Co-morbidities & Special Situations

Extrapulmonary TB .................................................. 174
  Central nervous system (CNS)

HIV ................................................................. 177

Diabetes mellitus ................................................. 180

Liver disease ......................................................... 182

Renal failure ........................................................ 183

Pregnancy ........................................................... 187
  Teratogenicity
  Infection control
  Management of the newborn

Solid organ transplant ......................................... 191

Resources and references ..................................... 193
Managing drug-resistant TB, never a simple endeavor, requires additional considerations in the presence of co-morbidities and special situations. Expert consultation is advised.

**Extrapulmonary TB**

There is scant information regarding extrapulmonary drug-resistant tuberculosis (TB) in the medical literature. The limited clinical data on MDR-TB suggest that the lessons from the treatment of drug-susceptible extrapulmonary TB are applicable to MDR-TB. Extrapulmonary involvement was not a risk factor for treatment failure in the 2012 summary by Kurbatova of outcomes in 4 large MDR-TB programs.

Many of the series from New York in the 1990s reported large proportions of HIV-positive individuals, who are known to have higher rates of extrapulmonary TB than HIV-negative hosts. More recently, several reports describe cases of MDR-TB meningitis and high mortality rates.

Treatment of drug-resistant extrapulmonary TB is complicated by several issues:

- **Several forms of extrapulmonary TB (meningitis/pericarditis) are treated with adjunctive corticosteroid treatment in conjunction with an optimal anti-tuberculosis regimen.** Use of corticosteroids for patients not receiving adequate anti-mycobacterial therapy could be problematic. Studies showing efficacy of corticosteroid therapy are reported for drug-susceptible cases. Although similar efficacy data are not available for patients with drug-resistant TB, expert opinion supports use of corticosteroids in cases of central nervous system (CNS) and pericardial disease.

- **Some forms of TB (particularly scrofula and intrathoracic adenopathy) are known to worsen as the TB is being successfully treated.** This is due to immune reconstitution as the organism is being eliminated and is particularly common in HIV-positive individuals, but known to occur in immunocompetent patients as well. This phenomenon is known as a “paradoxical reaction” or the immune reconstitution inflammatory syndrome (IRIS) and is a condition of exclusion. Other diagnoses, unrecognized drug resistance and microbiologic failure should be excluded first before the diagnosis of IRIS is accepted. If these other etiologies are not appropriately excluded, the correct diagnosis (drug resistance and treatment failure) will be delayed.
• Drug regimens and durations of treatment for drug-susceptible extrapulmonary TB are based on: 1) known penetration of first-line anti-tuberculosis drugs into tissues; 2) clinical experience; and 3) limited clinical trials. Unfortunately, much less is known regarding the penetration of second-line drugs into tissues.

• Serial cultures are often not available. Clinical and radiographic assessments should be used to determine duration of therapy. Other imaging modalities, such as computed tomography, ultrasound or MRI, are often useful in following treatment progress in these patients.

Role of surgery

Some forms of extrapulmonary TB (e.g., vertebral involvement) might benefit from surgical debridement or resection in order to decrease the burden of disease. Surgery is not a replacement for full medical treatment of TB, but may offer a greater likelihood of success and may give the patient some symptomatic relief while the disease is being treated medically.

Drug-resistant CNS TB

Several reports detail poor outcomes of drug-resistant TB meningitis. Most of the patients in these series were HIV-positive and many developed meningitis while already receiving treatment for MDR-TB. Mortality in two series from South Africa—one in adults and one in children—ranged from 57% to 88%. The majority of patients were HIV-positive. Any degree of drug resistance will hinder the treatment of TB meningitis or other CNS TB because isoniazid (INH) is the most important drug in the treatment of TB meningitis. Interestingly, one series showed no increased risk of in-hospital mortality with INH resistance.

TB drugs and their CNS penetration

INH is the most important drug in the treatment of TB meningitis. INH readily diffuses into the cerebrospinal fluid (CSF), independent of meningeal inflammation, due to its small size and lipophilic nature. Levels approach those in serum. Because of this, some experts recommend the use of higher-dose INH in MDR-TB meningitis, especially in the setting of low-level INH resistance.

Rifampin (RIF), rifabutin (RFB), ethambutol (EMB), and para-aminosalicylate (PAS) penetrate poorly into the CSF with non-inflamed meninges, but better with inflamed meninges. For RIF, CSF levels reach 10-20% of serum levels in the setting of inflamed meninges (still exceeding the minimum inhibitory concentration [MIC] of sensitive isolates). However, in one study of RIF, CSF with uninflamed meninges showed similar results, with CSF levels 13% to 42% of serum. High-dose RIF (900 mg IV daily) in the initial treatment of TB meningitis was associated with a better outcome in one 2013 study.

Streptomycin (SM) and the other aminoglycosides do not enter the CSF in very high concentrations, although 20% or more of serum concentrations may be achieved (CSF concentrations of 1-9 μg/mL in most patients). Successful use of intrathecal administration has been described in at least one case of CNS MDR-TB.

Pyrazinamide (PZA) crosses freely into the CSF. One pediatric trial detected a significantly improved outcome for short-course treatment of TB meningitis in children who received PZA vs. longer treatment in those who did not, suggesting a benefit of PZA in the regimen.
Ethionamide (ETA) and cycloserine (CS) also have good CNS penetration, with levels in CSF approaching that in serum, but a South African study evaluated CSF levels of ETA and concluded that doses of 20 mg/kg/day should be used in order to achieve useful levels in the CSF.

Levofloxacin (LFX) and moxifloxacin (MFX) both have moderate CNS penetration, even with uninflamed meninges. In one study, LFX levels in the CSF were 37% of serum levels. Levels up to 65% of serum have been found in CFS in the setting of inflamed meninges. In the same study, MFX CSF levels were 23% of levels in serum. MFX has shown good CSF penetration in several animal studies (CSF levels approximately 50% of serum). Both LFX and MFX have been used successfully in MDR-TB meningitis.

Linezolid (LZD) has good CNS penetration. One study of patients undergoing neurosurgery found levels in CSF that averaged 70% of serum levels after a single 600 mg dose. The drug has been successfully used to treat gram-positive drug-resistant meningitis in patients.

Data on the CSF penetration of clofazimine (CFZ) and bedaquiline (BDQ) are not available.

**Route of administration**

If the patient is obtunded or severely ill, consider using drugs that can be given parenterally: INH, RIF, fluoroquinolones, and aminoglycosides. Oral-gastric or nasogastric administration of medications has also been effective.

Two reports of treatment of MDR-TB meningitis in HIV-negative individuals describe the use of intrathecal aminoglycosides and fluoroquinolones via Ommaya reservoir with good success and tolerability. Since most of the reports of fatal MDR-TB meningitis were in HIV-positive individuals, it is hard to compare the outcomes of intrathecal vs. systemic administration of second-line anti-tuberculosis drugs. It is appealing, however, to consider this option for patients not responding quickly to systemic treatment.

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**Summary**

**EXTRAPULMONARY TB**

- Data regarding treatment of extrapulmonary drug-resistant TB are limited. A few cases are described within larger series of MDR-TB cases.

- In general, extrapulmonary involvement other than meningitis is not a risk factor for treatment failure in drug-resistant TB.

- Surgical resection (scrofula) and drainage (empyema, abscesses, vertebral disease, and arthritis) may decrease bacterial burden and improve outcome. Full medical treatment is still indicated.

- Drug-resistant TB meningitis is challenging to treat due to the incomplete CSF penetration of many second-line drugs. Intrathecal administration of medications and the use of later-generation fluoroquinolones may improve outcome and should be evaluated prospectively.
HIV

Patients with HIV/AIDS are at increased risk of developing TB once infected compared to immunocompetent individuals. Additionally, TB increases HIV replication, promoting a vicious cycle of viral and mycobacterial proliferation. Patients who are HIV-positive with low CD4 counts are more likely to have atypical presentations of TB, such as extrapulmonary TB (including lymphadenopathy, miliary TB, and meningitis), sputum smear-negative TB, and sputum culture-positive TB in the absence of an abnormal chest radiograph. These individuals may be less likely to have cavitary disease and more likely to have mid- and lower-lung disease than are individuals who are HIV-negative.

TB progresses much more rapidly among persons with severe immunodeficiency; therefore, clinicians should have a lower threshold to use regimens with expanded coverage for drug resistance among patients with advanced HIV disease and who have risk factors for infection with a drug-resistant strain of M. tuberculosis.

Factors that increase the risk for exposure to or development of drug-resistant TB in HIV-positive individuals include:

- Previous exposure to rifamycins (e.g., the use of rifabutin [RFB] to prevent disseminated Mycobacterium avium intracellulare disease)
- Use of highly intermittent rifamycin treatment
- Malabsorption of drugs
- Drug-drug interactions (e.g., inadequate rifamycin dosing due to antiretroviral coadministration)
- Residence in congregate settings
- Co-morbid conditions, including those that may interfere with adherence (e.g., substance abuse issues)
- CD4 lymphocyte count below 100 cells/mm³

Unfortunately, HIV-positive individuals with MDR-TB have higher mortality rates than HIV-negative patients with MDR-TB, particularly when the TB is not treated early or aggressively, or when the CD4 lymphocyte count is already very low. In the series describing the highest mortality with HIV and drug-resistant TB, the patients had advanced AIDS, and MDR-TB was not recognized initially—therefore, drug therapy was inadequate. A large series of HIV-positive persons with TB from Thailand showed that early detection and optimal treatment of MDR-TB improved survival, as did anti-retroviral therapy (ART). ART should be initiated in all patients with HIV and TB.

Knowledge about the metabolism of the traditional second-line drugs (ethionamide [ETA], cycloserine [CS] and para-aminosalicylic acid [PAS]) is incomplete because they were licensed decades ago. However, based on knowledge of chemical structure and/or metabolism of related agents, these drugs should not have significant drug-drug interactions with antiretroviral medications. Second-line injectable drugs are primarily renally excreted unchanged and should not have interactions with antivirals. The fluoroquinolones are also unlikely to have significant interactions with antiretrovirals. Nonetheless, overlapping toxicities such as nephrotoxicity, QT prolongation on ECG, psychiatric side effects and gastrointestinal [GI] intolerance may limit options for treating co-existing MDR-TB and HIV.

Patients with HIV are more likely to have atypical presentations of TB.
Treatment of drug-resistant TB in HIV-positive individuals is complicated by:

- Drug toxicity exacerbated by underlying conditions or toxicity from other drugs
- The sheer volume of medicines that must be taken for both conditions
- Overlapping drug side effects of medications used to treat both conditions
- The fact that the immune system cannot always contribute to control of the TB disease
- Malabsorption of drugs
- Drug-drug interactions
- Paradoxical reactions (TB disease appears to worsen when immune reconstitution occurs)
- Complex social, mental health, and substance abuse confounders
- Coinfection with hepatitis C or hepatitis B, which increases the risk of hepatotoxicity, especially when combined with some types of HIV therapy
- Variable penetration of second-line drugs into CNS sites of disease

To maximize care of HIV-positive patients:

- Identify all HIV-positive patients by screening all patients with TB disease for HIV.
- Utilize rapid molecular diagnostic testing for earlier diagnosis for both TB disease and drug resistance.
- Work closely with the patient’s HIV provider. If that provider does not have extensive HIV/TB expertise, consult such an expert throughout the course of therapy.
- It is critically important to appropriately treat the HIV infection as well as the drug-resistant TB. Consider the best HIV regimen for immune reconstitution as well as the timing of initiation of ART for antiretroviral-naive patients. Initiation of ART is associated with increased drug toxicity as well as the phenomenon of immune reconstitution. Immune reconstitution may exacerbate clinical symptoms of TB by stimulating an inflammatory response.
  - In patients with CD4 lymphocyte counts over 50, it is reasonable to delay ART for 2-8 weeks.
  - In patients with CD4 less than 50, it is advisable to begin ART as soon as TB therapy is well tolerated (ideally within 2 weeks). The exception may be CNS TB in which early initiation of antiretrovirals in drug-susceptible TB has been associated with poorer outcomes due to occurrence of IRIS within the CNS.

Consider alternate drugs when interactions between TB and HIV drugs are present (e.g., RFB in place of rifampin [RIF]).

- Rifamycins are inducers of cytochrome P-450 and interact with many drugs. RIF in particular leads to lower levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Current recommendations about concomitant use of rifamycins (RIF and RFB) and ART should be consulted. (See Resources at the end of this chapter.)
- The rifamycins and other TB drugs interact with a number of the anti-infectious agents that may be taken by HIV-positive patients, including the macrolide drugs, cidofovir, anti-fungal drugs, and others.
• Didanosine products that contain an antacid should not be dosed in close proximity to fluoroquinolones. As with all other milk- and divalent cation-containing products, dosing at least 2 hours apart from the fluoroquinolone dose is advised.

• Efavirenz increases the clearance of PAS by approximately 50%.

• Use of lopinavir/ritonavir alters the metabolism of bedaquiline (BDQ) and leads to higher serum levels and effects of BDQ.

• Intervene to avoid or treat symptomatic toxicity. Peripheral neuropathy, cutaneous reactions, GI side effects, renal impairment, and neuropsychiatric effects may all be worse in HIV/TB patients.

• Use daily directly observed therapy (DOT). During treatment for drug-resistant-TB, also consider DOT of antiretroviral drugs.

• Closely monitor signs and symptoms of malabsorption: diarrhea, abnormal stools, abnormal nutritional studies, evidence of vitamin deficiencies, and weight loss.

• Consider therapeutic drug monitoring to detect malabsorption, drug-drug interactions for MDR-TB, or clinical suspicion of malabsorption.

• Involve a nutritionist and pay close attention to weight and nutrition. Consider use of appetite stimulants in situations of extreme malnutrition.

• Involve ancillary services such as social workers, substance abuse clinics, and mental health facilities.

• Involve the patient’s social support system, as appropriate.

Summary HIV

• MDR-TB patients who are HIV-positive have higher mortality rates, particularly when they are profoundly immunocompromised (CD4 lymphocyte count less than 100) and an optimal TB regimen is not initiated early in the course of disease.

• Antiretroviral therapy is a critical part of the treatment of drug-resistant TB in HIV-positive persons.

• HIV-positive patients can be cured of their drug-resistant TB disease, but require special monitoring and concurrent care of their HIV disease. Early initiation of ART increases survival.

• Malabsorption and drug interactions increase risk of drug-resistant TB as well as complicate its treatment.

• Rifamycins can be used in HIV-positive patients on ART, but dose adjustments may be required. RFB generally has fewer drug interactions than does RIF.
Diabetes mellitus

The association of diabetes mellitus (DM) with TB was noted millennia ago. As treatment became available for both diseases in the last century, this association was no longer thought to be important and there was little interest in research on TB in persons with diabetes. However, the emergence of an epidemic of diabetes throughout the developing world has led to an increased awareness of this important syndemic.

There is little controversy about the increased risk of progression to active TB among persons with latent TB infection (LTBI) and diabetes. However, it has only been appreciated recently that outcomes for patients who have both TB and diabetes are poorer than for TB patients without diabetes. The role of DM in furthering drug resistance has remained controversial, but new evidence is accumulating that diabetes does increase the risk of drug-resistant TB.

One mechanism for poorer outcomes and acquired drug resistance has been linked to sub-optimal drug levels, particularly of rifampin (RIF). This was first described in diabetic patients in an Indonesian cohort, and associated with the higher body mass index of patients with TB and diabetes. More recently, researchers at the University of Virginia have reported on the results of therapeutic drug monitoring for first-line drugs in patients who were slow to respond to therapy, defined as no improvement in symptoms or persistent smear positive at 6 weeks of treatment. Diabetic patients were 6.3 times more likely to be slow responders when adjusted for age, gender, country of origin, prior TB cavitary disease, HIV, alcohol and tobacco use. They found that 82% of these slow responders had low levels of either isoniazid (INH) or RIF, with statistically significantly lower serum rifampin levels.

A recent study from Taiwan followed 192 patients (60 with DM and TB, 132 with TB only) who were treated for a full course of anti-TB medication and prospectively followed for over one year. The DM and TB patients had higher treatment failure rates (17% vs. 2%) and longer time to clearance of mycobacteria from sputum (2.5 months vs. 1.6 months) than did the TB only patients. After one year, 3 DM and TB patients (5.0%) and one TB-only patient (0.8 %) had MDR-TB.

Once patients with DM and TB have MDR-TB, there is evidence that outcomes of treatment are also poorer. A recent Korean study looked at 1,407 patients with MDR-TB treated between 2000 and 2002 and followed them for 8-11 years. Diabetes was present in 239 of these or 17%. Patients with MDR-TB and DM had a significantly lower treatment success rate than those without DM (36.0% vs. 47.2%). DM was a significant predictor of poor long-term survival in multivariate analyses.

Patients with diabetes and MDR-TB may be at increased risk of adverse events since many of the anti-TB drugs have side effects that place diabetic patients at special risk. Patients with long-standing diabetes may have underlying renal impairment that can be worsened by the second-line injectable drugs used in MDR-TB. Neuropathy is a common complication of diabetes and also can be worsened by several drugs used to treat MDR-TB such as high-dose INH, cycloserine (CS), linezolid (LZD), and the fluoroquinolones. Patients with diabetes may have decreased gastric motility (gastroparesis) and may be at increased risk of nausea and vomiting with medications like ethionamide (ETA) or other MDR-TB medications.
Recommendations when treating patients who have MDR-TB and diabetes

- Follow renal function carefully and use intermittent dosing for injectable drugs if there is pre-existing or newly developing renal impairment.
- Treat symptoms of gastroparesis aggressively with gastric motility agents such as metoclopramide.
- If neuropathy develops, change the offending drug, if possible. If that cannot be done safely, consider use of agents such as tricyclic anti-depressants, gabapentin, and/or adding or increasing the dosage of Vitamin B-6.
- Consider therapeutic drug monitoring to be sure that adequate blood levels are being obtained, and adjust doses if levels are low.

In addition, for diabetic patients who have initial INH mono-resistance, consider obtaining blood levels of RIF and ethambutol (EMB) to be sure that adequate blood levels are present.

Summary DIABETES

- Diabetes adversely affects treatment outcomes for TB.
- Blood levels of anti-TB medications may be lower and sub-therapeutic in patients with diabetes.
- Diabetic patients are at increased risk of adverse reactions to anti-TB drugs.
- Follow recommendations for treating patients who have diabetes-complicating TB.
Liver disease

Many TB medications have the potential to cause hepatotoxicity, and their use must be contemplated in the setting of severe liver dysfunction. Fortunately, the most important second-line anti-tuberculosis drugs used for treatment of drug-resistant disease do not affect the liver. The following is a list of anti-tuberculosis medications and their effects on the liver:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>INH is most likely to cause hepatitis. In individuals with normal hepatic function, the hepatotoxic effects are usually reversible if the drug is stopped as soon as symptoms are evident. INH hepatotoxicity appears to be increased when rifampin (RIF) is used.</td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
<td>RIF more commonly causes a cholestatic jaundice, but can potentiate the hepatocyte damage caused by INH.</td>
</tr>
<tr>
<td>Pyrazinamide (PZA)</td>
<td>PZA causes fewer episodes of hepatotoxicity than INH, but the events can be severe and prolonged, and worsen even after stopping therapy. PZA is thought to cause the most severe liver toxicity.</td>
</tr>
<tr>
<td>Ethionamide (ETA)</td>
<td>ETA and PAS have also been implicated in hepatotoxic drug reactions.</td>
</tr>
<tr>
<td>Para-aminosalicylate (PAS)</td>
<td>ETA and PAS have also been implicated in hepatotoxic drug reactions.</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Some of the fluoroquinolone drugs (ciprofloxacin and moxifloxacin) have been associated with occasional cases of liver damage. Travaloxacin has been associated with severe liver toxicity in rare cases.</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Not commonly associated with liver dysfunction.</td>
</tr>
<tr>
<td>Bedaquiline (BDQ)</td>
<td></td>
</tr>
<tr>
<td>Clofazimine (CFZ)</td>
<td></td>
</tr>
<tr>
<td>Cycloserine (CS)</td>
<td></td>
</tr>
<tr>
<td>Ethambutol (EMB)</td>
<td></td>
</tr>
<tr>
<td>Linezolid (LZD)</td>
<td></td>
</tr>
</tbody>
</table>

Treatment of drug-resistant TB in the setting of liver failure is complicated and depends on the degree of liver damage. At least one patient has successfully undergone liver transplantation for toxicity of multidrug-resistant (MDR) TB treatment.

- **If the patient has end-stage liver disease and further worsening could be life-threatening** (transplant is challenging in the setting of TB disease), **consider avoiding all hepatotoxic drugs.** The use of LFX, EMB, an aminoglycoside, and CS should be considered, if appropriate. LZD, BDQ, and CFZ are additional alternatives.
- **If the liver disease is not imminently life-threatening,** the **use of a rifamycin** in the regimen is advised if the isolate is susceptible.
Renal failure

Compared to the general population, patients with chronic renal failure undergoing hemodialysis are at a 10- to 25-fold increased risk of developing TB disease once infected. These patients require careful monitoring for treatment of TB, and drug-resistant TB in particular.

Data regarding clearance of anti-tuberculosis drugs are best documented for patients with creatinine clearance less than 30 mL/minute, or for those undergoing hemodialysis. For individuals with mild renal failure or undergoing peritoneal dialysis, the data are less available. In addition to the effects on drug clearance, the diseases that cause renal failure, and concomitant treatments can also impact drug levels (by altering absorption or through drug interactions). Table 1 describes dosing changes for patients with renal insufficiency.

For TB drugs that are cleared by the kidney, the general strategy is to increase the interval between dosing rather than to decrease the dose.
**TABLE 1.**

**Dosing recommendations for adult patients with reduced renal function and for adult patients receiving hemodialysis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in frequency?</th>
<th>Recommended dose and frequency for patients with creatinine clearance &lt; 30 ml/min or patients receiving hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>No change</td>
<td>300 mg once daily, or 900 mg 3 times/week</td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
<td>No change</td>
<td>600 mg once daily, or 600 mg 3 times/week</td>
</tr>
<tr>
<td>Pyrazinamide (PZA)</td>
<td>Yes</td>
<td>25–35 mg/kg/dose 3 times/week (not daily)</td>
</tr>
<tr>
<td>Ethambutol (EMB)</td>
<td>Yes</td>
<td>15–25 mg/kg/dose 3 times/week (not daily)</td>
</tr>
<tr>
<td>Levofloxacin (LFX)</td>
<td>Yes</td>
<td>750–1000 mg/dose 3 times/week (not daily)</td>
</tr>
<tr>
<td>Moxifloxacin (MFX)</td>
<td>No change</td>
<td>400 mg daily</td>
</tr>
<tr>
<td>Cycloserine (CS)</td>
<td>Yes</td>
<td>250 mg once daily, or 500 mg/dose 3 times/week*</td>
</tr>
<tr>
<td>Ethionamide (ETA)</td>
<td>No change</td>
<td>15–20 mg/kg/day (can be in divided doses)</td>
</tr>
<tr>
<td>Para-aminosalicylate (PAS)</td>
<td>No change</td>
<td>4 gm/dose twice daily</td>
</tr>
<tr>
<td>Linezolid (LZD)</td>
<td>No change</td>
<td>600 mg daily</td>
</tr>
<tr>
<td>Clofazimine (CFZ)</td>
<td>No change</td>
<td>100–200 mg daily</td>
</tr>
<tr>
<td>Amikacin (AK)</td>
<td>Yes</td>
<td>12–15 mg/kg/dose 2–3 times/week (not daily)</td>
</tr>
<tr>
<td>Capreomycin (CM)</td>
<td>Yes</td>
<td>12–15 mg/kg/dose 2–3 times/week (not daily)</td>
</tr>
<tr>
<td>Kanamycin (KM)</td>
<td>Yes</td>
<td>12–15 mg/kg/dose 2–3 times/week (not daily)</td>
</tr>
<tr>
<td>Streptomycin (SM)</td>
<td>Yes</td>
<td>12–15 mg/kg/dose 2–3 times/week (not daily)</td>
</tr>
</tbody>
</table>

**Note:** Bedaquiline (BDQ) needs no change with mild to moderate renal dysfunction but should be used with caution in severe renal disease.

- Standard doses are given unless there is intolerance.
- The medications should be given after hemodialysis on the day of hemodialysis.
- Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive accumulation, and to assist in avoiding toxicity.
- There should be careful monitoring for evidence of neurotoxicity.
- Data currently are not available for patients receiving peritoneal dialysis. Until data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing using serum concentration monitoring.
- Refer to Chapter 5, *Medication Fact Sheets* for dosing of aminoglycosides, pyrazinamide, and ethambutol in obese patients.

---

**Estimated creatinine clearance calculations**

- **Men:** Ideal Body Weight (kg) × (140 – age) / 72 × serum creatinine (mg/dl)
- **Women:** 0.85 × Ideal Body Weight (kg) × (140 – age) / 72 × serum creatinine (mg/dl)


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Table adapted from the American Thoracic Society Treatment Guidelines.

* The appropriateness of the 250 mg daily dose has not been established.
While there are some recommendations for giving large doses before dialysis and supplemental doses after dialysis, the easiest and most consistent method is to give the medications immediately following hemodialysis. In most cases, the hemodialysis staff will administer both the parenteral and enteral therapy by directly observed therapy (DOT) and work closely with the provider and TB case manager. Their assistance is particularly helpful for monitoring toxicity and drug levels in these challenging patients.

### Specific TB drugs

**Ethambutol (EMB)**

- Up to 80% cleared by the kidney
- Incompletely dialyzed
- Dose should be adjusted as per Table 1, but there may be an increased risk of accumulation of the drug and eye toxicity in the setting of renal failure
- Drug levels may be helpful in cases where EMB is important for the regimen
- In some circumstances (e.g., peritoneal dialysis, moderate renal failure without dialysis), the use of EMB should be considered carefully (and avoided, if appropriate)
- Little data are available regarding anti-tuberculosis drug dosing for patients on continuous ambulatory peritoneal dialysis (CAPD); however, a dose of 15 mg/kg/dose every 48 hours has been used successfully
- Peak serum concentrations (2 to 3 hours post-dose) generally should be maintained within the normal range of 2 to 6 mcg/mL
- The initial dose of EMB should be based on ideal body weight rather than total body weight if the patient is above his/her ideal body weight (see link to calculator in Estimated creatinine clearance calculations box, following Table 1)
- Monitor carefully for red-green color discrimination and visual acuity changes

**Aminoglycosides (Streptomycin [SM], Kanamycin [KM], Amikacin [AK]) and Capreomycin [CM]**

- Cleared nearly entirely by the kidneys and only about 40% of the dose is removed by dialysis.
- There may be some accumulation of drug and this might increase the risk of ototoxicity. These patients should be monitored closely for ototoxicity (both hearing loss and vestibular dysfunction). Serum drug concentrations can be used to verify that adequate peak concentrations are achieved (for efficacy). Predialysis trough concentrations may be above the usual target ranges since these patients will be unable to clear the drugs without the help of dialysis.
- The aminoglycosides have sometimes been instilled with peritoneal dialysate with careful serum concentration monitoring.
- The serum level of AK is most readily available in commercial labs. The aminoglycoside doses should be based on ideal body weight rather than total body weight if the patient is above his/her ideal body weight (see calculator at bottom of Table 1).
- For patients with creatinine clearance less than 30 mL/min or those receiving hemodialysis, 12-15 mg/kg 2 to 3 times per week is recommended. Some experts would recommend considering 3 times per week dosing for patients with creatinine clearance 50-70 mL/min, and twice-weekly dosing if less than 50 mL/min.
Levofloxacin (LFX)

- Cleared more extensively by the kidney than is moxifloxacin (MFX).
- A dose of 750 to 1000 mg/dose 3 times weekly (not daily) is recommended for treatment of TB. The manufacturer’s literature for dosing LFX for non-tuberculosis infections suggests using smaller doses that may not be adequate. Again, drug concentration monitoring might be beneficial and general toxicity monitoring is imperative.

Moxifloxacin (MFX)

- In one small study, MFX clearance was unaltered in the presence of renal insufficiency following single oral doses. Another recent study found that MFX pharmacokinetics in critically ill patients who had acute renal failure and were undergoing dialysis was similar to those in healthy subjects without renal impairment. Therefore, MFX dosage should not be altered in patients with renal disease.

Cycloserine (CS)

- Cleared by the kidney; toxicity appears to be closely related to elevated serum concentration
- Peak serum concentrations (2 hours post-dose) generally should be maintained within the normal range of 20 to 35 mcg/mL

Para-aminosalicylate (PAS)

- Metabolized in the gastrointestinal (GI) tract and liver, but its inactive metabolite acetyl-PAS is eliminated renally. No specific toxicity of the metabolite is known. The manufacturer does not recommend its use in end-stage renal failure. However, in a well-performed study, clearance of the metabolite (and PAS) by dialysis was documented. In several case reports, PAS was used after dialysis.
- The American Thoracic Society (ATS) recommends using the usual daily dose and dosing after dialysis. There are few data regarding use of PAS in patients with renal failure not yet on dialysis, but no clear evidence of toxicity.

**Summary RENAL FAILURE**

- INH, RIF, MFX, ETA, PAS, LZD, and CFZ are not cleared by the kidney, and their dosing does not require adjustment for renal failure. Most other anti-tuberculosis drugs require dose adjustment for significant renal insufficiency.
- Dosing guidelines are well established for patients with creatinine clearance less than 30 mL/minute or undergoing hemodialysis. Adjustment for patients with more mild renal impairment or undergoing peritoneal dialysis is not as well described.
- Therapeutic drug monitoring is always indicated for patients with impaired renal function receiving an injectable drug, EMB, or CS, and may be helpful for other medications as well.
Pregnancy

Treatment of drug-resistant TB during pregnancy is very challenging. All female patients of childbearing age with MDR-TB should be strongly advised to avoid pregnancy, and if sexually active, to use highly effective forms of contraception (e.g., IUDs or implantable hormonal contraceptives). Some clinicians do monthly laboratory screening to detect pregnancy early. Many of the medications used to treat drug-resistant TB are either teratogenic or their safety during pregnancy is unknown. For these reasons, there has been a reluctance to aggressively treat pregnant MDR-TB patients. However, this view is changing.

The largest case series published to date included 38 pregnant patients with MDR-TB. Outcomes were comparable to non-pregnant patients. Of the 38 pregnancies, 5 ended in spontaneous abortions, and 1 child was stillborn. One study in 2005 described long-term follow-up of 6 children (average age 3.7 years) exposed to MDR-TB drugs while in utero. All 6 showed normal development. One child demonstrated mildly increased thresholds on auditory brainstem response testing, but his language development was normal, as was an otorhinolaryngological assessment. The majority of these children were exposed to both an injectable agent and a fluoroquinolone in utero.

- Consult with an MDR-TB expert throughout the course of pregnancy.
- Have serial discussions with the patient and concerned family members to discuss risks and benefits of various treatment options.

For pan-susceptible TB during pregnancy, use of pyrazinamide (PZA) is generally avoided in the United States due to lack of safety data. In the case of drug-resistant TB, PZA should be used when the isolate is susceptible.

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Medications</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH monoresistance</td>
<td>RIF + EMB + PZA</td>
<td>6–9 months</td>
</tr>
<tr>
<td>PZA monoresistance</td>
<td>INH + RIF + EMB Followed by INH and RIF</td>
<td>2 months At least 7 more months</td>
</tr>
<tr>
<td>(M. bovis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIF monoresistance</td>
<td>INH + EMB + PZA</td>
<td>At least 18 months</td>
</tr>
<tr>
<td>Consider addition of a fluoroquinolone or injectable drug after delivery to shorten course.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Several options face the pregnant MDR-TB patient and her team of healthcare providers:

- Treatment of drug-resistant TB with the best possible, albeit frequently weak, MDR-TB regimen, avoiding the known (potential) teratogens: the aminoglycosides and ethionamide (ETA). The regimen can be strengthened after the baby delivers. A potential regimen might include cycloserine (CS), para-aminosalicylate (PAS), and EMB or PZA if still susceptible. Experience with the fluoroquinolones during pregnancy is still limited, but small series have not shown teratogenicity.
- Using a standard MDR-TB regimen with an injectable agent and/or a fluoroquinolone and additional second-line agents as guided by susceptibility testing. It is
essential to discuss the potential risks and benefits with the patient and family prior to beginning such a regimen.

- No treatment at all for very stable disease pending delivery of the baby. An example might be an asymptomatic patient picked up during screening who has a small infiltrate, is smear-negative, and is within a month or two of delivery.
- If the mother’s life is at risk without use of known teratogenic drugs, termination of the pregnancy is sometimes reluctantly considered.

**Teratogenicity**

- **Aminoglycosides** are the only TB drugs that have well-documented teratogenicity. **Streptomycin (SM)** and **kanamycin (KM)** have been implicated as the cause of mild to severe bilateral congenital deafness (eighth nerve toxicity) in up to 17% of pregnancies. For that reason, **amikacin (AK)** and **capreomycin (CM)** are also not recommended during pregnancy, but have been used safely in some reports.

- **ETA** use has been associated with congenital defects in several children. In general, there are not enough data to determine its safety during pregnancy.

- **Fluoroquinolones** are generally avoided during pregnancy due to the observation of arthropathy in puppy models and adverse events in monkeys receiving norfloxacin. **Levofloxacin (LFX)** has not been found to be teratogenic in animals, but large doses have led to decreased fetal weight and increased fetal mortality in rats. One series reported 200 women exposed to fluoroquinolones in the first trimester and none of the babies suffered musculoskeletal abnormalities. Fluoroquinolone drugs have been used in the treatment of MDR-TB in pregnancy and have not been associated with identified teratogenicity.

- **PZA** is not included in the TB regimens of most pregnant women in the United States with drug-susceptible TB due to lack of controlled data during pregnancy. The World Health Organization (WHO) and the International Union Against TB and Lung Disease (IUATLD) do recommend routine use of PZA during pregnancy (as do some jurisdictions in the United States), and toxicity to the fetus has not been documented. For women who are HIV-positive or have drug-resistant TB disease, PZA should be included in the TB regimen if the isolate is susceptible.

- **INH**, **RIF**, and **EMB** have not been associated with teratogenic effects. **Rifabutin (RFB)**, **CS**, and **PAS** have not been extensively studied, but animal models and anecdotal human reports have not shown toxicity. **Linezolid (LZD)** is classified by the FDA as pregnancy category C. Some animal studies failed to reveal evidence of fetal harm; however, studies using high doses demonstrated fetotoxicity and teratogenicity. There are no controlled data in human pregnancies. **LZD** should only be given during pregnancy when benefit outweighs risk.

### Infection control during pregnancy and childbirth

Infection control is particularly challenging during pregnancy and childbirth.

- Consult with experts in infection control and TB treatment to ensure that appropriate measures are in place in settings where these women will receive obstetrics (OB) care.
- If the patient is still contagious at the time of delivery, make plans for delivery well in advance. Arrange for a negative pressure birthing room and appropriately fit test personnel for N-95 or more efficient masks. It will not be realistic to expect that a laboring mother will be able to keep a mask on herself.
Management of the newborn

Management of the infant born to a mother with TB disease includes 2 major issues:

1. Is the baby already infected with TB (congenital TB)?
2. How can we prevent the baby from becoming infected with TB?

**BREASTFEEDING**

Most TB drugs cross into the breast milk at low levels. Mothers receiving INH, CS and ETA and their breastfed infants should be supplemented with vitamin B6 (pyridoxine). The doses of TB drugs that babies receive via breast milk are insufficient to treat or prevent TB in the infant. Small amounts of fluoroquinolones have been detected in human breast milk. Because of the risk of arthropathy in immature animal models, ATS does not recommend use of fluoroquinolones during breastfeeding. However, in the setting of MDR-TB, where fluoroquinolones play such an essential role, the potential benefit may outweigh the potential risk. In these situations, the family should be informed of the theoretical risk.

**Congenital TB**

- Fortunately, congenital TB is exceedingly rare. It most commonly occurs when the mother has untreated (and often undetected) TB disease shortly after her primary infection, disseminated TB, or disease of the uterus or genital tract.
- Congenital TB is usually diagnosed in the first weeks to months of life and frequent findings include the following:
  - Fever
  - Irritability
  - Poor feeding
  - Skin lesions
  - Liver and/or spleen enlargement
  - Enlarged lymph nodes
  - Cough or increased work of breathing
  - Various chest radiographic abnormalities
- Routine evaluation of a baby whose mother has known or suspected TB disease should include physical examination to evaluate for these findings as well as a chest radiograph. Abdominal ultrasound is also sometimes helpful to evaluate for hepatosplenomegaly.
- Culture and examination of the placenta by a pathologist is sometimes helpful. Granulomata in the placenta increase the likelihood that the baby is infected. Fortunately, the placenta is an efficient organ and most babies born to mothers with granulomatous placenta will not themselves be infected.
- If the baby has physical findings or radiographic abnormalities to suggest congenital TB, the baby should immediately undergo gastric aspirate collection, a procedure...
that has a very high yield for both smear and culture (around 90% each) in cases of congenital TB. See Chapter 6, *Pediatrics*, for details on obtaining gastric aspirates. Lumbar puncture for cell count, protein, glucose, bacterial and acid-fast bacilli (AFB) smear and culture should be performed for a child with suspected congenital TB. Mycobacterial culture of blood, skin lesions, and ear drainage are also sometimes helpful.

Evaluation of the sick newborn for neonatal sepsis and other congenital infections should also be considered, given the rarity of congenital TB.

**Treatment of suspected congenital TB**

If a newborn is suspected of having active or congenital TB, treatment for TB disease should be initiated as soon as the aforementioned studies are collected (collect 2 to 3 gastric aspirates on the first day). Treatment should be based on the mother’s TB isolate susceptibility pattern in consultation with a pediatric TB expert.

**Prevention of infection in the newborn**

- If the mother is still potentially infectious with drug-resistant TB, mother and baby should be separated until the mother is not infectious. However, mother-infant bonding is important and there are trade-offs to be considered in making a decision about separating a newborn and its mother. Options such as outdoor visitation with the mother wearing a mask may be appropriate.

- If an infant whose mother has known infectious or suspected TB disease is vigorous, afebrile, and has a completely normal physical exam and chest radiograph, consider treating the infant prophylactically for latent TB infection (LTBI), in case the baby has been infected during the birth process and does not yet have TB disease, or to prevent post-natal acquisition of the organism. If the mother’s isolate is sensitive to INH or RIF, that drug should be employed. If the mother has MDR-TB, seek the advice of a pediatric TB expert.

- If the baby is treated with INH and is breastfeeding, the baby should also receive 6.25 mg or one-fourth of a 25-mg tablet of pyridoxine. If the mother is receiving INH, ETA, or CS, the breastfed baby should also receive pyridoxine.

- **Because it is possible for an infant to have early, subclinical congenital TB, the infant should be followed closely (weekly) by an experienced pediatric provider and observed for development of the aforementioned findings.**

- If separation of the mother and infant is not possible and no practical prophylactic regimen is available, the Bacille Calmette-Guérin (BCG) vaccine is sometimes administered. BCG prevents some cases of disseminated TB and TB deaths in infants. Unfortunately, BCG does not prevent TB infection, and it may make the interpretation of the tuberculin skin test (TST) challenging for the first year or two after administration. (See *Resources* at the end of this chapter for information about how to obtain and administer the BCG vaccine.)

- If the baby is asymptomatic and the mother has been receiving effective TB therapy and is deemed to be non-infectious, and there are no other potentially infectious source cases in the infant’s home, close monitoring without chest radiograph or prophylactic treatment is appropriate.
**TST/IGRA**

The TST and interferon gamma release assay (IGRA) tests are rarely positive in newborns, and a negative result contributes little to the early evaluation. The TST is not contraindicated in infants. Most experts recommend considering the skin test reliable after 6 months of life for immunocompetent children. Note that this practice differs from current guidance from the American Academy of Pediatrics, which recommends repeating a TST/IGRA at 3-4 months in infants potentially exposed to perinatal TB. IGRA may be less reliable than the TST in children under age 3, but may be used on a case-by-case basis.

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**Summary**  
**PREGNANCY**

- Treatment of drug-resistant TB during pregnancy is challenging due to:
  - Risk of teratogenicity of anti-tuberculosis drugs
  - Infection control risks during OB care
  - Risk of transmission to the infant

- While PZA is avoided in drug-susceptible TB, it is recommended for use in drug-resistant TB during pregnancy.

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**Solid organ transplant**

The occurrence of TB among solid organ transplant (SOT) recipients varies based on the background rates of TB in the general population. It has been estimated that TB among the SOT population is 20–74 times higher than that of the general population. True incidence estimates in the SOT population are often difficult to measure because most studies have calculated a cumulative prevalence of TB. The prevalence of TB in the SOT population in low TB burden regions ranges from 0.2% to 6.5%. TB among persons who have received a SOT is associated with a mortality of 6%–22%, which is substantially higher than the 5% mortality among all TB patients in the United States.

TB can occur in a person who has received a SOT due to five reasons:

1) reactivation of latent TB infection (LTBI)  
2) relapse of previously treated TB  
3) donor-derived reactivation  
4) transmission of TB  
5) person with active TB requiring urgent transplantation (e.g., drug-induced hepatotoxicity)

The most common scenario is reactivation of LTBI.

Although the onset of TB varies based on the reason, the majority of TB cases occur during the first 6 months post-transplant. However, for renal transplant patients the onset can be later. The diagnosis of TB among persons who have received a SOT can be challenging due to the lack of traditional TB risk factors, atypical symptoms at presentation,
and a wide range of radiographic manifestations including focal infiltrate, miliary pattern, pulmonary nodules, and pleural effusions. Although most SOT patients are diagnosed with pulmonary TB, 16% have extrapulmonary disease and 33% have disseminated TB disease, which can also make the diagnosis difficult.

Treatment of MDR-TB in a person who has received a SOT can be complicated, primarily due to the interactions between TB medications and immunosuppressive medications. Treatment of MDR-TB in a person who has received a SOT will require close coordination between the TB clinician and the transplant team to determine whether the dose of immunosuppressants can be safely reduced during TB treatment. Common interactions between MDR-TB drugs and immunosuppressants are summarized in Table 1. Due to the occurrence of these interactions, MDR-TB treatment will require close monitoring and consideration of use of intermittent dosing of medications (e.g., aminoglycosides or capreomycin, and linezolid) to ensure completion of a course of treatment.

**TABLE 1.**

Interactions between immunosuppressants and commonly used MDR-TB medications

<table>
<thead>
<tr>
<th>Immunosuppressant</th>
<th>Pyrazinamide</th>
<th>Ethambutol</th>
<th>Aminoglycoside or capreomycin</th>
<th>Moxifloxacin or Levofloxacin</th>
<th>Linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Increased risk of tendonitis</td>
<td>None</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>None</td>
<td>None</td>
<td>Combination increases nephrotoxicity</td>
<td>May increase cyclosporine levels (usually, LFX only)</td>
<td>None</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>None</td>
<td>None</td>
<td>Combination increases nephrotoxicity</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Rapamycin/sirolimus</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Mycophenolate mofetil (Cellcept)</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>May decrease mycophenolate level</td>
<td>None</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Resources


Information about how to obtain BCG:
BCG can be ordered from any wholesaler that distributes Merck vaccines. You may also contact Merck (800-672-6372) directly to determine if the product is available as shortages may occur. It is important to clarify your request for BCG vaccine for percutaneous use (not the BCG live for intravesical administration for bladder cancer).

Instructions for BCG application.

References

**EXTRAPULMONARY TB**


**HIV**


• Centers for Disease Control and Prevention. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. MMWR. 2000;49(9):185-189.


**DIABETES**


LIVER DISEASE


RENAL FAILURE


PREGNANCY


SOLID ORGAN TRANSPLANT