If a patient is suspected of harboring drug-resistant *M. tuberculosis* based on treatment failure, a history of previous therapy, or epidemiologic information, consider using an empirically expanded regimen, particularly if the patient is seriously ill and/or has extensive disease (increased risk of relapse and failure).

**Introduction**

Ideally, a treatment regimen for drug-resistant TB would be designed and initiated based on *in-vitro* drug-susceptibility test results for each patient’s *M. tuberculosis* isolate. The choice of drugs would be based on:

- The pattern of drug resistance
- Which drugs have been taken previously
- Whether the patient has underlying medical conditions
- The adverse effects associated with the drug

Unfortunately, first-line susceptibility results are not available for several weeks and second-line results are frequently not available for 2 or more months. In several situations, the risk of drug resistance is anticipated and treatment for drug-resistant TB may be initiated even before susceptibility data returns:

- 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 drug-resistant TB is prevalent

The treatment regimen can be changed once the results of drug-susceptibility tests are available. More information regarding when and how to initiate an empiric regimen for drug-resistant TB prior to susceptibility results can be found later in this chapter.

Once drug resistance has been documented by *in vitro* drug susceptibility testing, the following treatment regimens are recommended:
Individualized Treatment Regimens

Monoresistant Mycobacterium Tuberculosis

Isolated Resistance to ISONIAZID (INH)
Effective treatment regimens for patients with isolated INH-resistant TB are readily available. There are at least 3 options for treatment of patients with INH-resistant disease.

Option 1: Patients can be treated with daily rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA), 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.

Option 2: For patients with extensive disease, a fluoroquinolone may be added to the regimen. Treatment should continue daily for at least 6 months.

Option 3: If the patient does not tolerate PZA, a regimen consisting of RIF and EMB given for 12 months is effective. As in Option 2, a fluoroquinolone may be added to the regimen, especially during the initial phase of treatment. Some experts would include a fluoroquinolone for the entire course of treatment for essentially all such patients.

Isolated Resistance to RIFAMPIN (RIF)
Rifampin monoresistance is uncommon. 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 and rifapentine. In over 80% of strains where RIF resistance is documented, the strain is also resistant to rifabutin. Therefore, use rifabutin only when in vitro susceptibility is documented. Resistance to rifapentine is universal in RIF-resistant isolates. RIF-resistant TB can be treated using at least 3 different regimens.

Option 1: Patients can be treated with INH, EMB, and a fluoroquinolone for 12 to 18 months, supplemented with at least 2 months of PZA.

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

Option 3: Alternatively, INH, PZA, and streptomycin (SM) (or another aminoglycoside/polypeptide) can be given for 9 months with acceptable results. However, extended use of an injectable may not be feasible for some patients.

Isolated Resistance to ETHAMBUTOL (EMB), PYRAZINAMIDE (PZA), or STREPTOMYCIN (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 monoresistant isolates are M. bovis.

Given the importance of having drug susceptibility results, every effort should be made to obtain high-quality specimens for culture and drug-susceptibility testing. Repeat 2 to 3 sputum cultures when changing regimens.
Polyresistant Mycobacterium Tuberculosis

TB due to organisms that demonstrate in vitro drug resistance to more than one anti-TB drug (but not INH and RIF) is referred to as polyresistant TB. Any number of combinations of resistance can occur, but the outcome of treatment is usually good. Treatment should include the addition 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>
<thead>
<tr>
<th>Pattern of Drug Resistance</th>
<th>Suggested Regimen</th>
<th>Minimum Duration of Treatment (mos)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH (± SM)</td>
<td>RIF, PZA, and EMB</td>
<td>6–9 months</td>
<td>A fluoroquinolone (FQN) may strengthen the regimen for patients with extensive disease.</td>
</tr>
<tr>
<td>INH and PZA</td>
<td>RIF, EMB, and FQN</td>
<td>9–12 months</td>
<td>A longer duration of treatment should be used for patients with extensive disease.</td>
</tr>
<tr>
<td>INH and EMB</td>
<td>RIF, PZA, and FQN</td>
<td>9–12 months</td>
<td>A longer duration of treatment should be used for patients with extensive disease.</td>
</tr>
<tr>
<td>RIF</td>
<td>INH, EMB, FQN, plus at least 2 months of PZA</td>
<td>12–18 months</td>
<td>An injectable drug may strengthen the regimen for patients with extensive disease.</td>
</tr>
<tr>
<td>RIF and EMB (± SM)</td>
<td>INH, PZA, FQN, plus an injectable agent for at least the first 2–3 months</td>
<td>18 months</td>
<td>A longer course (6 mo) of the injectable may strengthen the regimen for patients with extensive disease.</td>
</tr>
<tr>
<td>RIF and PZA (± SM)</td>
<td>INH, EMB, FQN, plus an injectable agent for at least the first 2–3 months</td>
<td>18 months</td>
<td>A longer course (6 mo) of the injectable may strengthen the regimen for patients with extensive disease.</td>
</tr>
<tr>
<td>INH, EMB, PZA (± SM)</td>
<td>RIF, FQN, plus an oral second-line agent, plus an injectable agent for the first 2–3 months</td>
<td>18 months</td>
<td>A longer course (6 mo) of the injectable may strengthen the regimen for patients with extensive disease.</td>
</tr>
<tr>
<td>PZA</td>
<td>INH, RIF plus at least 2 months of EMB</td>
<td>9 months</td>
<td>Most commonly seen in M. bovis infections.</td>
</tr>
</tbody>
</table>
Multidrug-Resistant *Mycobacterium Tuberculosis* (MDR-TB)

Patients with MDR-TB, defined as resistance to at least INH and RIF, should always be treated with a minimum of 4 or more drugs to which the isolate is susceptible. In choosing drugs, begin with the available first-line drugs, and then add a fluoroquinolone and an injectable agent. Additional oral second-line drugs should be added to have a total of 4 to 6 drugs in the regimen. In patients with highly resistant organisms, alternative third-line drugs (in vitro activity against *M. tuberculosis*, limited clinical experience) may be needed. These should be chosen in consultation with someone who has experience using these drugs to treat MDR-TB (Figure 1).

**FIGURE 1.**

**Building a Treatment Regimen for MDR-TB**

**STEP 1**

- Begin with any **first-line** agents to which the isolate is susceptible.
- Add a fluoroquinolone and an injectable drug based on susceptibilities.
- Use any available **first-line drugs**:
  - Pyrazinamide
  - Ethambutol
- One of these **fluoroquinolones**:
  - Levofloxacin
  - Moxifloxacin
- One of these **injectable agents**:
  - Amikacin
  - Capreomycin
  - Streptomycin
  - Kanamycin

**STEP 2**

- Add **second-line** drugs until you have 4–6 drugs to which the isolate is susceptible (and preferably which have not been used to treat the patient previously).
- Pick one or more of these **oral second-line drugs**:
  - Cycloserine
  - Ethionamide
  - PAS

**STEP 3**

- If there are not 4–6 drugs available in the above categories, consider **third-line** drugs in consultation with an MDR-TB expert.
- Consider use of these **third-line drugs**:
  - Clofazimine
  - Linezolid
  - Amoxicillin/clavulanate
  - Imipenem
  - Macrolides
  - High-dose isoniazid
• A single new drug should never be added to a failing regimen.

• When initiating or revising therapy, always attempt to employ at least 3 previously unused drugs to which there is demonstrated in vitro susceptibility. One of these should be an injectable agent.

• Sufficient numbers of oral drugs should be started at the onset of therapy to make sure there is an adequate regimen once the injectable agent is discontinued.

• Do not limit the regimen to 4 agents if other previously unused drugs that are likely to be active are available.

• Patients should receive either hospital-based or domiciliary directly observed therapy (DOT).

• Intermittent therapy should not be used in treating TB caused by multidrug-resistant organisms, except perhaps for injectable agents after an initial period (usually 2 to 3 months) of daily therapy.

• The use of drugs to which there is demonstrated in vitro resistance is not encouraged because there is little or no efficacy of these drugs (assuming the test results are accurate). In the case of low-level resistance to INH, high doses are sometimes given intermittently to complement the regimen.

• Resistance to RIF is associated in most cases with cross-resistance to rifabutin and in all cases to rifapentine.

• Cross-resistance between amikacin and kanamycin is nearly universal. There is emerging data that certain mutations may confer cross-resistance between amikacin, kanamycin and capreomycin.

• Determination of resistance to PZA is technically problematic and thus, is not determined in all laboratories. However, resistance to PZA is uncommon in the absence of resistance to other first-line drugs. PZA monoresistance in vitro is essentially universal for Mycobacterium bovis isolates.

Individual Regimens for Specific MDR-TB Resistance Patterns

Resistance to INH and RIF
A regimen consisting of PZA, EMB, and a fluoroquinolone given for a total of 18 to 24 months beyond culture conversion is recommended. Give an injectable agent for at least the first 6 months of therapy (longer durations may be considered in cases of extensive disease and delayed culture conversion). In patients with extensive or cavitary disease, consider addition of 1 or more oral second-line drugs such as cycloserine, ethionamide, or PAS. The use of more than 1 additional oral drug should especially be entertained if there has been prior use of PZA or EMB in a failing regimen.

Resistance to INH, RIF, and EMB
A regimen consisting of PZA, a fluoroquinolone, and 2 second-line oral agents (cycloserine, ethionamide, or PAS) for 18 to 24 months beyond culture conversion is recommended. Give an injectable agent for at least the first 6 months of therapy (longer may be considered in cases of extensive disease and delayed culture conversion). In patients with extensive or cavitary disease, consider an additional oral drug. Consider surgery if there is focal cavitary disease. (See “Role of Surgery in the Treatment of Drug-Resistant Tuberculosis” later in this chapter.)

Resistance to INH, RIF, and PZA
A regimen consisting of EMB, a fluoroquinolone, and 2 second-line oral agents (cycloserine, ethionamide, or PAS) for 18 to 24 months beyond culture conversion is recommended. Give an injectable agent for at least the first 6 months of therapy. Administer EMB at a higher dose of 25 mg/kg/day until culture conversion has occurred (at which point the dose should be decreased to 15 mg/kg/day). Monitor the patient monthly for evidence of optic neuritis while receiving EMB. In patients with extensive or cavitary disease, consider an additional oral drug. Consider surgery if there is focal cavitary disease.

Resistance to INH, RIF, PZA, and EMB
A regimen consisting of a fluoroquinolone and 3 second-line and/or third-line oral agents should be given for 24 months beyond culture conversion. Give an injectable agent for at least 6 months and preferably for 12 months, if tolerated. Strongly consider surgery if there is focal cavitary disease.

Treatment must be more aggressive in situations where the patient has long-standing disease (years), extensive disease, or multiple previous failed treatment efforts.

The duration of therapy will depend on the anti-tuberculosis drugs used and the extent of the disease.
Resistance to All First-Line Drugs and Fluoroquinolones

In this setting, a regimen containing an injectable agent such as an aminoglycoside or polypeptide is critical. Capreomycin can sometimes be used with an aminoglycoside, as they are different classes of drugs. Since their toxicities are additive, close monitoring of hearing, vestibular, and renal function will be required. An injectable agent should be used for at least 12 months. Additionally, at least 3 second-line oral drugs should be used. Third-line agents should also be considered. Some investigators have had success using intravenous imipenem for approximately 6 months, followed by oral amoxicillin/clavulanate potassium. Linezolid and the newer macrolides have also been utilized in this setting when *in vitro* susceptibility has been documented. Strongly consider surgery if there is focal cavitary disease. Treat the patient for 24 months beyond culture conversion.

Resistance to All First-Line Drugs and Injectables

The chance of cure in a patient whose isolate is resistant to so many drugs is unacceptably low. Treat the patient with a fluoroquinolone and all other available second-line oral agents and perform surgery, whenever possible. Consider additional third-line agents, such as intravenous imipenem or possibly linezolid, particularly if surgery is not an option. Treat these patients for 24 months beyond culture conversion.

NOTE:

Some strains of *M. tuberculosis* demonstrate resistance at low isoniazid concentrations (0.2 mg/ml), but are susceptible at higher concentrations (1.0 mg/ml). In these situations, high-dose (900 mg per day) intermittent therapy may be indicated. Use of isoniazid 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 isoniazid.
Extensively Drug-Resistant Mycobacterium Tuberculosis (XDR-TB)

XDR-TB is defined as resistance to at least INH, RIF, a fluoroquinolone, and one of three injectables (amikacin, kanamycin, or capreomycin). Treatment of patients with XDR-TB is challenging because of the lack of potent anti-TB drugs. However, the approach to designing a treatment regimen is the same as with MDR-TB. First, begin with any first-line drugs that demonstrate in vitro activity, followed by second- and third-line drugs (Figure 2). Surgery should be a strong consideration in patients with XDR-TB.

Table 2 presents recommended regimens for the treatment of XDR-TB.

FIGURE 2.

Building a Treatment Regimen for XDR-TB

- **STEP 1**
  - Begin with any **first-line** agents to which the isolate is susceptible (PZA and EMB are commonly not susceptible)
  - Add an injectable drug based on susceptibilities
  - Use any available **First-line drugs**
    - Pyrazinamide
    - Ethambutol
  - One of these (if susceptible)
    - **Injectable agents**
      - Amikacin
      - Capreomycin
      - Streptomycin
      - Kanamycin

- **STEP 2**
  - Pick one or more of these
    - **Oral second-line drugs**
      - Cycloserine
      - Ethionamide
      - PAS

- **STEP 3**
  - Consider use of these
    - **Third-line drugs**
      - Clofazimine
      - Imipenem
      - Linezolid
      - Macrolides
      - Amoxicillin/clavulanate
      - High-dose isoniazid
## Table 2.

<table>
<thead>
<tr>
<th>Pattern of Drug Resistance</th>
<th>Suggested Regimen</th>
<th>Minimum Duration of Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH and RIF (± SM)</td>
<td>PZA, EMB, FQN, injectable agent ± another second-line agent.</td>
<td>18–24 months beyond culture conversion</td>
<td>Extended treatment is necessary to lessen the risk of relapse.</td>
</tr>
<tr>
<td>INH, RIF (± SM), and EMB or PZA</td>
<td>FQN, (EMB or PZA if available), injectable agent, plus 2 other second-line agents.</td>
<td>18–24 months beyond culture conversion</td>
<td>Consider surgery. Consider high-dose INH treatment if low-level resistance is documented.</td>
</tr>
<tr>
<td>INH, RIF, EMB, PZA (± SM)</td>
<td>FQN, injectable agent, 3 other second-line drugs</td>
<td>24 months beyond culture conversion</td>
<td>Consider surgery. Consider high-dose INH treatment if low-level resistance is documented.</td>
</tr>
<tr>
<td>INH, RIF, EMB, PZA, FQN</td>
<td>3 second-line drugs, an injectable agent, plus consider third-line agent</td>
<td>24 months beyond culture conversion</td>
<td>Consider surgery. Consider high-dose INH treatment if low-level resistance is documented.</td>
</tr>
<tr>
<td>INH, RIF, EMB, PZA, injectables</td>
<td>FQN, 3 other second-line drugs, ± additional third-line agents. Include an injectable drug if there is one available to which the isolate is susceptible.</td>
<td>24 months beyond culture conversion</td>
<td>Surgery should be performed if possible. Consider high-dose INH treatment if low-level resistance is documented.</td>
</tr>
<tr>
<td>INH, RIF, FQN injectable</td>
<td>EMB, PZA, 3 second-line drugs ± additional third-line agent. Include an injectable drug if there is one available to which the isolate is susceptible.</td>
<td>24 months beyond culture conversion</td>
<td>Surgery should be performed if possible. Consider high-dose INH treatment if low-level resistance is documented.</td>
</tr>
<tr>
<td>INH, RIF, EMB, FQN, injectable</td>
<td>PZA, 3 second-line drugs, plus a third-line agent. Include an injectable drug if there is one available to which the isolate is susceptible.</td>
<td>24 months beyond culture conversion</td>
<td>Surgery should be performed if possible. Consider high-dose INH treatment if low-level resistance is documented.</td>
</tr>
<tr>
<td>INH, RIF, PZA, FQN, injectable</td>
<td>EMB, 3 second-line drugs, plus a third-line agent. Include an injectable drug if there is one available to which the isolate is susceptible.</td>
<td>24 months beyond culture conversion</td>
<td>Surgery should be performed if possible. Consider high-dose INH treatment if low-level resistance is documented.</td>
</tr>
<tr>
<td>INH, RIF, EMB, PZA, FQN, injectable</td>
<td>3 second-line drugs, plus 2-3 third-line agents. Include an injectable drug if there is one available to which the isolate is susceptible.</td>
<td>24 months beyond culture conversion</td>
<td>Surgery should be performed if possible. Consider high-dose INH treatment if low-level resistance is documented.</td>
</tr>
</tbody>
</table>
Selection and Dosing of Individual Drugs—Building the Regimen

The number of drugs required to cure MDR-TB is not known. Most studies that have been published have used 4- to 6-drug regimens. Table 3 lists most published series of MDR-TB treatment and outcomes. These regimens have resulted in cure in 56% to 83% of patients. The outcome of treatment is likely to vary depending on the number of drugs to which the isolate is resistant, the drugs used, the duration of therapy, the extent of disease, and the presence of other medical conditions, such as HIV infection.

Unfortunately, recommendations for MDR-TB are based on expert opinion rather than data from randomized controlled trials.

The following predictors have been noted in small trials or series:

Predictors of a good outcome include:
- Susceptibility to and use of PZA and/or EMB
- Susceptibility to and use of a fluoroquinolone
- Use of > 5 drugs for treatment
- Sputum culture conversion by 2 months of treatment
- Surgical resection

Predictors of failure include:
- History of previous therapy
- Greater number of drugs to which the organism is resistant
- Presence of cavitation on the chest radiograph
- Positive cultures after 2 to 3 months of treatment
- HIV infection
## TABLE 3. Selected Series of MDR-TB, Variables, and Outcomes

<table>
<thead>
<tr>
<th>Study site, study dates, study design, and citation</th>
<th>Number of patients and comments</th>
<th>Mean number of drugs to which the isolate was resistant</th>
<th>Mean number of drugs given</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NJMRC</strong> Denver, CO (1973–1983) Retrospective chart review Goble 1993</td>
<td>( N = 171 ) (134 eligible for outcome analysis) Mean inpatient stay &gt;7 months</td>
<td>6 drug resistance</td>
<td>6 drugs</td>
</tr>
<tr>
<td><strong>Bellevue Hospital, New York</strong> (1983–1994) Retrospective chart review Park 1996</td>
<td>( N = 173 )</td>
<td>37% 2 drugs 26% 3 drugs 37% ≥ 4 drugs</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>New York City</strong> (1990–1993) Outbreak investigation Frieden 1996</td>
<td>( N = 357 ) “Strain W” 96% likely nosocomially acquired</td>
<td>6–7 drug resistance</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Istanbul, Turkey</strong> (1992–1999) Retrospective chart review Tahaoglu 2001</td>
<td>( N = 158 ) Mean inpatient stay 200 days</td>
<td>4.4 drug resistance</td>
<td>5.5 drugs 4.4 effective drugs</td>
</tr>
<tr>
<td><strong>Florida</strong> (1994–1997) Retrospective chart review Narita 2001</td>
<td>( N = 81 ) 39 patients managed at specialized TB hospital; 42 managed in the community Outpatients who survived &gt;2 mo included in outcome analysis</td>
<td>4.8 drug resistance Community management: 3.2 drugs Hospital management: 6.6 drugs</td>
<td>Effective drugs: Community management: 2.9 drugs Hospital management: 5.5 drugs</td>
</tr>
<tr>
<td><strong>Lima, Peru</strong> (1996–1999) Retrospective chart review Mitnick 2003</td>
<td>( N = 75 ) Community-based therapy</td>
<td>6 drug resistance</td>
<td>6 drugs</td>
</tr>
<tr>
<td><strong>NJMRC</strong> Denver, CO (1983–1998) Retrospective chart review Chan 2004</td>
<td>( N = 205 ) Mean inpatient stay 93 days</td>
<td>6 drug resistance</td>
<td>6 drugs</td>
</tr>
<tr>
<td><strong>Riga, Latvia</strong> (2000) Retrospective cohort study Leimane 2005</td>
<td>( N = 204 )</td>
<td>Median of 4</td>
<td>Median of 6</td>
</tr>
</tbody>
</table>

* Statistically significant on multivariate analysis  ** National Jewish Medical and Research Center  *** Treatment with 2 or more drugs to which the isolate was susceptible
<table>
<thead>
<tr>
<th>HIV status</th>
<th>Outcomes</th>
<th>Variables associated with good outcome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not reported</td>
<td>37% mortality (all causes) 21% mortality (TB) 65% initial culture conversion (56% cure; 9% relapse)</td>
<td>History of exposure to fewer drugs Female gender</td>
</tr>
<tr>
<td>52% HIV+ 24% unknown</td>
<td>58% mortality (all causes) 20% mortality (TB)</td>
<td>HIV seronegative status Appropriate therapy*** Isolated pulmonary involvement Cavitary disease at diagnosis (HIV-)</td>
</tr>
<tr>
<td>86% HIV+ 7% unknown</td>
<td>83% mortality (all causes) 20% mortality (TB)</td>
<td>Capreomycin use CD4 lymphocyte &gt; 200 Fluoroquinolone use INH use</td>
</tr>
<tr>
<td>0% HIV+</td>
<td>4% mortality 77% overall success 49% cure</td>
<td>Lack of previous fluoroquinolone use Younger age Resistance to more than 5 drugs</td>
</tr>
<tr>
<td>Community management: 48% HIV+ 32% unknown Hospital management: 41% HIV+ 5% unknown</td>
<td>32% mortality (all causes, all patients) Community management: 45% mortality 48% cure Hospital management: 18% mortality 79% cure</td>
<td>Treatment at specialized TB hospital</td>
</tr>
<tr>
<td>1.3% HIV+ 13% unknown</td>
<td>23% mortality (all causes) Of n=66 completing &gt; 4 mo treatment, 83% probable cure</td>
<td>Pyrazinamide use, if susceptible Ethambutol use, if susceptible</td>
</tr>
<tr>
<td>Not reported</td>
<td>25% mortality (all causes) 12% mortality (TB) 75% long-term favorable outcome</td>
<td>Surgical resection Fluoroquinolone use</td>
</tr>
<tr>
<td>96% HIV negative, 1% HIV positive, 3% unknown</td>
<td>135 (66%) cured or competed therapy 14 (7%) died. 26 (13%) defaulted. 29 (14%) failed treatment Of 178 adherent patients, 135 (76%) achieved cure</td>
<td>No previous treatment for MDR Treatment with over 5 drugs Susceptibility to ofloxacin Body mass index of ≥18.5 at start of treatment</td>
</tr>
</tbody>
</table>
Specific Drugs

Fluoroquinolones

There are few clinical data to help decide which fluoroquinolone to choose. Levofloxacin has been used extensively for the treatment of drug-resistant TB. Limited data suggest that levofloxacin may be more efficacious than ofloxacin when treating drug-resistant TB. Ciprofloxacin is the least potent of the available fluoroquinolones and should not be used to treat drug-resistant TB. Moxifloxacin has better in vitro activity against *M. tuberculosis* compared with levofloxacin, ofloxacin, and ciprofloxacin. In addition, recent studies have demonstrated excellent early bactericidal and sterilizing activity with moxifloxacin.

The dose of levofloxacin has been successfully increased to 1 gram/day or more on a case-by-case basis and tolerated well. The dose of moxifloxacin should not be increased beyond the Food and Drug Administration (FDA) recommended dose without measuring serum for concentration because of the possibility of more drug-related toxicity.

Aminoglycosides and Polypeptides

When choosing an aminoglycoside or polypeptide agent, weigh the cost and toxicity profiles of the different drugs.

SM and kanamycin are the least expensive. There is a large amount of clinical trial data to support the use of SM. However, SM resistance is one of the most common forms of resistance found in the world.

Amikacin has excellent in vitro activity against *M. tuberculosis*, but it is more expensive than SM and some authorities (and patients) say that intramuscular SM is less painful than amikacin. However, it is easier to obtain amikacin serum concentrations than SM, kanamycin, or capreomycin concentrations, and amikacin is tolerated well for long periods.

Capreomycin is also expensive, but the drug has been well tolerated when given for long periods of time. Significant electrolyte disturbances can occur with capreomycin (as well as with the aminoglycosides), so close monitoring is required.

An injectable drug is administered 5 to 7 times weekly by IM injection or via indwelling catheter during the initial phase. After 2 to 6 months, the injectable drug is given 3 times weekly. The injectable drug should be continued at least 6 months and longer if the patient has extensive disease, slow microbiologic response, or extensive resistance.

Additional Oral Second-Line Drugs

The drugs para-aminosalicylate (PAS), ethionamide, and cycloserine are generally bacteriostatic (ethionamide may be weakly bactericidal at higher doses). There are few data supporting one drug over the other in terms of efficacy. The decision of which drug(s) to use is often based on the side effect profile of the drug and the ability to measure drug serum concentrations in the case of cycloserine.

When INH resistance occurs at low concentrations, the organism may also be resistant to ethionamide. Mutations in the inhA region of *M. tuberculosis* can confer resistance to ethionamide as well as to isoniazid at low concentrations. In this situation, ethionamide
may not be the best choice of a second-line drug unless the organism has been shown to be susceptible with in vitro testing.

Alternative or Third-Line Drugs

In this Guide, we refer to third-line anti-tuberculosis drugs (e.g., imipenem, clofazimine, amoxicillin/clavulanate potassium, clarithromycin, azithromycin, and linezolid) as those that have demonstrated in vitro activity against M. tuberculosis, but for which there are little clinical data supporting their use. Most of these drugs are expensive, and in some cases require intravenous administration. At least one study demonstrated activity of imipenem in vitro and in patients with MDR-TB. Linezolid has been reported to be an active agent in several reports, but this drug is associated with a high rate of peripheral neuropathy that is usually not completely reversible and optic neuritis that usually is reversible. In one small study, decreasing the dose of linezolid from 600 mg twice daily to 600 mg once daily did not appear to decrease the frequency of neuropathy. Third-line drugs should only be used in consultation with an expert in the treatment of drug-resistant TB.

Several novel agents are currently being studied and have promise for treatment of drug-resistant TB. PA-824 is a nitroimidazole that has both bactericidal and sterilizing activity in mice. TMC-207, a diarylquinoline, is a novel anti-tuberculosis agent that targets ATP synthase. Because of its mechanisms of action, the drug has significant activity against both drug-susceptible and drug-resistant strains of M. tuberculosis. OPC-67683 is a nitroimidazo-oxazole that also has bactericidal and sterilizing activity against M. tuberculosis. These compounds are currently undergoing Phase I and II tests in patients with tuberculosis and MDR-TB.

Be aware of potential cross-resistance that can occur between certain drug classes (Table 4).
### TABLE 4.
Cross-resistance for anti-tuberculosis drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cross-Resistance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Ethionamide</td>
<td>Cross-resistance to ethionamide may occur when there is low-level resistance to isoniazid.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Rifamycins</td>
<td>Cross-resistance among the rifamycin class of drugs is typical. In a few strains that are resistant to rifampin, rifabutin may retain susceptibility <em>in vitro</em>.</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>Kanamycin</td>
<td>High likelihood of cross-resistance since it is associated with the same mutation.</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Amikacin</td>
<td>High likelihood of cross-resistance since it is associated with the same mutation.</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Amikacin/Kanamycin</td>
<td>Variable frequency of cross resistance has been reported.</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Other fluoroquinolones</td>
<td>In general, there is a complete class effect cross-resistance among fluoroquinolones <em>in vitro</em>. However, data suggest that moxifloxacin may continue to demonstrate some activity despite <em>in vitro</em> resistance to ofloxacin.</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>PAS</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Isoniazid</td>
<td>Cross-resistance to isoniazid may occur when there is low-level resistance to ethionamide.</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
Avoid Drugs that Have Been Used Previously to Treat The Patient’s TB

Data from National Jewish Medical and Research Center 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.

Consider Side Effects When Choosing Drugs

For example, in someone with depression, it may be desirable to avoid cycloserine. When possible, try to avoid using drugs that have similar toxicity profiles. For example, the combination of PAS and ethionamide increases the risk of hypothyroidism. On the other hand, in some patients there is no choice because these may be the only drugs 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 easier to use or 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, will usually be stopped prior to completion of therapy. Therefore, the patient should receive a sufficient number of oral drugs from the beginning of therapy to make sure that there are at least 3 to 5 oral drugs remaining after the injectable is discontinued.

Ultimately, the choice of anti-tuberculosis drugs will depend on in vitro susceptibility results, anti-tuberculosis drugs taken previously, and possibly, cost.

It is important to note that intolerance to one agent does not necessarily mean the patient will be intolerant to another agent. Other oral or intravenous second-line agents may be needed depending on the drug-resistance pattern. In some cases, with highly resistant organisms, the regimen may require the addition of third-line drugs.

Administration of the Treatment Regimen

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

Treat all forms of drug-resistant TB with DOT and in consultation with experts in the treatment of resistant disease.

DOT can be delivered in the field or clinic. Although intermittent therapy is not recommended for the treatment of MDR-TB (except in the case of injectables), 5-day-a-week directly observed dosing can be used for patients who are not hospitalized or institutionalized, with medications self-administered on weekends. In patients who are severely ill, treatment should be administered 7 days per week (including the injectable drugs).
Escalation of Dosages (Drug Ramping)

The second-line anti-tuberculosis drugs are commonly associated with adverse effects. Some authorities recommend hospitalization at the time of initiation of therapy in order to monitor for drug toxicity or intolerance. During this period, serum drug concentrations can be determined as the dosages of the drugs are slowly increased to targeted serum concentrations. On the other hand, when resources and infrastructure are available, and transmission to contacts can be prevented, patients can be treated as outpatients and serum drug concentrations measured, if necessary. Most drugs should be started at full dose except cycloserine, ethionamide, and PAS, in which case the dose of the drug can be increased over a 2-week period.

In some patients, beginning with a low dose and gradually increasing the dose is more acceptable and allows the clinician time to manage drug-related adverse effects. This approach of slowly escalating drug dosage is referred to as “drug ramping” and is most often used with the drugs PAS, ethionamide, and cycloserine. Examples of drug ramping can be seen in Figure 3.

**FIGURE 3.**
**Dose escalation (drug ramping)**

![Figure 3: Dose escalation (drug ramping)](image)

- **Cycloserine**
  - Initial Dose: 250 mg daily
  - Escalating Doses: 250 mg bid, 2 gm qam/4 gm qhs (keep peak serum level < 35 mcg/ml)
  - 250 mg qam/500 mg qhs

- **PAS**
  - Initial Dose: 2 gm bid
  - Escalating Doses: 250 mg bid, 2 gm qam/4 gm qhs (keep peak serum level < 35 mcg/ml)
  - 250 mg qam/500 mg qhs

- **Ethionamide**
  - Initial Dose: 250 mg daily
  - Escalating Doses: 250 mg bid

Dose escalation should be completed within 2 weeks.

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 cycloserine to once daily dosing which can enhance adherence.
Role of Surgery in the Treatment of Drug-Resistant TB

Surgery is sometimes necessary to cure patients with MDR-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. Most patients who undergo resectional surgery have evidence of focal cavitary disease. However, if the clinical situation is such that the treatment options are severely limited, resection of a primary site of focal non-cavitary disease has been used with good outcomes.

Surgery should be considered:

• When cultures continue to be positive beyond 4 to 6 months of treatment for MDR-TB; and/or
• When extensive patterns of drug resistance exist that are unlikely to be cured with chemotherapy alone

At National Jewish Medical and Research Center, the median time to culture conversion was 2 months, with the majority of patients becoming negative by 4 months. If a patient remained culture-positive after 4 months of treatment and had high levels of drug resistance, surgery was recommended.

To maximize the potential success of surgery:

• The disease should be sufficiently localized to allow lobectomy or pneumonectomy, and the remaining lung tissue should be relatively disease-free. In all cases, 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 culture conversion has occurred.
• Even after successful lung resection, the patient should complete a full course of treatment. Surgery does not allow shortening of the treatment course for any pulmonary or extrapulmonary TB disease (drug-susceptible or resistant).

Groups at High-Risk of Having Drug-Resistant Tuberculosis

Treatment Failures

Recognition of a Failing Regimen

Treatment failure is defined as continued or recurrently positive cultures in a patient receiving appropriate chemotherapy. Studies have demonstrated that approximately 90% to 95% of patients with drug-susceptible pulmonary TB will be culture-negative after 3 months of treatment with a regimen that contains INH and RIF.

A treatment regimen has failed when sputum cultures remain positive after 4 months of treatment or become positive again after a period of negative cultures. However, the possibility of a failing treatment regimen should be considered well before 4 months of
treatment. Patients who are not clinically improving and/or remain smear-positive during the first months of treatment should be considered for the possibility of drug resistance.

There are several potential reasons for treatment failure:

- Nonadherence to the treatment regimen
- Acquired drug resistance
- Malabsorption of drugs
- Reinfection with a new strain of *M. tuberculosis*
- Inadequate treatment regimen

The Clinician’s Response to Treatment Failure

Determine the cause of treatment failure:

- Verify drug-susceptibility results by reviewing written reports and/or discussing the results with the laboratory.
- Perform repeat drug-susceptibility testing to determine if drug resistance has developed while on therapy. However, patients with treatment failure should be assumed, until proven otherwise, to have drug-resistant organisms.
- Treat persons who were being treated with self-administered therapy with DOT.
- In patients who were being treated with DOT, measurement of serum drug concentrations may be indicated, particularly if drug resistance has developed on therapy or there are risk factors for malabsorption.

Consider a Treatment Regimen Change

If treatment failure is presumed to be due to underlying drug resistance and the patient does not have severe TB, either initiate an empiric regimen (see “Starting an Expanded Empiric Treatment Regimen” later in this chapter) or wait for the results of drug-susceptibility testing. In most cases, the first-line drug regimen should be continued pending second-line susceptibility test results. If the patient is seriously ill or has a positive sputum acid-fast bacilli (AFB) smear, start and continue an empiric regimen until drug-susceptibility test results are available.

Never add a single drug to a failing regimen.

Persons Who Have Relapsed After Prior Treatment

Relapse occurs when a patient who has completed TB therapy and has documented negative sputum cultures either becomes culture-positive again or experiences clinical or radiographic deterioration consistent with TB disease.

Persons who have been treated previously for TB and subsequently relapse are at increased risk of presenting with drug-resistant organisms. Numerous studies have identified previous treatment as one of the greatest risk factors for the acquisition of drug-resistant TB.

Acquired drug resistance is more likely in persons who were not treated initially with DOT.
In patients who received DOT and were adherent to therapy, the risk of developing acquired resistance is small unless the patient has advanced HIV infection and received highly intermittent therapy (e.g., weekly or twice weekly).

As with treatment failures, there are several possible causes for relapse:

- Nonadherence to the treatment regimen
- Acquired drug resistance
- Malabsorption of drugs
- Reinfection with a new strain of *M. tuberculosis*
- Inadequate treatment regimen

**Re-Treatment Options**

In patients who relapse after initial treatment with a regimen that included INH, RIF, PZA, and EMB administered under well-documented DOT, initiate re-treatment with the same 4-drug regimen pending the results of drug-susceptibility tests.

If the patient previously received any self-administered therapy or an inappropriate treatment regimen, consider use of an expanded treatment regimen. An expanded regimen is indicated especially in patients with impaired immunity, limited respiratory reserve, central nervous system involvement, or other life-threatening circumstances.

Ideally, at least 2, preferably 3, new drugs that are added to the standard 4-drug treatment regimen should be ones that the patient has not received previously.

**TB Disease in a Contact of a Drug-Resistant Case**

Consider the infectious period of the source case, and tuberculin skin test (TST) or interferon-gamma release assay (IGRA) conversion of the contact, to confirm when infection was likely to have occurred. If the source case had progressive drug resistance, consider the susceptibility pattern of the source case at the time of exposure.

Assume that the secondary case has the same pattern of drug resistance as the source case, unless there is evidence to the contrary.

In general, base the empiric treatment regimen on the drug-susceptibility pattern of the source case. If drug-susceptible disease is documented subsequently, switch to a standard 4-drug treatment regimen.

**Persons Who Come from Regions Where Drug-Resistant TB Is Prevalent**

In situations where data about a region’s prevalence of drug resistance is lacking or possibly inaccurate, consider using an expanded regimen by adding 2 to 3 additional drugs to the treatment regimen in patients who are seriously ill and at risk of dying from TB. (See Appendix 3, “International Resources for TB Treatment and Policies.”)
Starting an Expanded Empiric Treatment Regimen

The decision to start an expanded empiric regimen (inclusion of second-line drugs) will be determined by the level of suspicion for drug-resistant TB and the severity of illness in the TB suspect. When suspicion for drug-resistant TB is high (e.g., previous treatment, especially if self-administered, or a close contact to a case with confirmed drug-resistant TB), then an expanded treatment regimen may be warranted. In addition, when a patient is suspected of having drug-resistant disease and has life-threatening TB, use an expanded treatment regimen. An expanded empiric regimen usually consists of the 4 first-line drugs and 2 or more additional drugs. When extensive disease or resistance is suspected, do not limit the empiric regimen to just 6 drugs.

There are situations where it may be more appropriate to initiate a 4-drug (first-line) regimen or 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. This is an appropriate option only if the patient is not particularly ill and can be isolated to prevent infection of contacts.

An Expanded Treatment Regimen*

When an expanded treatment regimen is warranted, the following regimen is recommended:

- INH
- RIF
- EMB
- PZA
- A fluoroquinolone
- An injectable agent (because of the frequency of SM resistance in the world, better alternatives would be capreomycin or amikacin)
- Consider use of ethionamide, cycloserine, or PAS

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 a specific region

* When extensive disease is present, extensive resistance is suspected, or the patient is seriously ill, do not limit the empiric regimen to 2 to 3 additional drugs.
Consultation with Experts

Treatment of 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 thus, inappropriate management of a drug-resistant case can have life-threatening consequences.

The management of drug-resistant TB is often complicated by drug toxicities and long durations of therapy. Even under the best circumstances, successful treatment outcomes for drug-resistant TB are often difficult to achieve compared with drug-susceptible disease, particularly when multidrug-resistance is present.

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 empirical 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 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

Expert Consultation

- Consult with a local or regional expert in the treatment of drug-resistant TB. Ideally, written communication will be shared for clarity of recommendations.
- 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.

Refer to Appendix 1, “List of Expert Resources for Drug-Resistant TB.”
Summary

• Each patient should be assessed for risks of drug resistance: previous TB treatment, exposure to a drug-resistant case, or travel to or immigration from an area of high resistance.

• An empiric expanded TB regimen is appropriate for patients at high risk for drug resistance, especially if they are seriously ill or have extensive disease.

• An empiric expanded regimen should be customized based on suspected resistance patterns and the patient's previous TB treatment. In general, an expanded empiric regimen should contain the 4 first-line TB drugs, a fluoroquinolone, and an injectable drug.

• Never add a single drug to a failing regimen.

• In treatment of MDR-TB, the number of drugs in the regimen depends on the susceptibility pattern, availability of first-line agents, and extent of disease.

• The minimum duration of treatment for pulmonary MDR-TB is 18 months beyond culture conversion.
References


