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Management of drug-resistant TB is often complicated. Even under the best circumstances, successful treatment outcomes can be difficult to achieve compared to drug-susceptible disease.

Consultation with experts

Treatment of tuberculosis (TB) caused by drug-resistant organisms should be done by, or in close consultation with, an expert in the management of these difficult cases. Second-line regimens often present the patient's best hope for cure, and inappropriate management of a drug-resistant case can have life-threatening consequences.

Experts in the management of drug-resistant TB provide consultation and assistance in a number of ways. Experts can:

- Help with the design of the empiric treatment regimen in patients suspected of having drug-resistant disease, and later assist with the design of the definitive treatment regimen when drug resistance has been documented.
- Help in the decision to pursue rapid drug resistance testing in a patient with risk factors.
- Help with management of toxicities and adjustments of treatment regimens when medications need to be discontinued.
- Help with decisions about when treatment should or can be modified (i.e., discontinuation of injectable drugs).
- Educate the provider about possible drug-related adverse reactions and suggest monitoring strategies.
- Provide guidance in managing contacts to drug-resistant cases.

Providers caring for a known or potential case with drug-resistant TB should:

- Consult with a local or regional expert in the treatment of drug-resistant TB. Ideally, written communication will be shared for clarity of recommendations after the discussion.
- Have ready access to the expert so decisions can be made in a timely manner.
- Stay in contact with the expert and communicate on a regular basis.
- Consult with an expert before making changes in the treatment regimen.
- Consult an expert for help in addressing slow response and managing adverse reactions.

See Appendix 1, Expert Resources for Drug-Resistant TB.

Classification of anti-tuberculosis drugs

Anti-tuberculosis drugs have classically been categorized into first-, second-, and thirdline drugs, which is the primary system used in U.S. guidelines and in this *Survival Guide*. First-line drugs are traditionally those drugs that are used as the core drugs in the treat-

Proper treatment with a second-line regimen often represents the patient's best hope for cure. Seek expert consultation when considering treatment initiation for drug-resistant TB. ment of drug-susceptible TB. Second-line drugs include the fluoroquinolones, aminoglycosides/polypeptides, and other drugs that are used to treat multidrug-resistant (MDR-) TB. Third-line drugs are also used to treat drug-resistant TB but typically have less activity, more adverse reactions, and less evidence supporting their use than first- and second-line drugs.

The classification system adopted by the World Health Organization (WHO) further divides the drugs into 5 groups. The 5-group system is based on efficacy, experience of use, safety, and drug class. Where new drugs fall within these systems has not been determined. The relationship between these two classification systems, and the primary anti-tuberculosis drugs currently in use globally, are shown in Figure 1.

FIGURE 1.

Comparison between standard U.S.-based classification and the WHO classification system for anti-tuberculosis drugs



1. Linezolid: Traditionally classified as third-line drug, but now often used as a second-line agent in the United States (but considered WHO Group 5)

2. Kanamycin, prothionamide, terizidone, and delamanid: Not currently available in the United States

3. Clavulanate (available as amoxicillin/clavulanate): Recommended as an adjunctive agent to imipenem/cilastatin and meropenem

Starting an expanded empiric treatment regimen

Molecular diagnostics have greatly decreased the time to obtain results from drug susceptibility tests (DST), allowing earlier initiation of an appropriate treatment regimen while awaiting additional phenotypic results. For many drugs, however, accurate molecular tests are not available and the risk of drug resistance must be anticipated. **Treatment for drug-resistant TB may need to be initiated even before susceptibility results** (molecular or growth-based) are available.

The decision to start an expanded empiric regimen (inclusion of second-line drugs), prior to DST results, will be determined by the level of suspicion for drug-resistant TB and the severity of illness. When suspicion for drug-resistant TB is high (e.g., concern for treatment failure or previous treatment, especially if self-administered), then an expanded empiric treatment regimen may be warranted. An expanded regimen is especially important in cases with life-threatening TB.

Who to consider for an expanded empiric MDR-TB regimen

- Patients in whom TB treatment is failing (i.e., who remain culture positive after 4 months of treatment)
- Persons who have been previously treated for TB
- Contacts to drug-resistant cases of TB
- Persons who were born in countries or reside in settings where drugresistant TB is prevalent

There are situations in which it may be more appropriate to initiate a 4-drug (firstline) regimen or to defer treatment completely until drug-susceptibility results are available.

- This is particularly true if an inappropriate regimen may risk amplification of drug resistance. If few treatment options remain, definitive treatment may be the patient's last chance for cure.
- Deferring treatment until drug-susceptibility results are available is an appropriate option only if the patient is not severely ill and can be isolated to prevent infection of contacts.
- Initiation with an empiric 4-drug (first-line) regimen may be appropriate if prior first-line treatment for pan-sensitive disease was completed under well-documented directly observed therapy (DOT) conditions, and primary suspicion is relapse due to the original strain.

Given the importance of having drug-susceptibility results, every effort should be made to obtain high-quality specimens for culture and DST.

Expanded empiric treatment regimen

An expanded empiric regimen usually consists of the 4 first-line drugs (isoniazid [INH], rifampin [RIF], ethambutol [EMB], pyrazinamide [PZA]) and 2 or more additional drugs. Additional drugs to consider include:

- A later generation fluoroquinolone
- An injectable agent, other than streptomycin (SM); because of the frequency of SM resistance in the world, better alternatives would be amikacin (AK) or capreomycin (CM)
- Consider use of linezolid (LZD), ethionamide (ETA), cycloserine (CS), or para-aminosalicylate (PAS)

The use of the standard 4 first-line drugs with the addition of a single drug (a fluoroquinolone or an injectable agent) is not a sufficient expanded empiric regimen for MDR-TB. When extensive disease or resistance is suspected, do not limit the empiric regimen to just 6 drugs.

When choosing the injectable agent and other second-line drugs, consider:

- The previous treatment history of the patient
- The drug-resistance pattern of the source case
- The likely patterns of resistance in the patient's region of origin

The treatment regimen can be changed once the DST results are available.

Individualized treatment regimens

Once drug resistance has been documented, the following individualized treatment regimens are recommended:

Mono-resistant *Mycobacterium (M.) tuberculosis* Isolated resistance to INH

INH mono-resistance is one of the most common forms of drug resistance. WHO, American Thoracic Society (ATS), and Infectious Diseases Society of America (IDSA) recommend **RIF, EMB, and PZA ± a later generation fluoroquinolone for 6-9 months.** The optimum regimen for the treatment of INH mono-resistant tuberculosis is unknown; however, effective treatment regimens are readily available.

- A 2009 systematic review/meta-analysis by Menzies, et al., found that among patients with INH mono-resistant TB, outcomes were improved with longer duration of RIF and PZA, use of daily treatment (not intermittent treatment) and with greater numbers of effective drugs.
- Studies in the United States have reported relapse rates of 2 to 5% using 3- to 4-drug regimens administered for 6 or more months. However, a large proportion (26-59%) of patients had treatment discontinued or the duration of treatment extended because of drug-related adverse reactions, usually associated with PZA.
- Treatment outcomes do not differ based on whether the isolate has low- or highlevel INH resistance *in vitro*.

- Addition of a fluoroquinolone was associated with improved outcomes in studies from Taiwan and the Republic of Korea.
- In the RIFAQUIN trial, a 6-month regimen that included daily RIF, EMB, PZA and moxifloxacin (MFX) (400 mg) for 2 months followed by once-weekly doses of both MFX and high-dose rifapentine (RPT) (1200 mg) for 4 months, was reported to be as effective as a standard 6-month regimen in drug-susceptible TB. Therefore, the 6-month regimen should be effective for INH mono-resistant TB as long as the isolate is susceptible to the fluoroquinolones.

Conclusion: Based on current evidence, there are at least 3 options for treatment of patients with INH-resistant disease.

OPTION 1: Daily RIF, EMB, and PZA (± fluoroquinolone), all given for 6 to 9 months depending on the microbiologic, clinical, and radiographic response to treatment

- If a patient was initiated on a standard 4-drug regimen, INH can be stopped when resistance is documented, and RIF, EMB, and PZA continued.
- Continuation of INH in the setting of documented isolated resistance to INH is not necessary, given the high cure rate with this regimen.
- A fluoroquinolone may be added to the regimen, especially in patients with extensive and/or cavitary disease. (Confirm fluoroquinolone susceptibility.)

OPTION 2: If the patient does not tolerate PZA, a regimen consisting of RIF, EMB and a later-generation fluoroquinolone for 9-12 months could be used

Confirm fluoroquinolone susceptibility.

OPTION 3: Daily RIF, EMB, PZA and MFX (400 mg) for 2 months followed by onceweekly doses of both MFX and high-dose RPT (1200 mg) for 4 months

Confirm fluoroquinolone susceptibility.

Isolated resistance to RIF

RIF mono-resistance is uncommon but increasing in some areas of the world. The loss of RIF from the treatment regimen requires a longer duration of therapy.

- Resistance to RIF is associated in most cases with cross-resistance to rifabutin (RFB) and RPT. In approximately 80% of strains where RIF resistance is documented, the strain is also resistant to RFB. Therefore, use RFB only when *in vitro* or molecular susceptibility is documented. Some experts may use RFB under these conditions, but not consider it a fully reliable drug in the regimen.
- Using molecular testing to identify the particular mutation associated with RIF resistance may help to rapidly identify isolates that retain susceptibility to RFB (see Chapter 3, Laboratory). This is also important as various labs use different cut points to test RFB susceptibility, and the molecular test is likely a better indicator.
- Resistance to RPT is universal in RIF-resistant isolates.

WHO recommends that patients with rifamycin mono-resistance be treated with a full MDR-TB regimen including INH until DST results to INH are available and appropriate adjustments can be made. However, in settings such as the United States where MDR-TB is relatively uncommon and reliable DST is readily available, other options are preferable:

OPTION 1 (preferred): INH, EMB, and a fluoroquinolone daily for 12 to 18 months, supplemented with PZA for at least 2 months during the intensive phase

OPTION 2: INH, EMB, PZA daily for 18 months

For both options 1 and 2:

- In patients with extensive cavitary disease, or to shorten the duration of therapy (e.g., 12 months), addition of an injectable agent for at least the first 2 months is recommended.
- Most experts would consider **Option 1** the preferred regimen.

OPTION 3: INH, PZA, SM daily for 9 months

• This option is generally not preferred, and susceptibility to SM must be documented.

Isolated resistance to EMB, PZA, or SM

Isolated resistance to EMB, PZA, or SM will have little impact on the efficacy of the treatment regimen.

- Loss of EMB or SM from the regimen will not decrease the efficacy or change the treatment duration.
- Loss of PZA from the regimen, however, requires prolonging the duration of therapy with INH and RIF by 3 months, for a total of 9 months of therapy.
- Most PZA mono-resistant isolates are due to M. bovis.

Poly-resistant M. tuberculosis

TB due to organisms that demonstrate *in vitro* drug resistance to more than 1 anti-TB drug (but not INH and RIF) is referred to as poly-resistant TB. Any number of combinations of resistance can occur, but the outcome of treatment is usually good.

• Treatment should include the use of as many first-line agents as possible plus a fluoroquinolone, and in some cases, an injectable drug.

Table 1 presents recommended regimens for the treatment of non-MDR drug-resistant TB.

TABLE 1.

Treatment regimens for the management of mono-resistant and poly-resistant TB

Pattern of drug resistance	Suggested regimen	Minimum duration of treatment (months)	Comments		
INH (± SM)	RIF, PZA, and EMB (± fluoroquinolone)	6–9 months	A fluoroquinolone may strengthen the regimen for patients with extensive disease. For additional options, see section: <i>Isolated resistance to</i> <i>INH.</i>		
INH and EMB	RIF, PZA, and fluoroquinolone	6–9 months	A longer duration of treatment should be used for patients with extensive disease.		
INH and PZA	RIF, EMB, and fluoroquinolone	9–12 months	A longer duration of treatment should be used for patients with extensive disease.		
INH, EMB, PZA (± SM)	RIF, fluoroquinolone, plus an oral second- line agent, plus an injectable agent for the first 2–3 months	9–12 months	A longer course (6 months) of the injectable may strengthen the regimen for patients with extensive disease.		
RIF	INH, EMB, fluoroquinolone, plus at least 2 months of PZA	12–18 months	An injectable drug may strengthen the regimen for patients with extensive disease. For additional options, see section: <i>Isolated resistance to</i> <i>RIF.</i>		
RIF and EMB (± SM)	INH, PZA, fluoroquinolone, plus an injectable agent for at least the first 2–3 months	12–18 months	A longer course (6 months) of the injectable may strengthen the regimen for patients with extensive disease.		
RIF and PZA (± SM)	INH, EMB, fluoroquinolone, plus an injectable agent for at least the first 2–3 months	18 months	A longer course (6 months) of the injectable may strengthen the regimen for patients with extensive disease.		
PZA	INH, RIF	9 months	Most commonly seen in <i>M. bovis</i> infections.		

Multidrug-resistant *M. tuberculosis* (MDR-TB)

Treatment of MDR-TB, defined as resistance to at least INH and RIF, requires a prolonged multidrug regimen. The optimal number of drugs, combination of drugs, and duration of therapy has not been established.

Number of drugs and stepwise approach to choosing

Recent reports of the outcomes of treatment for MDR-TB describe better outcomes in terms of lower rates of mortality, treatment failure, and recurrent TB, and faster rates of sputum conversion in those who received at least 5 likely effective drugs compared with 4 likely effective drugs. Taking into consideration current evidence and U.S. expert opinion, this *Survival Guide* recommends 4-6 likely effective drugs (and optimally at least 5) for the treatment of MDR-TB. Four drugs may be sufficient in some cases with limited disease and/or limited extent of resistance (e.g., a patient with lymph node disease and resistant only to INH and RIF).

Data from another individual data meta-analysis reported treatment success was highest if at least 6 drugs were used in the intensive phase and 4 in the continuation phase in the treatment of XDR-TB.

Figure 2 describes a step-wise approach to building an individualized MDR-TB regimen.

FIGURE 2.

Building a Treatment Regimen for MDR-TB



1 Not available in U.S.

2 SM: use only if not previously used and if documented susceptibility

3 Although traditionally considered a third-line drug, many experts now use LZD as a second-line drug option

4 Awaiting FDA approval

Duration of therapy

The optimal duration of therapy is not known. Based on expert opinion, the 2003 ATS/ IDSA/CDC guidelines recommended 18-24 months of therapy depending on the extent of disease and resistance pattern. Earlier editions of this *Survival Guide* expanded upon these recommendations to suggest minimum treatment durations for MDR-TB of 18-24 months beyond culture conversion, again based on expert opinion. New U.S. guidelines that specifically address treatment for drug-resistant TB are under development, as are updates to the 2011 recommendations by WHO.

• The only study that has attempted to define the optimum duration of therapy was the individual patient meta-analysis used by WHO to formulate the 2011 treatment recommendations.

WHO 2011 treatment recommendations for MDR-TB

WHO recommendations were based on the results of a systematic review and individual patient meta-analysis that included 32 studies and over 9,000 patients (XDR-TB patients were excluded) reported by Ahuja, et al., in 2012. Based on this review:

- WHO recommends that patients with MDR-TB be treated with at least 4 likely effective drugs as well as PZA during the intensive phase, defined as the time that the injectable is being given.
- Drugs likely to be effective are those that have not been taken previously by the patient and/or to which *in vitro* drug susceptibility has been documented.
- Regimens should include an injectable (AK, CM, KM), a higher-generation fluoroquinolone, ETA, and either CS or PAS (if CS cannot be used), and PZA.
- In patients with highly-resistant organisms, Group 5 drugs may be needed. These should be chosen in consultation with someone who has experience using these drugs to treat MDR-TB.

WHO recommendations for duration of therapy:

- Intensive phase should be at least 8 months in duration.
- Total duration of therapy should be at least 20 months in those who have never been previously treated for MDR-TB, and at least 24 months in those previously treated for MDR-TB.

Concerns exist regarding the applicability of the WHO individual patient meta-analysis to U.S.-based care of drug-resistant TB. More evidence for practice guidance on optimum treatment duration using an individualized approach (based on phenotypic and genotypic DST) is needed. With the capacity for earlier diagnosis using rapid molecular methods, successful and safer application of LZD, and strong overall treatment success rates, U.S. expert consensus continues to support utilization of culture conversion as the primary guide for minimum treatment duration within the practice conditions of a high-resource setting. On an individual basis, the extent of disease, resistance pattern, and clinical response to treatment will influence final regimen choices and treatment duration.

Recommended duration of therapy, based on current U.S. expert opinion and practice

As with drug-susceptible TB, the treatment is typically divided into two periods: **intensive phase** and **continuation phase**. The intensive phase is the initial period during which the injectable agent is administered. The period of treatment after the injectable agent is removed is referred to as the continuation phase. Newer regimens under investigation may not include two distinct phases.

- Intensive phase: recommend at least 6 months beyond culture conversion for the use of injectable agent.
- Total duration treatment: recommend at least 18 months beyond culture conversion.

There may be patients in whom a shorter duration of therapy would be sufficient, as good treatment outcomes with 9–12 months of therapy have been reported (see section: *Short-course regimens*). Some experts would use shorter treatment durations in patients with **minimal radiographic disease, low bacillary burden**, and **children**. Studies have shown that, in patients who have converted cultures to negative within 2–3 months, treatment success is highly likely to be achieved.

As newer and more effective drugs become available, the strength of the regimen and treatment response may be the most important factors in determining treatment duration.

Short-course regimens

Recent studies have reported excellent treatment outcomes using shorter durations of therapy than typically used for the treatment of MDR-TB.

- As reported in 2010 by Van Duen, et al., a 9-month regimen consisting of clofazimine (CFZ), high-dose gatifloxacin (GFX), EMB, and PZA throughout the course of treatment, supplemented by prothionamide, KM, and high-dose INH for a minimum of 4 months was associated with a relapse-free cure of 88% among 206 patients with MDR-TB in Bangladesh.
- In a 2014 follow-up report including 515 consecutive patients, the 4-month intensive phase was extended until culture conversion. Of the 515 patients enrolled into the observational study, 84.4% had a bacteriologically successful outcome. Due to extensive disease, only half of the patients completed treatment within 9 months but 95% did so within 12 months. The strongest predictor for a bacteriologically unfavorable outcome was high-level fluoroquinolone resistance, particularly when compounded by initial PZA resistance.
- In Niger, 75 patients with MDR-TB were prospectively followed and treated with a standardized 12-month regimen similar to the aforementioned studies. Cure was achieved in 58 (89.2%) of patients.
- Among 150 MDR-TB patients in Cameroon, 89% successfully completed treatment with a 12-month standardized regimen.

Conclusion: There is growing evidence that optimizing the use of currently available drugs can shorten treatment duration for MDR-TB to 9-12 months. These results must be confirmed in a randomized clinical trial before becoming the standard of care.

Selection and dosing of individual drugs: Additional considerations when building an MDR-TB regimen

Design of the treatment regimen can be difficult and must take into account several factors.

When building the treatment regimen, consider:

- In vitro susceptibility results of the drugs
- Cross-resistance
- Whether the patient has taken the drug before
- Potential overlapping drug toxicity or tolerability issues

Cross-resistance

Providers must be aware of the potential for cross-resistance when using DST results to guide the building of an individualized regimen. While mutations associated with resistance to specific drugs and those that confer risk for cross-resistance are clearly described for some anti-TB drugs, it is important to note that for many of the drugs currently in use, neither the mutations nor mechanisms for resistance are known.

Be aware of potential cross-resistance that can occur between certain drug classes (Table 2).

Avoid drugs used previously to treat the patient's TB

Data from National Jewish Health suggest that patients who have taken a drug for over 1 month in the past have less effect from that drug, even if *in vitro* susceptibility tests demonstrate the isolate to be susceptible. Despite this, most experts recommend that first-line drugs with documented susceptibility be included in the treatment regimen. Some experts may choose not to count previously used drugs as one of the target 4-6 likely effective drugs.

Consider side effects when choosing drugs

For example, in someone with depression, it may be desirable to avoid **CS**. When possible, try to avoid using drugs that have similar toxicity profiles. For example, the combination of **PAS** and **ETA** increases the risk of hypothyroidism and gastrointestinal toxicity. On the other hand, in some patients there is no choice because these may be the only drugs

TABLE 2.

Cross-resistance for anti-tuberculosis drugs

Drug	Cross-Resistance	Comments
Isoniazid	Ethionamide	Cross-resistance to ethionamide is very common (up to 70%) when there is low-level resistance to isoniazid due to a mutation in <i>inhA</i> or the promoter region.
Rifampin	Rifamycins	Cross-resistance among the rifamycin class of drugs is typical. In <20% of strains that are resistant to rifampin, rifabutin may retain susceptibility <i>in vitro</i> . The clinical significance of this is unknown.
Ethambutol	None	
Pyrazinamide	None	
Streptomcyin	Kanamycin	Rarely may be cross-resistant to kanamycin.
Amikacin	Kanamycin	High likelihood of cross-resistance because it is associated with the same mutations (<i>rrs</i>).
Kanamycin	Amikacin	High likelihood of cross-resistance because it is associated with the same mutations (<i>rrs</i>). However, there are some kanamycin mutations (<i>eis</i>) that do not cause amikacin resistance.
Capreomycin	Amikacin/Kanamycin	Variable frequency of cross-resistance has been reported.
Fluoroquinolones	Other fluoroquinolones	In general, there is a complete class effect cross-resistance among fluoroquinolones <i>in vitro</i> . However, data suggest that moxifloxacin may continue to demonstrate some activity despite <i>in vitro</i> resistance to ofloxacin. For details, see Chapter 3 , <i>Laboratory</i> , Table 3.
Cycloserine	None	
PAS	None	
Ethionamide	Isoniazid	Low-level cross-resistance to isoniazid may occur due to mutation in <i>inhA</i> or the promoter region.
Clofazimine	Bedaquiline	Cross-resistance has been demonstrated in both directions through efflux-based resistance.
Linezolid	None	
Bedaquiline	Clofazimine	Cross-resistance has been demonstrated in both directions through efflux-based resistance.
Delamanid	None	Evidence for cross-resistance to Investigational drug PA-824.

to which the isolate is susceptible, and hypothyroidism can easily be managed with the addition of thyroid replacement medications until treatment completion. Additionally, in persons with renal or hepatic disease, certain drugs may be safer. Ultimately, the safest and most effective drugs to complete the treatment regimen should be chosen. It is important to recognize that some drugs, such as the aminoglycoside/polypeptide antimicrobials, should be stopped prior to completion of therapy. Therefore, the patient should receive a sufficient number of drugs from the beginning of therapy, i.e. 4 to 6 likely effective drugs (and optimally at least 5), to make sure that there are at least 3 to 5 oral drugs remaining after the injectable is discontinued. Ultimately, the safest and most effective drugs to complete the treatment regimen should be chosen.

- TREATMENT
- It is important to note that intolerance to 1 agent does not necessarily mean the patient will be intolerant to another agent in the same classification group.
- Given the limited number of drug options, every effort should be made to manage side effects to maintain an adequate and effective regimen. See Chapter 9, Adverse Reactions, for details on management of side effects.

Individual regimens for specific MDR-TB resistance patterns

Resistance to INH and RIF

A regimen consisting of an injectable agent during the intensive phase (for at least 6 months beyond culture conversion), and PZA, EMB, and a newer-generation fluoroquino-lone (MFX or high-dose levofloxacin [LFX, 750-1000 mg] and 1 additional oral agent (LZD, ETA, CS or PAS) given for at least 18 months beyond culture conversion is recommended. In patients with extensive or cavitary disease, a longer duration for the injectable agent may be considered, as well as an additional oral drug. The use of more than 1 additional oral drug should be considered if there has been prior use of PZA or EMB.

Resistance to INH, RIF, and EMB

A regimen consisting of an injectable agent during the intensive phase (for at least 6 months beyond culture conversion), and PZA, a newer-generation fluoroquinolone (MFX or high-dose LFX [750-1000 mg]), and 2 additional oral agents (LZD, ETA, CS, or PAS) for at least 18 months beyond culture conversion is recommended. In patients with extensive or cavitary disease, a longer duration for the injectable agent may be considered, as well as an additional oral drug.

Resistance to INH, RIF, and PZA

A regimen consisting of an injectable agent during the intensive phase (for at least 6 months beyond culture conversion), and EMB, a newer-generation fluoroquinolone (MFX or high-dose LFX [750-1000 mg]), and 2 additional oral agents (LZD, ETA, CS, or PAS) for at least 18 months beyond culture conversion is recommended. In patients with extensive or cavitary disease, a longer duration for the injectable agent may be considered, as well as an additional oral drug.

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Resistance to INH, RIF, PZA, and EMB

A regimen consisting of an injectable agent during the intensive phase (for at least 6 months beyond culture conversion), and a newer-generation fluoroquinolone (MFX or high-dose LFX [750-1000 mg]), and 3-4 oral agents (LZD, ETA, CS, PAS or additional third-line agents if needed) should be given for at least 18 months beyond culture conversion. In patients with extensive or cavitary disease, a longer duration for the injectable agent may be considered.

Resistance to all first-line drugs and fluoroquinolones (Pre-XDR-TB)

In this setting, a regimen containing an injectable agent such as an aminoglycoside or polypeptide (e.g., CM) is critical. Consider extended use of an injectable agent for at least 12 months if tolerated. Additionally, 4–5 second- and third-line oral drugs (WHO Groups 4 and 5) should be used. LZD, bedaquiline (BDQ) or delamanid (DLM) (if available) should be used when possible. However, caution should be used if BDQ and DLM are given together as there are currently no safety data available for co-administration of these drugs. High-dose MFX can be considered unless there is documented *in vitro* resistance to high concentrations of the drug (MIC \geq 3). See **Chapter 3**, **Labo**-

Treatment must be more aggressive in situations where the patient has extensive resistance, extensive disease, or multiple previous failed treatment efforts. The duration of therapy will depend on the anti-tuberculosis drugs used, the extent of the disease, and treatment response.

ratory. Treat the patient for at least 24 months. Therapeutic drug monitoring (TDM) may be useful in this situation. Consider surgery if there is focal cavitary disease.

• Consider extending treatment for at least 24 months beyond culture conversion.

Resistance to all first-line drugs and injectables (Pre-XDR-TB)

MFX (or high-dose LFX [750-1000 mg]) plus at least 4-5 second-line oral drugs (WHO Groups 4 and 5) should be used. LZD, BDQ or DLM (if available) should be used when possible. However, caution should be used if BDQ and DLM are given together as there are currently no safety data available for co-administration of these drugs. Treat the patient for at least 24 months. TDM may be useful in this situation. Consider surgery if there is focal cavitary disease.

• Consider extending treatment for at least 24 months beyond culture conversion.

The chance of cure diminishes as the patient's isolate acquires additional resistance.

Extensively drug-resistant *M. tuberculosis* (XDR-TB)

XDR-TB is defined as resistance to at least INH, RIF, a fluoroquinolone, and 1 of **3** second-line injectable agents (AK, KM, or CM). Treatment of patients with XDR-TB is challenging because of the lack of potent anti-TB drugs, frequency of adverse reactions, and poor treatment outcomes. However, the approach to designing a treatment regimen is the same as with MDR-TB (Figure 2). Surgery should be a consideration in patients with XDR-TB.

- In a 2010 systematic review and meta-analysis by Jacobson, et al., evaluating 13 observational studies including 560 patients, the pooled treatment success rate was 43.7% with a mortality of 20.8%.
 - Patients who received a later-generation fluoroquinolone reported a higher proportion of favorable treatment outcomes (p = 0.012) despite documented in vitro resistance to earlier generation fluoroquinolones.
- Results from the 2013 individual data meta-analysis by Falzon, et al., reported treatment success was highest if at least 6 drugs were used in the intensive phase and 4 in the continuation phase. New drugs such as BDQ and DLM were not included in this analysis.
- Treatment success has varied with worsening outcomes as additional resistance occurred. Treatment success for MDR only, MDR + injectable, MDR + fluoroquinolone, XDR was 64%, 56%, 48%, 40%, respectively.
- Among XDR-TB patients, the odds of treatment success are lower in those with isolates resistant to all second-line injectables.

Conclusion:

- Based on these studies, XDR-TB patients should be treated with **at least 6 likely** effective drugs, if possible.
 - Repurposed or new drugs such as LZD, BDQ, and DLM (if available) should be strongly considered.
 - High-dose MFX (600-800 mg daily) should be used unless there is documented *in vitro* resistance to high concentrations of the drug.
 - Consider high-dose INH treatment if only low-level resistance is documented.
 - Use PZA and/or EMB if organism remains susceptible.
 - Consider CFZ.
 - Meropenem (MPM) or imipenem (IMP) are additional choices.
- When resistance to AK has been documented or in the setting of an empiric regimen for suspected XDR-TB, CM is the injectable of choice. If the injectable agent is a key component necessary for an effective regimen, duration should be at least 12 months (or potentially longer if tolerated).
- Duration of treatment for XDR-TB should be at least 24 months beyond culture conversion.
- Expert consultation should be obtained to assist management throughout the treatment duration.

Table 3 presents recommended regimens for the treatment of MDR/XDR-TB.

TABLE 3.

Treatment regimens for the management of patients with MDR/XDR-TB

Pattern of drug resistance	Suggested regimen	Minimum duration of treatment	Comments			
INH and RIF (± SM)	PZA, EMB, newer-generation fluoroquinolone (MFX or high-dose LFX), and injectable agent during the intensive phase (for at least 6 months beyond culture conversion), and 1 additional oral agent (LZD, ETA, CS or PAS).	18 months beyond culture conversion	In patients with extensive or cavitary disease, a longer duration for the injectable agent may be considered, as well as an additional oral drug. Consider using more than 1 additional oral drug if there has been prior use of PZA or EMB.			
INH, RIF (± SM), and EMB or PZA	EMB or PZA (if available), a newer- generation fluoroquinolone (MFX or high-dose LFX), injectable agent during the intensive phase (for at least 6 months beyond culture conversion), and 2 additional oral agents (LZD, ETA, CS, or PAS).	18 months beyond culture conversion	In patients with extensive or cavitary disease, a longer duration for the injectable agent may be considered, as well as an additional oral drug.			
INH, RIF, EMB, PZA (±SM)	Injectable agent during the intensive phase (for at least 6 months beyond culture conversion), and a newer- generation fluoroquinolone (MFX or high-dose LFX), and 3-4 oral agents (LZD, ETA, CS, PAS or additional second- or third- line agents if needed).	18 months beyond culture conversion	In patients with extensive or cavitary disease, a longer duration for the injectable agent may be considered.			
INH, RIF, EMB, PZA, fluoroquinolone (Pre-XDR)	4-5 second- or third-line drugs (include LZD, BDQ, or DLM) and an injectable agent.	24 months beyond culture conversion	Duration of injectables should be at least 12 months if tolerated. Consider high-dose MFX. Consider surgery. TDM may be useful.			
INH, RIF, EMB, PZA, injectables (Pre-XDR)	MFX (or high-dose LFX) plus at least 4-5 second- or third-line oral drugs. Include LZD, BDQ, or DLM, if available. Include an injectable drug if there is 1 available to which the isolate is susceptible.	24 months beyond culture conversion	Consider surgery. TDM may be useful.			
INH, RIF, fluoroquinolone, injectable (XDR)	5-6 second- and third-line agents. LZD, BDQ, or DLM should be used; high-dose MFX can be added (unless documented resistance). Use PZA and/or EMB if remains susceptible. Include an injectable drug if there is 1 available to which the isolate is susceptible.	24 months beyond culture conversion	Consider high-dose INH treatment if low-level resistance is documented. Consider surgery. TDM may be useful. For more recommendations, see section: XDR-TB.			

Specific drugs First-line (WHO Group 1)

PZA

PZA is an essential first-line drug that allows shortening of an INH- and RIF-based regimen to 6 months. Its role in the treatment of MDR-TB has been uncertain because of limited availability, reliability, and reproducibility of phenotypic DST.

WHO recommends that PZA be included in all treatment regimens for MDR/XDR-TB. This recommendation is based on a systematic review and meta-analysis that reported a small benefit in treatment outcomes when PZA was included in MDR-TB regimens.

- In a 2012 retrospective analysis of the outcomes of MDR-TB in Hong Kong by Chang, et al., 194 patients were stratified by PZA use and drug susceptibility. PZA users with documented PZA susceptibility were more likely to demonstrate early culture conversion and treatment success than non-PZA users and PZA users with PZA-resistant organisms.
- In a 2015 retrospective study by Franke, et al., of 668 patients with MDR-TB in Peru, the mortality rate for a regimen of 5 likely effective drugs, including likely effective PZA (usually based on DST results), was similar to that for regimens of 5 likely effective drugs without PZA. There was no demonstrated benefit of PZA when the drug was considered unlikely to be effective.

Conclusion: Based on the studies noted, PZA should be included if deemed likely to be effective (drug susceptible and/or never used). In situations in which PZA resistance is documented, the drug may be discontinued.

Rifamycin

The rifamycins (RIF, RFB, RPT) are essential first-line drugs for the treatment of drugsusceptible TB. Loss of RIF from the treatment regimen results in the need to prolong the duration of therapy to 12-18 months. By definition, MDR- and XDR-TB are resistant to RIF *in vitro* or by molecular assays documenting mutations in the *rpoB* region of the genome.

- RIF-resistant strains may be susceptible to RFB in <20% of strains tested by various DST methods. Susceptibility to RFB and resistance to RIF is strongly associated with a specific mutation Asp-516-Val which can be identified by line-probe assays or sequencing.
- RPT should not be used to treat MDR- or XDR-TB because cross-resistance with RIF is 100%.

Conclusion: RFB should be considered for addition to the MDR-TB treatment regimen when *in vitro* susceptibility has been documented in a reliable laboratory and especially if molecular assays document the Asp-516-Val mutation. Under these conditions, most experts would consider RFB as an adjunct to a regimen containing 4-6 likely effective drugs.

Second-line: Injectable agents (WHO Group 2)

The aminoglycosides (KM and AK) and polypeptide (CM) are active *in vitro* against *M. tuberculosis* and represent a critical component in treatment regimens during the initial phase of therapy. They can be given either intramuscularly (IM) or intraveneously (IV). SM is relatively well tolerated, but resistance to this drug is common. Many experts avoid the use of SM, even if testing shows susceptibility, if the drug has been used before. There have been no clinical trials comparing the effectiveness of the different injectables. When choosing an aminoglycoside or polypeptide agent, weigh toxicity profiles, cost, and likelihood of cross-resistance of the different drugs.

- In the WHO sponsored meta-analysis, no second-line parenteral agent was found to be superior (except that CM was more effective if the case was resistant to kanamycin [KM]).
- All of the injectable agents have potential for renal toxicity and electrolyte disorders.
- **AK** has excellent *in vitro* activity against *M. tuberculosis* and is widely available in the United States. It is easier to obtain AK serum concentrations than CM concentrations. Ototoxicity and vestibular toxicity are more common with AK than CM. The volume of injection for AK IM is larger than for the comparable dose of CM.
- **CM** has less ototoxicity and vestibular toxicity than AK and is more expensive, but the drug has been well tolerated when given for long periods of time.
- Significant electrolyte disturbances can occur with CM (as well as with the aminoglycosides), so close monitoring is required. There are case reports of safe use of CM in pregnancy and during breast-feeding. See Chapter 7, Co-Morbidities and Special Situations, section on Pregnancy.
- **SM** should be considered in patients with XDR-TB in whom the drug is likely to be effective (*in vitro* susceptible and no history of prior use). SM may be less painful than AK when given IM.
- **KM** is no longer available in the United States.

Cross-resistance among injectables

Resistance to the aminoglycosides and polypeptides is most commonly conferred through a mutation in the *rrs* gene. Studies have reported variable rates of cross-resistance among these drugs, but in general:

- **AK**-resistant isolates are resistant to KM and occasionally CM.
- KM-resistant isolates are usually resistant to AK and possibly CM.
- **CM**-resistant isolates are variably resistant to KM and AK.
- **SM**-resistant isolates are usually susceptible to **other injectables** unless the other drugs have been used previously.

Conclusion: AK is usually the first choice for an injectable, because of the ease of procurement, administration, and of obtaining serum levels. **CM** should be reserved for situations in which there is demonstrated resistance to **AK** and in patients with XDR-TB, and possibly if there is pre-existing hearing loss. **CM** may also have a role in pregnant MDR-TB patients.

Second-line: Fluoroquinolones (WHO Group 3)

The fluoroquinolones have potent *in vitro* and *in vivo* activity against *M. tuberculosis* and the loss of a fluoroquinolone from an MDR treatment regimen is associated with poor treatment outcomes. Data from *in vitro*, murine, and human studies have demonstrated that later generation fluoroquinolones (LFX, MFX, GFX) are more active than ciprofloxacin or ofloxacin (OFX) and in a murine model; MFX had superior efficacy compared with LFX.

- WHO recommends that all patients with MDR-TB receive a later generation fluoroquinolone (and specifically avoid the use of ciprofloxacin). In the individual patient meta-analysis used to formulate WHO recommendations, use of the fluoroquinolones was associated with cure and this association was strongest with later generation fluoroquinolones.
- In two retrospective studies, LFX (500-1000 mg/day) and MFX (400 mg/day) showed similar treatment success in MDR-TB patients.
- In a 2012 randomized open label trial by Koh, et al., LFX (750 mg/day) and MFX (400 mg/day) were shown to have similar culture conversion rates at 3 months.

Resistance to the fluoroquinolones is conferred by mutations in gyrase A and B. Cross-resistance among the fluoroquinolones is common but not universal. Recent studies report that approximately 30% of OFX-resistant strains are still susceptible to MFX. Several recent studies have evaluated the significance of this retained susceptibility.

- *In vitro* data and murine models have demonstrated better treatment outcomes with use of later generation fluoroquinolones in the setting of OFX resistance.
- A 2010 systematic review/meta-analysis by Jacobson, et al., reported that use of a later generation fluoroquinolone in the setting of XDR-TB was associated with better treatment outcomes.
- In a 2014 retrospective study from the Republic of Korea by Jo, et al., MDR-TB patients with OFX-resistant disease had significantly better treatment outcomes when the isolate was MFX-susceptible (treatment success in 73% vs. 42%).

Potential side effect profiles may influence choice of fluoroquinolones. Some general considerations include:

- LFX has less effect on the QT interval compared with MFX; therefore, LFX may be warranted in some cases where this is a concern such as in cases receiving CFZ and BDQ. LFX requires dose-adjustment with renal impairment (if creatinine clear-ance <50 mL/min), but is presumed to be safe to use with liver disease.
- MFX does not require dose adjustment in renal failure, but is infrequently associated with hepatotoxicity and thus should be used with caution in cases of liver impairment.
- For more details see Chapter 5, *Medication Fact Sheets.*

Conclusion: MFX or high-dose LFX (750-1000 mg) should be used in the treatment of all cases of MDR- and XDR-TB except in the setting of documented *in vitro* resistance to high concentrations of MFX. Recent studies suggest no clinical advantage between MXF or LFX for MDR-TB. When fluoroquinolone resistance is found by critical concentration or by molecular testing, an MIC—usually for MFX—can help inform whether an increase in dose may benefit the patient. Although there is minimal published evidence to support this approach, some MDR-TB experts use "high-dose" MFX at 600mg or 800mg daily for patients with MFX MIC of 1 or 2 mcg/mL. Potential side effect profiles may influence the

choice between these two agents. For further information on use of MICs or on mutations for fluoroquinolone resistance, see **Chapter 3**, *Laboratory*.

Second-line: Other oral agents (WHO Group 4) LZD

LZD has traditionally been considered a third-line agent, but many experts now utilize this drug as a second-line drug, and in some circumstances, as a preferred agent over other second-line and third-line drugs when building a regimen. LZD exhibits variable activity *in vitro*, modest activity in murine models, and limited early bactericidal activity at 600 mg once or twice daily. Despite the limited activity in these settings, there are case reports, observational reports, and two randomized studies that suggest excellent activity in humans, although the drug is associated with a high frequency of adverse events.

- In a systematic review (11 studies, 148 patients) the pooled success rate was 68% with no significant difference in success with ≤ 600 mg vs > 600 mg per day. Pooled estimate of any adverse event was 62%, with 36% discontinuing LZD due to adverse events.
- In 2 randomized studies, XDR-TB patients treated with LZD had higher culture conversion and treatment success than those in control arms.
 - However, in both studies, 82% of the patients had clinically significant adverse events; of these patients, 93% had events that were possibly or probably related to LZD. A 300 mg dose was associated with a lower rate of adverse reactions, but there was a trend towards acquired resistance at the lower dose.
- Early experience with LZD documented high rates of myelosuppression and neurologic toxicity (with peripheral and optic neuropathy often not reversible). Reduction in the dose from 600 mg twice daily to once daily was associated with reduced hematologic toxicity but neurotoxicity remained high with discontinuation rates as high as 70%.
- Administration of LZD concurrently with serotonergic agents, i.e. antidepressants such as selective serotonin reuptake inhibitors (SSRI), can lead to serious (sometimes fatal) reactions such as serotonin syndrome or neuroleptic malignant syndrome-like reactions.
- Using 300 mg per day, Koh, et al., in the Republic of Korea reported good treatment outcomes in XDR-TB patients, but still reported discontinuation of LZD in 27% of the patients due to peripheral neuropathy and optic neuritis.

Conclusion: LZD is an active drug and should be considered for all MDR- and XDR-TB regimens. In order to avoid hematologic toxicity, LZD should be given once daily at 600 mg per day. Patients should be monitored closely for development of neurologic or hematologic toxicity, and the dose reduced to 300 mg per day in selected patients who develop toxicity.

ETA, CS, PAS

The drugs ETA, CS, and PAS are generally bacteriostatic (ETA may be weakly bactericidal at higher doses). There are few data supporting one drug over the other in terms of efficacy. In an individual data meta-analysis used to formulate current WHO recommendations, the association with cure was higher with ETA than CS, which was higher than PAS.

The decision of which drug(s) to use is often based on the side effect profile of the drug, the presence of low level cross-resistance, and the ability to measure drug serum concentrations (in the case of CS).

- Both PAS and ETA can have gastrointestinal side effects, and the combination of the two is likely to cause hypothyroidism.
- Mutations in the *inhA* region of *M. tuberculosis* can confer resistance to ETA as well as to INH at low concentrations. In this situation, ETA may not be the best choice of a second-line drug unless the organism has been shown to be susceptible with *in vitro* testing and/or no *inhA* mutation is detected.
- CS may be associated with significant neuropsychiatric adverse reactions, so serum drug concentrations should be measured. Use with caution in patients with pre-existing depression or other mental health issues. As the drug does not have significant gastrointestinal adverse reactions, it is a good companion drug with either ETA or PAS.

Conclusion: When choosing an oral second-line drug, **ETA** would be the first choice except in the setting of low-level INH resistance and/or the presence of an *inhA* mutation. The combination of ETA and PAS is associated with high rates of gastrointestinal intolerance and hypothyroidism.

Third-line (WHO Group 5)

CFZ

CFZ is approved for treatment of multibacillary *M. leprae*, but has been used also to treat drug-resistant TB and nontuberculous mycobacterial infections for which it has excellent activity *in vitro* and in murine models. Synergy has been demonstrated between CFZ and EMB or MFX *in vitro*. In November 2004, the manufacturer, Novartis, discontinued drug distribution in the United States. CFZ is now available through an investigational new drug (IND) application to the U.S. Food and Drug Administration (FDA). See **Chapter 5**, *Medication Fact Sheets* for procurement information.

- There have been three systematic reviews examining the use of CFZ for the treatment of MDR-TB. CFZ appears to be well tolerated (despite associated skin discoloration and photosensitivity).
 - Pooled severe adverse drug reactions were 0.1%, requiring withdrawal of CFZ.
 - Treatment success ranged from 17% to 88% with pooled proportion of 62% to 65%.
- CFZ-containing regimens have been associated with a higher percentage of culture conversion (40% vs 29%) and an independent predictor of conversion and survival in patients with XDR-TB.
- In a small randomized controlled trial, sputum culture conversion and cavity closure occurred earlier in patients in the CFZ-containing regimen, and treatment success was higher (74% vs. 54%).

Conclusion: CFZ appears to be a well-tolerated drug and likely contributes activity to a multidrug regimen.

Carbapenems

 β -lactam antibiotics undergo rapid hydrolysis by beta lactam enzymes in *M. tuberculosis* rendering them inactive. However, the combination of amoxicillin plus a β -lactamase inhibitor was shown to be active *in vitro* against *M. tuberculosis* and in an early bactericidal study in humans. Although the carbapenem antibiotics are poor substrates for β -lactam enzymes, they have variable *in vitro* and *in vivo* activity against *M. tuberculosis*. The combination of carbapenems with the β -lactamase inhibitor clavulanate has been shown to improve the MIC of MPM and is bactericidal in murine tuberculosis. Clinical experience with carbapenems for the treatment of MDR/XDR-TB is limited and the duration of treatment is generally restricted to the intensive phase.

- Eight of ten patients treated with intravenous **IMP** as part of a multidrug regimen converted sputum cultures to negative, and 7 remained culture negative after treatment.
- Five of six patients with severe XDR-TB converted cultures to negative with a regimen containing **MPM plus amoxicillin/clavulanate** (included as a source for clavulanate which is not available as a free-standing drug).

Conclusion: Based on these studies, it appears that a **carbapenem plus clavulanate** can be used as an active component of an MDR/XDR-TB regimen.

High-dose INH

Resistance to INH is most commonly conferred through mutations in *katG* or *inhA*. Resistance to *katG* results in inhibition of catalase activity and the development of high-level resistance (resistance at 1.0 mg/mL on solid media) to INH whereas mutations in *inhA* or the promoter region result in lower levels of resistance (resistance at 0.2 mg/mL). Theoretically, **it may be possible to overcome the resistance in the setting of low-level resistance by increasing the dose of INH.**

- Use of INH (standard dose) was associated with better survival rates in patients with the W-strain variety of multidrug-resistant *M. tuberculosis* that was susceptible to higher concentrations of INH.
- In a double-blind randomized controlled trial of high-dose INH (16-18 mg/kg) vs placebo in addition to second-line drugs, those who received high-dose INH were 2.38 times more likely to convert cultures to negative than those on placebo and they had a 2.37 times higher rate of being culture negative at 6 months. There was a higher frequency of peripheral neuropathy in the high-dose INH arm (but pyridoxine was not provided).

Conclusion: High-dose INH should be considered in patients whose isolate has low-level resistance *in vitro* and evidence of an *inhA* mutation with no evidence of a *katG* mutation.

New drugs

Bedaquiline (BDQ)

BDQ is a diarylquinoline drug with significant *in vitro* and *in vivo* activity against *M. tuber-culosis*. Both WHO and the CDC have issued guidelines for the use of BDQ in the treatment of MDR- and XDR-TB based on the following studies:

• Efficacy of the drug has been assessed in 3 Phase IIb studies, 2 of which were randomized placebo-controlled trials and the other a noncomparative single-arm openlabel trial.

- Sputum culture conversion at 8 weeks and 24 weeks was higher in the BDQ arm compared with placebo.
- A higher mortality was noted in the BDQ (12.6%) compared with the control arm (4.9%) in the 2014 Phase IIb studies by Diacon, et al. Seven patients died during the trial at a median of 386 days after the last dose. No common cause for the excess mortality was identified, but follow-up observational studies have not reported a high mortality rate.
- A total of 35 patients with MDR-TB, including 19 with XDR-TB, were treated with BDQ in a compassionate use protocol in France, reported by Guglielmetti, et al. At 6 months of treatment, culture conversion was achieved in 97%. Seven patients (20%) experienced a ≥ 60 milliseconds increase in QT interval leading to discontinuation in 2 (6%).
- CDC recommends that BDQ be used for 24 weeks of treatment in adults with laboratory-confirmed pulmonary MDR-TB when an effective treatment regimen cannot be provided without it. BDQ may be used on a case-by-case basis in children, HIV-positive persons, pregnant women, extrapulmonary MDR-TB, and patients with co-morbid conditions. It may be used on a case-by-case basis for longer than 24 weeks. EKG monitoring at baseline and 2, 12, and 24 weeks of treatment is advised.
- WHO recommends that BDQ may be added to a WHO-recommended regimen in adult MDR-TB patients when an effective treatment regimen containing 4 second-line drugs in addition to PZA cannot be designed, and when there is documented evidence of resistance to any fluoroquinolone in addition to multidrug resistance.
- Use of BDQ as a replacement for the injectable agent in MDR-TB is currently under investigation.
- Unfortunately, acquired resistance to BDQ has been reported.

Conclusion: BDQ is recommended for the treatment of MDR- and XDR-TB as part of a combination therapy (minimum 4-drug therapy) administered by DOT when an effective treatment regimen cannot be otherwise provided. There are currently no safety data on the concurrent use of DLM and BDQ.

Delamanid (DLM)

DLM is a nitro-dihydro-imidazooxazole derivative which was approved for the treatment of MDR-TB by the European Medicines Agency (EMA), but has not yet received FDA approval. Although data regarding the use of DLM in the treatment of MDR-TB are limited, WHO has issued recommendations for the use of DLM.

- In a 2012 randomized controlled trial published by Gler, et al., 481 patients were randomized to receive DLM 100 mg twice daily, 200 mg twice daily, or placebo for 2 months in combination with a WHO-recommended regimen. Sputum culture conversion in liquid broth occurred in 45.4% of the patients taking DLM at 2 months compared with 29.6% on the placebo regimen. QT prolongation was more common, but there were no clinical events related to QT prolongation.
- In an open label study by Skripconoka, et al., reported in 2013, mortality was reduced to 1% among those who received DLM for 6 months vs 8.3% in those who received ≤ 2 months in a combined analysis of 3 studies.

Conclusion: DLM appears to be an active agent in a multidrug regimen which should be considered for treatment of MDR/XDR-TB once the drug becomes available through FDA approval (or when obtained through a compassionate use program). There are currently no safety data on the concurrent use of DLM and BDQ.

Administration of the treatment regimen

Case management and appropriate DOT are key activities that contribute to quality care and successful outcomes in the treatment of drug-resistant TB.

For detailed information on monitoring and case management best practice, see **Chapter 8**, *Monitoring* and **Case Management**.

Outcomes of treatment are worse with MDR-TB compared with susceptible disease, and drug-related toxicities are common. Although the cure rate remains high with TB caused by mono-resistant organisms, additional resistance can develop as a result of treatment errors, nonadherence to treatment, or amplification of mono-resistance. Therefore, DOT is strongly recommended for all forms of drug-resistant TB.

Treat all forms of drug-resistant TB utilizing strong case management, DOT, and in consultation with experts in the treatment of resistant disease.

MDR-TB can be treated primarily in the outpatient setting.

- 1. DOT can be delivered in the field or clinic (or through newer video technology).
- Dosing of oral medications for MDR/XDR-TB should always be daily, not intermittent.
- **3.** Although 7-days-per-week DOT is optimal, this is may not be programmatically feasible. If 7-days-per-week is not possible, 5-daysper-week DOT can be used for patients who are not hospitalized or institutionalized, with medications self-administered on weekends.
- 4. Injectable agents are typically given 5 days per week for at least 2-3 months (and until culture conversion is documented); after which, 3-days-per-week dosing can be used for the remaining duration of injectable use, normally through at least 6 months beyond culture conversion.
- **5.** In patients who are severely ill, treatment should be administered 7 days per week (including the injectable drugs).

Treat all forms of drug-resistant TB utilizing strong case management, DOT, and in consultation with experts in the treatment of resistant disease.

Escalation of dosages (drug ramping)

Most drugs should be started at full dose except **CS**, **ETA**, and **PAS**, in which case the dose of the drug can be increased over a 1-2-week period. Beginning with a low dose and gradually increasing the dose leads to greater tolerability and allows the clinician time to manage drug-related adverse effects. This approach of slowly escalating drug dosage is referred to as "drug ramping." Obtain serum drug levels (especially for CS) 1-2 weeks after the goal dose has been reached. See examples of drug ramping in Figure 3.

FIGURE 3.

Dose escalation (drug ramping)



The patient is begun on a low starting dose and the dose is increased every few days until the targeted dose is reached. The dose escalation should be completed within 2 weeks. Some patients will tolerate consolidation of all three drugs to once daily dosing which can enhance adherence.

* For some patients, daily dose of cycloserine 500 mg may achieve goal serum concentration.

**Goal of PAS 6 gm daily may be appropriate for smaller patients.

Therapeutic drug monitoring (TDM)

When to order TDM

TDM is routinely used for several circumstances:

- **Aminoglycoside/CM** serum concentrations, especially in patients with renal impairment
- CS concentrations in order to minimize risk of central nervous system (CNS) toxicity and to safely use optimal dose
- Known or suspected malabsorption (e.g., diabetes, gastrointestinal disorders)
- Lack of expected clinical response or relapse while on appropriate drugs and doses, administered by DOT
- Patients with **few effective drugs** in their regimen, in order to optimize the effect of available drugs

- Patients with potentially significant drug-drug interactions such as rifamycins and antiretrovirals
- EMB concentrations in patients with significant renal impairment

Many drug-resistant TB experts routinely monitor certain TB drug concentrations in anticipation of toxicity and to escalate a drug dose when possible.

How to interpret results of TDM

Interpret drug levels in the context of several factors:

- Timing of blood draw relative to administration
- Evidence for poor response to treatment or side effects
- Known factors likely to increase or decrease clearance of drug (e.g., renal dysfunction, liver dysfunction, drug interactions)

Serum concentrations answer the question, "Does my patient have adequate drug exposure?"

- Published normal ranges, under most circumstances, represent safe and effective drug exposures.
- Like other tests, serum concentrations cannot by themselves predict failures or relapses. They can indicate if the patient has lower than expected drug exposure for a given dose of a given drug, and that problem is readily correctable with concentration-guided dose escalation.
- If a reported drug concentration is not consistent with the clinical scenario, consider repeating the test prior to dose adjustment.

Maximum concentration (C_{max}) and half-life (t_{1/2}): Two concentrations separated by several hours (usually 4 hours) can be used by a pharmacist to calculate a maximum concentration (C_{max}) and a half-life (t_{1/2}). These concentrations can also detect delayed absorption and malabsorption. Generally, the 2-hour sample is higher than the 6-hour sample. When there is delayed absorption, 6-hour values are higher than 2-hour values, and the 6-hour level may approach the therapeutic range. In cases of malabsorption, both values are low. Calculation of C_{max} and t_{1/2} is not appropriate when 6-hour values are higher than 2-hour values.

- If drug concentration is higher than planned, consider reducing dose of the drug especially if signs of toxicity are present (e.g., agitation or depression with a high CS level, or hearing loss with AK).
- If drug concentration is lower than planned, consider increasing dose of the drug to achieve a concentration in the planned range. Typical "maximum" doses of drugs can be exceeded when serum concentrations are low, but this should be done with caution and monitoring.

For information on where to obtain TDM tests, instructions on timing of blood collected for specific anti-TB drugs, and processing of specimens, see **Chapter 3**, *Laboratory*.

Role of surgery in the treatment of drug-resistant TB

Surgery is sometimes necessary to cure patients with MDR- or XDR-TB. The decision to perform resectional surgery should be made in consultation with an expert in treating drug-resistant TB and should be based on the degree of underlying drug resistance, the presence of focal cavitary disease, and the patient's ability to tolerate surgery.

Two systematic reviews/meta-analyses and an extensive review have evaluated the impact of surgery and its associated risks:

- Estimated pooled treatment success rate of pulmonary resection for patients with MDR-TB of 84%, with 92% achieving early success (30 days post-operative) and 87% long-term success. Patients who had surgical resection were twice as likely to have a favorable outcome as those who received chemotherapy alone and they were less likely to die.
 - Predictors of good outcomes across the studies included surgical resection, body mass index (BMI) ≥ 18.5, and use of ≥ 4 effective drugs in the treatment of MDR/XDR-TB.
 - Perioperative morbidity and mortality has ranged between 0-39% (median 23%) and 0-5% (median 1.3%), respectively.
 - In a subgroup analysis of 5 studies reporting outcomes of 422 XDR-TB patients, there was an even larger treatment effect related to surgery.

Surgery should be considered:

- When cultures continue to be positive beyond 4 to 6 months of treatment for MDR/ XDR-TB; and/or
- When extensive patterns of drug resistance exist that are unlikely to be cured with chemotherapy alone; and/or
- When patients develop complications such as massive hemoptysis or persistent bronchopleural fistula.

To maximize the potential success of surgery:

- The patient must represent an acceptable surgical risk and have adequate pulmonary function reserves to tolerate resectional surgery.
- Surgery should be performed by an experienced surgeon and only after several months of chemotherapy have been given.
- Whenever possible, the surgery should be performed after smear conversion has occurred, and ideally after culture conversion.
- Even after successful lung resection, the patient should complete a full course of treatment. If there are no positive cultures after surgery, the date of surgery can be considered the date of culture conversion.

Outcomes of treatment

Treatment outcomes for MDR-TB vary depending on a number of factors, including the drug-resistance pattern and the drugs used in the treatment regimen. Two systematic reviews including 36 observational studies reported pooled treatment success rates of 62% (range: 36% to 79%). None of the studies included in the systematic reviews included new drugs such as BDQ and DLM.

Factors associated with treatment success include:

- Treatment duration of at least 18 months
- DOT throughout treatment
- Surgical resection
- Fluoroquinolone use
- No previous treatment

Factors associated with **unfavorable outcomes** include:

- Male gender
- Alcohol abuse
- Low BMI (lack of weight gain)
- Smear positivity at diagnosis
- Fluoroquinolone resistance
- Presence of XDR resistance pattern

As described in a 2014 paper by Marks, et al., treatment outcomes in the United States are more favorable. Among 134 patients with MDR/XDR-TB who were alive at diagnosis and followed for treatment outcomes in the United States between 2005-2007, 78% completed therapy, 9% were transferred, 2% lost to follow-up, 1% stopped because of adverse reactions, and 9% died. Ninety-seven percent of the patients' sputum cultures converted to negative.

Summary

- Consultation with an expert should be obtained in all cases of MDR/XDR-TB.
- Design of individualized MDR-TB regimens should be based on DST results, prior history of TB treatment, potential for cross-resistance, potential for overlapping drug toxicities, and other key clinical and epidemiologic factors.
- MDR-TB regimens should contain at least 4-6 likely effective drugs (optimally 5), and XDR-TB regimens should contain at least 6 likely effective drugs.
- For MDR-TB:
 - The intensive phase of treatment should continue at least 6 months beyond culture conversion.
 - The continuation phase should continue at least 18 months beyond culture conversion.
- For XDR-TB:
 - The total duration of treatment should be at least 24 months beyond culture conversion.
- Case management is critical to successful treatment in drug-resistant TB.
- DOT should be used for all patients with MDR/XDR-TB.
- New drugs may eventually lead to better outcomes and shorter durations of therapy.

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