB) approval and signed consent from the patient. Once FDA approval is obtained, a unique IND number is assigned to the patient. Novartis requires a copy of the consent form and the IND approval letter from the FDA, as well as a prescription for the drug. A supply of 200 tablets, 50 mg each, of the drug is sent to the institution. The treating physician is responsible for sending annual reports to the FDA, Novartis, and IRB, as well as immediate reporting of adverse events. The patient is monitored monthly, or more frequently if necessary, for continued need for the drug and side effects.

SIDE EFFECTS:

- Pink to brownish-black discoloration of the skin. The degree of discoloration is dose-related and is most pronounced on exposed parts of the body
- Photosensitivity
- Ichthyosis and dry skin; pruritus and non-specific rash
- Reversible, dose-related red-brown discoloration of the conjunctiva, cornea, and lacrimal fluid
- Prolongation of the QTc interval and possible arrhythmia including Torsade de Pointes

- GI side effects such as abdominal and epigastric pain, diarrhea, nausea, vomiting, and GI intolerance
- Central nervous system (CNS) effects (reported in less than 1% of patients) such as dizziness, drowsiness, fatigue, headache, giddiness, neuralgia, and taste disorders
- Rare adverse effects may include splenic infarction, bowel obstruction, stomach or intestinal bleeding

BEDAQUILINE

BDQ is a diarylquinoline, a new chemical class of drugs. In 2012, the FDA gave BDQ fast-track approval for the treatment of MDR-TB, as it demonstrated decreased time to sputum culture conversion. BDQ interferes with the energy metabolism of the cell. It must be used in combination with at least three other drugs to which the patient's TB strain is susceptible, except when used as part of the BPaL regimen. As with any patient treated for MDR-TB, BDQ must be given under DOT. Currently, it is believed there is little resistance to BDQ in the U.S. Previously, BTBC has used BDQ for the treatment of pre-XDR and XDR-TB patients; it is increasingly being used for patients with MDR-TB and mono-RIF resistance. New guidelines place greater emphasis on the use of BDQ as one of the initial agents of an all-oral regimen used to treat MDR-TB.

BDQ is lipophilic and has a long half-life. BDQ should be taken with food. BDQ may prolong the QTc interval and therefore an EKG is obtained before the initiation of therapy and at two, 12, and 24 weeks after the start of therapy. Caution must be used when the patient is taking other medications or has a clinical condition that may prolong the QTc interval. BDQ is metabolized through the cytochrome P450 (CYP) system. Co-administration with rifamycins (e.g., RIF, RPT, and RBT) or other strong CYP3A4 inducers should be avoided. There is limited data on patients with concomitant HIV and MDR-TB.

The recommended dose for an adult being treated for 24 weeks is as follows:

WEEK 1-2: 400 mg (four tablets of 100 mg) given orally, once daily with food

WEEK 3-24: 200 mg (two tablets of 100 mg), given orally three times per week with food, for a total dose of 600 mg per week; the drug can be taken at least 48 hours between doses if a dose is missed

In some cases, patients may receive an additional course of BDQ if necessary to establish a sufficiently potent regimen.

BDQ is generally well-tolerated. The patient should be monitored for symptoms of hepatitis with laboratory tests (ALT, AST, alkaline phosphatase, and bilirubin) at baseline and monthly or as indicated clinically.

Other frequent adverse events include:

- Nausea
- Arthralgia
- Headache

If the patient is insured, BDQ can usually be obtained through the insurance company. Copayment may be required. Many companies may require prior authorization through the patient's insurance/pharmacy coverage. If the patient is not insured, the Johnson & Johnson Patient Assistance Program should be contacted at 1-800-652-6227 or https://www.jjpaf.org/eligibility/?medication=SIRTURO%C2%AE#step1.

BDQ is supplied by a single distributer. Use of BDQ is coordinated through BTBC's Medical Affairs Office. Call the TB HOTLINE at 844-713-0559 for additional information.

DELAMANID

Delamanid is a nitroimidazole, a class of novel agents used for TB treatment. It has a new mechanism of action, inhibiting the cell wall of TB but the exact mode of action is unknown. It must be given along with a background MDR-TB treatment regimen. It has mild adverse effects, primarily gastrointestinal, and few drug-to-drug interactions; however, it can prolong the QTc interval. In the US, it is available through a compassionate use program.

PRETOMANID

Pretomanid is another nitroimidizole that is used in a regimen, along with BDQ and LZD (BPaL), that has FDA approval for the treatment of pulmonary XDR-, treatment-intolerant, or non-responsive MDR-TB for six to nine months. It is generally well-tolerated, but side effects include peripheral neuropathy, acne, vomiting, headache, low blood sugar, diarrhea, and liver inflammation.

SUGGESTED REGIMENS FOR SPECIFIC DRUG RESISTANCE PATTERNS

Treatment of DR-TB is seldom clear-cut. The use of any medication that was used in a patient who has had prior treatment for DR-TB when DST results are not available should be avoided. Opinions may vary on the best medications to use for an individual patient. Whenever possible, a regimen is crafted based upon available specimen drug-resistance profiles. (See *Table 6.2: Traditional Suggested Regimens for Treatment of Drug-Resistant Tuberculosis*.)

INH-resistant, RIF-susceptible (INH-R) tuberculosis is one of the most common forms of drug resistance, and is associated with failure, relapse, and acquired RIF resistance if the regimen is not adjusted appropriately.

Mono-RIF resistance is rare and can be associated with cross-resistance to rifabutin (RBT) and rifapentine (RPT). When RIF resistance is present but in vitro susceptibility to RBT is reported, treatment should be the same as in the case of RIF resistance.

The use of laboratory diagnostics is crucial in formulating a successful MDR-TB treatment regimen. Although molecular methods enable the clinician to obtain results more rapidly for certain mutations associated with drug resistance and allow quicker initiation of appropriate therapy, these methods have

different specimen requirements (e.g., Xpert MTB/RIF is performed directly on sputum, WGS is performed on culture). Conventional DST requires a pure culture and laboratories test drugs sequentially. (Standard treatment drugs [i.e., first-line drugs] INH, RIF, PZA, EMB, and SM are tested first, and additional drugs are only tested when resistance has been detected in the standard treatment drugs.) (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.)

The regimens listed below are suggested recommendations based on specific drug resistance patterns. (See *Table 6.2: Traditional Suggested Regimens for Treatment of Drug-Resistant Tuberculosis*.) For a list of medications for the treatment of MDR-TB and XDR-TB, see *Appendix H: Dosages, Adverse Reactions, and Monitoring for Additional Medications Used to Treat Tuberculosis* and *Appendix G: Dosages, Adverse Reactions, and Monitoring for First-Line Medications Used to Treat Tuberculosis*.

ISONIAZID RESISTANCE

Most patients with TB are started on a four-drug regimen consisting of INH, RIF, PZA, and EMB. Once INH resistance is documented, INH is discontinued. High-dose INH is not recommended for patients with INH-resistant TB disease, even when DST indicates that the isolate is susceptible to a high level of INH, but resistant to lower levels of INH.

OPTION A: In 2018, the World Health Organization (WHO) published guidelines for the treatment of INH-resistant TB. The WHO recommended RIF/PZA/EMB/FQN for a total of six months. In 2019, guidelines from ATS/CDC/ERS/IDSA recommended a regimen of RIF/PZA/EMB/FQN for two months followed by RIF/EMB/FQN for four months as the preferred regimen for INH-resistant TB when there is toxicity anticipated or experienced because of PZA or when the patient has noncavitary, lower burden of disease. The BTBC agrees with the recent guidelines that add a FQN to the regimen for treatment of INH-resistant TB.

OPTION B: RIF, PZA, and EMB are used for the duration of treatment. This is the preferred regimen for pregnant patients, as relapse rates are high with RIF and EMB alone. RIF, PZA, and EMB is the only regimen when treating INH-resistant TB that can be given intermittently. If given intermittently, treatment three times per week is preferred. This regimen is given for six to nine months total; the regimen is extended to nine months if the patient is still culture-positive at two months.

After a two-month intensive phase of a RIF, EMB, and PZA regimen, PZA may be discontinued and RIF and EMB are continued for seven more months. The total length of treatment for this regimen is nine months.

OPTION C: If PZA cannot be given during the entire two-month intensive phase (because of drug resistance or intolerance), a regimen of RIF and EMB is used along with a FQN for nine months.

OPTION D: MFX, RIF, PZA, and EMB are used daily for a two-month intensive phase, followed by once weekly MFX and rifapentine (RPT) (1200 mg dose once per week) for four months. This regimen is an acceptable alternative for INH-resistant TB disease if the organism is susceptible to the FQNs. The total length of treatment with this regimen is six months.

TABLE 6.2: Traditional suggested regimens for treatment of drug-resistant tuberculosis

	INITIAL PHASE		CONTINUATION PHASE		TOTAL LENGTH AND NOTES
Resistance Pattern	Drugs	Duration	Drugs	Duration	
INH ± SMN	**OPTION A:** RIF/PZA/EMB/FQN	2 months	RIF/FQN/EMB ± PZA	4 months	• 6 months • Extend to 9 months if still culture-positive at 2 months • PZA may be discontinued for toxicity or noncavitary, lower burden of disease
	OPTION B: RIF/EMB/PZA	2 months	RIF/EMB/PZA RIF/EMB	4-7month 7 months	• 6-9 months • Consider adding a FQN • RIF/PZA/EMB is the preferred regimen in pregnancy
	OPTION C: RIF/EMB/FQN	2 months	RIF/EMB + FQN	7 months	9 months
	OPTION D: MFX/RIF/PZA/EMB	2 months	MFX/RPT[1]	4 months	6 months
INH/PZA ± SMN	RIF/EMB/FQN	2 months	RIF/EMB/FQN	7 months	9 months
RIF	**OPTION A:** INH/PZA/EMB/FQN	2-3 months after culture conversion	INH/PZA/EMB/FQN	10-16 months	• 18 months is the preferred option • 12 months of INH/PZA/EMB/FQN is an alternative option • Consider discontinuation of PZA after 2 months
	OPTION B: *(no SM resistance)* INH/PZA/SM ± EMB				9 months
PZA ± SMN	INH/RIF	2 months	INH/RIF	7 months	9 months
INH/EMB ± SM	RIF/PZA/FQN	2 months	RIF/PZA/FQN	4-7 months	9 months or 6 months after culture conversion, whichever is longer
INH/RIF ± SM	PZA/EMB/FQN/ BDQ/LZD	6 months after culture conversion	PZA/EMB/FQN ± LZD Consider a second course of BDQ	12 months	15-21 months after culture conversion

TABLE 6.2: Traditional suggested regimens for treatment of drug-resistant tuberculosis *(continued)*

	INITIAL PHASE		CONTINUATION PHASE		TOTAL LENGTH AND NOTES
Resistance Pattern	Drugs	Duration	Drugs	Duration	
INH/RIF/ EMB ± SM	PZA/FQN/BDQ/LZD/ CFZ or CS	6 months after culture conversion	PZA/FQN/LZD ± CFZ or CS Consider a second course of BDQ	12 months	15-21 months after culture conversion
INH/RIF/ PZA ± SM	EMB/FQN/BDQ/ LZD/CFZ or CS	6 months after culture conversion	EMB/FQN/LZD ± CFZ or CS Consider a second course of BDQ	12 months	15-21 months after culture conversion
INH/RIF/ PZA/EMB ± SM	FQN/BDQ/LZD/CFZ/ CS	6 months after culture conversion	FQN/LZD/CFZ or CS Consider a second course of BDQ	12 months	15-21 months after culture conversion
INH/RIF/ EMB/SM/ KM/ETA/ RBT ± PZA (Pre-XDR-TB)*	FQN/BDQ/LZD/CFZ/ CS Consider BDQ/LZD/ Pretomanid (BPaL) regimen	6 months after culture conversion	FQN/LZD/CFZ or CS Consider a second course of BDQ	12 months	15-21 months after culture conversion • This resistance pattern is associated with NYC strain W and W variants • Consider BPaL regimen for 6 months
INH/RIF/ EMB/SM/ FQN + second-line reserve injectable agent ± PZA *(XDR-TB)**	FQN/BDQ/LZD/CFZ/ CS Consider BDQ/LZD/ Pretomanid (BPaL) regimen	6 months after culture conversion	FQN/LZD/CFZ or CS Consider a second course of BDQ	Unknown	18-24 months after culture conversion • Consider BPaL regimen for 6 months

1. Jindani A, Harrison TS, Nunn AJ, et al; RIFAQUIN Trial Team. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med*. 2014 Oct 23;371(17):1599-608.

*Based on 2006 WHO definition of XDR-TB

Abbreviations Used: BDQ=bedaquiline; CFZ=clofazimine; CM=capreomycin; CS=cycloserine; EMB=ethambutol; ETA=ethionamide; FQN=fluoroquinolone; INH=isoniazid; KM=kanamycin; LZD=linezolid; MFX=moxifloxacin; PZA=pyrazinamide; RBT=rifabutin; RIF=rifampin; SM=streptomycin; XDR-TB=extensively drug-resistant tuberculosis

RIFAMPIN RESISTANCE

Isolated rifampin resistance without associated resistance to isoniazid is a rare occurrence. Mono-RIF resistant TB can be treated with INH/EMB/PZA/FQN for a total of 12-18 months. BDQ is increasingly being used in the treatment of rifampin mono-resistant TB and may lead to shorter treatment duration.

A nine-month regimen of INH/PZA/SM ± EMB has proven efficacy but is seldom used due to the difficulties associated with the prolonged use of SM, which must be given for the entire duration of the regimen.

PYRAZINAMIDE RESISTANCE

Isolated pyrazinamide resistance is usually seen in *M. bovis* and requires an extension of therapy. The pyrazinamide is discontinued from the regimen and INH and RIF are used for a total of nine months.

TREATMENT REGIMENS FOR MULTIDRUG-RESISTANT TUBERCULOSIS

In December 2018, the WHO released updated guidelines and recommendations with key changes for the treatment of MDR-TB and RIF-resistant TB (RR-TB). The guidelines were developed based on a review of global clinical trials that investigated the effectiveness and safety of various MDR-TB treatment regimens. Major changes in the new WHO guidelines include:

- Recommendation of an all-oral regimen for 18 to 20 months in most patients
- No longer recommending injectable agents KM and CM for use in treatment
- Updated priority ranking of medicines with BDQ, LZD, and CFZ rising in importance in the treatment regimen
    - ETA and the injectable agents AK and SM are becoming less important in the treatment regimen (see *Strategy for Building a Treatment Regimen for MDR-TB*)

CURRENT BTBC PRACTICE

Evolving evidence from innovative research, ongoing clinical trials, and updated guidelines for the treatment of MDR-TB has led to new recommendations for the treatment of MDR-TB. Guidance from the WHO and ATS/CDC/ERS/IDSA based on the information provided by a large individual patient data analysis have led to changes in the recommendations for the treatment of MDR-TB at the BTBC.

Key publications influencing the change in recommendations include the 2018 Lancet article from Ahmad et al. “Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis” and updated WHO guidelines. ATS/CDC/ERS/IDSA have also developed guidelines for the treatment of MDR-TB.

BTBC has had great success in treating patients with MDR-TB and limiting the development of drug resistance, but emerging data and recommendations are helpful in continuing to ensure positive patient outcomes.

Changes in practice at the BTBC include:

- Crafting an all-oral regimen, when possible
- Prioritizing newer drugs that allow shorter treatment duration, such as BDQ, LZD, and CFZ as "first-line" MDR-TB drugs; increasingly, we are transitioning to using the shorter BPaL regimen as first-line treatment for MDR-TB and XDR-TB
- Ensuring susceptibility of medications whenever possible
- Limiting use of injectable agents and prioritizing amikacin or streptomycin if an injectable agent is needed
- Using at least five drugs in the "initiation phase" and at least four in the "continuation phase," except when using the BPaL regimen
- Treating for at least 15 months (range: 15 to 21 months) after culture conversion; XDR or pre-XDR TB may need to be treated up to 24 months after culture conversion

Providers must incorporate updated guidance into clinical practice whenever it is of benefit to patients. BTBC will re-evaluate treatment recommendations as additional information becomes available.

The construction of a regimen to treat MDR-TB integrates all of the information from all types of DST to the extent possible. Currently, molecular testing is not available for all drugs. Cross resistance may develop between some drugs and should be considered when constructing a regimen.

In some instances, it takes time to procure all of the drugs for an all-oral regimen and injectable drugs may need to be used until a regimen with an adequate number of effective drugs can be initiated. This type of regimen is called a bridging regimen.

STRATEGY FOR BUILDING A TREATMENT REGIMEN FOR MDR-TB

The following is adapted from ATS/CDC/ERS/IDSA guidelines; updated guidelines are anticipated in 2022.

OPTION A: ALL-ORAL REGIMEN WITH FIVE EFFECTIVE DRUGS

Step 1: Choose one later-generation fluoroquinolone:

- Levofloxacin
- Moxifloxacin

Step 2: Choose both of these prioritized drugs:

- Bedaquiline
- Linezolid

Step 3: Choose both of these prioritized drugs:

- Clofazimine
- Cycloserine

OPTION B: INJECTABLES

If a regimen cannot be assembled with five effective oral drugs, and the isolate is susceptible, use one of these injectable agents:

- Amikacin
- Streptomycin

Amikacin and streptomycin should be used only when the patient's isolate is susceptible to these drugs. Because of their toxicity, these drugs should be reserved for when more-effective or less-toxic therapies cannot be assembled to achieve a total of five effective drugs.

OPTION C: ALTERNATIVE ALL-ORAL REGIMEN

If needed or if oral agents preferred over injectable agents in Option B, use the following drugs:

- Pyrazinamide
- Ethambutol
- Delamanid

Use pyrazinamide and ethambutol only when the isolate is documented as susceptible. Data on dosing and safety of delamanid are available in children > 3 years of age. Delamanid is only available for compassionate use in the U.S.

Considerations in selecting Option C agents over injectables in order to prescribe an all-oral regimen:

- Patient preferences in terms of the harms and benefits associated with injectables (the use of which is no longer obligatory)
- Capacity to appropriately monitor for significant adverse effects
- Drug-to-drug interactions
- Patient comorbidities

OPTION D: ADDITIONAL DRUGS

If limited options and cannot assemble a regimen of five effective drugs, consider use of the following:

DRUG	CONSIDERATIONS
Ethionamide	Mutations in the inhA region of the Mycobacterium tuberculosis genome can confer resistance to ethionamide as well as to INH. In this situation, ethionamide may not be a good choice unless the isolate is shown to be susceptible with in vitro testing.
Imipenem–cilastatin/ clavulanate or meropenem/clavulanate	Divided daily intravenous dosing limits feasibility. Optimal duration of use not defined. May be used if patient is hospitalized as part of a bridging regimen. Clavulanate is given as amoxicillin/clavulanate.
p-Aminosalicylic acid	Fair/poor tolerability and low performance. Adverse effects reported to be less common in children.
High-dose isoniazid	High-dose isoniazid can be considered despite low-level isoniazid resistance but not with high-level INH resistance.

- Capreomycin and kanamycin
- Amoxicillin/clavulanate (when used without a carbapenem)
- Azithromycin and clarithromycin

PRINCIPLES OF MONITORING DRUG-RESISTANT TUBERCULOSIS DISEASE

›› Sputum AFB smear and cultures (for patients with pulmonary disease) and clinical laboratory tests should be performed monthly for patients with TB isolates resistant to RIF or INH and RIF

›› Monthly clinical laboratory tests are obtained for patients with DR-TB when indicated to monitor for potential drug toxicities

›› Chest radiograph (CXR) is obtained at two months of treatment, periodically when clinically indicated during the continuation phase, and at the end of treatment for patients with DR-TB

›› Other imaging studies are obtained when clinically indicated during treatment

›› If a patient has a positive TB culture after four months of treatment, the most recent positive culture is sent to the clinical laboratory for first- and second-line DST. There are at least two treatment options while the DST results are pending:

1. If the patient is not acutely ill or clinically deteriorating, the current or most recent anti-TB regimen may be continued until the new DST results are available;
2. If the patient is acutely ill or clinically deteriorating, at least two new anti-TB medications are added to the current regimen based on an assessment of the other medications to which the isolate is not known to be resistant. The regimen is revised when the new DST results are available, as indicated

›› If the patient is having an adverse reaction to a specific medication:

1. The medication responsible for the adverse reaction is omitted and the remainder of the anti-TB treatment regimen is continued if enough medications are left in the regimen
2. A previously unused agent is substituted
3. If the adverse reaction cannot be readily identified, all medications are discontinued and restarted one at a time. In some instances of severe toxicity, hospitalization for re-challenge with multiple drugs may be needed
4. If the adverse reaction is mild, the physician may choose to continue treating through the adverse reaction

QTc PROLONGATION

The QT interval is the length of time required for the heart to repolarize following the onset of depolarization. The QT interval is measured from the start of the QRS complex to the end of the T wave on the electrocardiogram (EKG). Rapid heart rate can lead to a shortened QT interval. In order to correct

for this, the QT interval is expressed as the heart rate corrected QT interval (QTc). Prolongation of the QTc interval may predispose the patient to potentially fatal ventricular arrhythmias and sudden death.

Several drugs used in the treatment of TB can cause QTc prolongation. These include the FQNs, CFZ, DLM, BDQ, and pretomanid. LFX is believed to prolong the QTc interval less than MFX. With respect to QTc prolongation, BDQ is the most concerning because of the long half-life of the drug. Patients receiving BDQ should receive an EKG at baseline, and at minimum at two, 12, and 24 weeks of treatment. Patients receiving multiple drugs that can prolong the QTc interval should have monthly EKG monitoring. 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.

Certain other conditions are associated with prolongation of the QTc interval. These include:

- Bradycardia
- Torsade de pointes
- Hypothyroidism
- Uncompensated heart failure
- Congenital long QT syndrome
- Electrolyte abnormalities: hypomagnesemia, hypokalemia, and hypocalcemia
    - Electrolyte abnormalities may be caused by the injectable agents

It is important to document any medications that the patient is taking. Examples of medication that may prolong the QTc interval include:

- Antiarrhythmic agents: Class IA (quinidine and procainamide) and Class III (amiodarone and sotalol)
- Antimicrobials (FQN, azole antifungals, and macrolides)
- Antidepressants
- Antipsychotics
- Antihistamines
- Antiretroviral agents (specifically protease inhibitors [PI] and efavirenz containing regimens)
- Methadone
- Gastrointestinal (GI) drugs: metoclopromide, cisapride, and ondansetron (Zofran)

SURGERY FOR PULMONARY TUBERCULOSIS DISEASE

In NYC, surgery is usually not recommended as an initial treatment option, because pulmonary TB disease is curable using modern drug regimens in most cases. Surgery remains an option for individuals with MDR-TB or XDR-TB in whom treatment has failed or is not possible because of a lack of sufficient and effective medications. Video-assisted thoracoscopic surgery (VATS) with partial lung resection (lobectomy or wedge resection) has been associated with improved treatment success among patients with MDR-

TB. Although improved outcomes may reflect patient selection and newer surgical techniques, partial lung resection surgery after culture conversion may improve treatment outcomes in patients who receive optimal medical therapy.

In patients with XDR-TB, surgery may be indicated earlier in the course of therapy as drug options are more limited.

INDICATIONS FOR SURGERY

In consultation with medical and surgical experts, surgery is considered when all of the following criteria are met:

- Adequate regimens for MDR-TB have failed to cure or to cause TB cultures to culture convert within four to six months
- The disease is sufficiently localized to allow lobectomy or pneumonectomy
- The remaining lung tissue is relatively free of disease
- The patient is an acceptable surgical risk, with sufficient pulmonary reserve to tolerate the resection
- Sufficient medications are available to treat the patient post-operatively

Even after lung resection, the patient must complete a full course of treatment (15 to 24 months after culture conversion) with medications to which the TB isolate is susceptible. If the patient is culture-negative after surgery, then the date of surgery is considered the culture conversion date.

Some clinical circumstances, such as major bronchial obstruction, severe hemoptysis, or bronchopleural fistula, are additional possible indications for surgery.

SHORTER REGIMENS FOR MULTIDRUG-RESISTANT TUBERCULOSIS

SHORTER REGIMENS USING INJECTABLE AGENTS

Historically, there have been efforts to reduce the treatment duration for MDR-TB using novel combinations of existing drugs. One of the first regimens was the nine-month Bangladesh Regimen, which has been used in some countries with modest success. The intensive phase includes four months of KM, MFX, prothionamide (PTH), CFZ, PZA, high-dose INH, and EMB, followed with five months of MFX, CFZ, PZA, and EMB (KM and PTH are not available in the US). This regimen has been used in countries where full DST is not routinely available.

The STREAM trial also looked at a nine-month regimen of oral drugs plus an injectable agent and high-dose INH along with other oral agents. The Bangladesh regimen, together with the STREAM trial, were important in the development of shorter, all-oral regimens, for the treatment of drug-resistant TB. BTBC does not use this nine-month regimen, as individualized regimens are accessible and preferred. A significant portion of BTBC patients would not be eligible for these regimens.

PRETOMANID AS PART OF THE NIX-TB REGIMEN

Pretomanid is a nitroimidazole approved by the FDA in 2019 for the treatment of XDR-TB. Currently, pretomanid is given in combination with BDQ and LZD. Pretomanid has been developed by the TB Alliance and is distributed by Mylan Pharmaceuticals. NIX-TB is a six-month all-oral three-drug regimen of BDQ, pretomanid, and LZD (BPaL).

- Pretomanid 200 mg orally once per day for 26 weeks
- Bedaquiline 400 mg orally once per day for two weeks and then three times per week for 24 weeks
- Linezolid 1200 mg orally once per day for 26 weeks

Most of the adverse effects of this regimen were due to the toxicities of the individual drugs in the regimen:

- Hepatoxicity
- Myelosuppression
- Peripheral and optic neuropathy (which was the most common)
- QTc prolongation
- Testicular atrophy and infertility
- Lactic acidosis

The regimen is generally well-tolerated. Peripheral neuropathy was a common side effect with dosing of LZD at 1200 mg/day. As a result, LZD is usually given at a dose of 600 mg/day. The recent ZeNix trial showed that LZD could be dosed at 600 mg/day with high cure rates but fewer side effects. It is recommended that drug levels of LZD should be obtained. Levels are drawn as a trough immediately before a dose and then at two hours after the dose. Elevated trough levels (greater than 2 mcg/ml) are associated with peripheral neuropathy. Levels are sent to Denver National Jewish Health Advanced Diagnostic Laboratories and are arranged by the Office of Medical Affairs. Monthly visual monitoring is required. EKG should be monitored monthly due to potential for QTc prolongation.

POST-TREATMENT EVALUATION

Patients with TB resistant to RIF alone or INH and RIF, regardless of the regimen used and the duration of treatment, are at greater risk for post-treatment relapse. The patient is scheduled for surveillance follow-up once completing treatment at four, eight, 12, 18, and 24 months post-treatment. If the patient is treated with a shorter regimen, the patient should have follow-up quarterly during the first year, then twice per year in the second year.

At each visit:

- A medical evaluation is performed to assess for signs and 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

For patients that remain stable and asymptomatic, no immediate clinical action is taken. For patients seen in a NYC Health Department TB clinic:

- An appointment to review the results of the smear or culture is not routinely needed
- Patients are informed that they will be contacted by telephone if any result is positive
- If the smear is positive for AFB, the patient is recalled for three additional sputa specimens
    - If any specimen is culture-positive for *M. tuberculosis*, the patient is recalled immediately for a complete clinical re-evaluation and the reinstitution of appropriate therapy

SUMMARY

Successful DR-TB treatment outcomes are more likely when effective partnerships are initially established with all members of the treatment team, providers caring for other medical issues, and the patient and family members. BTBC providers craft individualized treatment regimens for DR-TB that are based upon a history of past TB disease treatment or exposure to an infectious person with DR-TB, DST results of the patient's TB isolate, and mutation analysis. Adverse effects of second-line medications are often serious and intolerable; such treatment decisions should be made in consultation with BTBC. BTBC supports ATS/CDC/ERS/IDSA guidelines for the treatment of MDR-TB. Shorter all-oral regimens are increasingly used. This is a rapidly changing field and providers should be kept abreast of new recommendations.

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