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Co-morbidities & Special Situations

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Managing drug-resistant TB (DR-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 DR-TB in the medical literature. The limited clinical data on extrapulmonary multidrug-resistant (MDR-)TB suggest that the lessons from the treatment of extrapulmonary drug-susceptible 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 four large MDR-TB programs.

Treatment of extrapulmonary DR-TB is complicated by several issues:

- **Lack of data:** 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.
- **Use of steroids:** Several forms of extrapulmonary TB 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, demonstrating a mortality benefit in TB meningitis.
  - Although corticosteroids were previously universally recommended in the setting of TB pericarditis, a 2014 randomized trial led to a narrower approach of adjunctive corticosteroids only in patients with constrictive TB pericarditis or those with — or at high risk for — constrictive pericarditis.
  - Although similar efficacy data are not available for patients with DR-TB, expert opinion supports use of corticosteroids in cases of central nervous system (CNS) and selected pericardial disease.
- **Paradoxical worsening:** Some forms of TB (particularly cervical lymphadenitis [scrofula] and intrathoracic adenopathy) are known to worsen as TB is being successfully treated. This is due to immune reconstitution as the organism is being eliminated. It is particularly common in persons with HIV 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 diagnosis of exclusion.

- Other diagnoses, unrecognized drug resistance, and microbiologic failure should first be excluded before the diagnosis of IRIS is accepted. If these other etiologies are not appropriately excluded, the correct diagnosis (drug resistance and treatment failure) can be delayed.
- Depending on symptoms and organs involved, management of paradoxical worsening may include observation with supportive care, nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids, and continued anti-TB therapy.
- In patients with severe, protracted, or recurrent paradoxical reactions despite corticosteroid treatment, specifically in the setting of CNS TB, there are some limited data on the use of host-directed therapies (e.g., infliximab, thalidomide, and anakinra), but these options should only be considered with the support of expert consultation.

Caution is also advised when considering standardized, shorter duration (6- and 9- to 12-month) DR-TB regimens.

- **Shorter-course, standardized, 6-month regimens** (bedaquiline, pretomanid, and linezolid [BPaL], BPaL and moxifloxacin [BPaLM]): There are minimal data from clinical trials or case series demonstrating efficacy of BPaL or BPaLM in extrapulmonary TB, and severe forms of extrapulmonary TB such as CNS TB or osteomyelitis were explicitly excluded from clinical trials to date. Case reports and pharmacokinetic data are limited and efficacy of these regimens in CNS TB specifically remains unclear (see ***Drug-resistant CNS TB***). Some experts have reported early successful treatment of non-severe extrapulmonary TB with these regimens.
- **Shorter-course, standardized, 9- to 12-month regimen:** Because of limited data, the standardized shorter-course (9- to 12-month) regimen for MDR-TB is not recommended in persons with disseminated TB, miliary TB, CNS TB, or in patients with HIV/AIDS with extrapulmonary disease. The World Health Organization (WHO) 2020 Operational Handbook for DR-TB treatment suggests this regimen can be used in non-complicated extrapulmonary disease.
- **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, cervical adenitis) might benefit from surgical debridement, resection, or drainage (e.g., empyema, abscesses) to decrease the burden of disease and facilitate resolution. 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.

Other forms of extrapulmonary TB may require surgical interventions to address complications arising from disease sequelae. Pericardiectomy may be required in cases of persistent constrictive pericarditis that is not responsive to anti-mycobacterial therapy. Ureteral stenting or nephrostomy may be indicated in cases of ureteral strictures from genitourinary TB. Surgical decompression or placement of a ventriculoperitoneal shunt may be indicated in cases of TB meningitis or CNS TB. Stabilization procedures may be required with severe spinal (Pott's) TB. Overall, surgical interventions are often used in the setting of extrapulmonary TB to provide diagnostic specimens or to treat complications of TB disease.

Drug-resistant CNS TB

Several reports detail poor outcomes of drug-resistant TB meningitis. Most of the patients in these series were people with HIV 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%. 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 (although one series showed no increased risk of in-hospital mortality with INH resistance). Considerations when treating TB meningitis or CNS TB include: Choice of medications to ensure CNS penetration, optimal dosing and route of administration, and evaluating and monitoring for complications, e.g., hydrocephalus, stroke/vasculitis, and tuberculomas.

TB drugs and their CNS penetration

Preferred drugs for use in CNS TB:

- **INH** is one of the most important drugs in the treatment of TB meningitis if the isolate remains susceptible. 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)** and **rifabutin (RFB)** penetrate poorly into the CSF (10-20%) but levels above the minimum inhibitory concentration (MIC) can still be achieved and RIF should be used if susceptible in CNS disease. Penetration is thought to be improved with inflamed meninges, but study results are mixed. One study showed similar penetration with uninflamed meninges, 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 in Indonesia, but findings were not replicated in a second trial in Vietnam using high-dose oral RIF. Nevertheless, many experts recommend high-dose RIF for TB meningitis due to potential survival benefit and improved early bactericidal activity. While the optimal dose of RIF is unknown, oral doses of 30-35 mg/kg appear to be well-tolerated, safe, and lead to increased RIF CSF exposure above the MIC.

- **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.
- **Levofloxacin (LFX)** and **moxifloxacin (MFX)** both have good 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 CSF 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, but addition of MFX to IV RIF for pan-susceptible CNS TB did not seem to improve outcomes.
- **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. LZD has been successfully used to treat gram-positive drug-resistant meningitis in patients.
- **Ethionamide (ETA)** and **cycloserine (CS)** also have good CNS penetration, with levels in CSF approaching that in serum. Note: A South African study evaluated CSF levels of ETA and concluded that doses of 20 mg/kg/day should be used to achieve useful levels in the CSF. ETA is better tolerated in children, as compared to adults, and is often used in individualized pediatric regimens.
- **Meropenem (MPM)** has excellent CNS penetration and is preferred over imipenem/cilastatin due to the increased risk for seizure with the latter agent. Carbapenems should always be paired with clavulanic acid which also penetrates the CNS.

Less preferred drugs for use in CNS TB:

- **Ethambutol (EMB)** has poor CNS penetration and given its bacteriostatic properties, many experts opt to use drugs with better CNS penetration in its place, especially in severe CNS disease. There are limited data on **para-aminosalicylic acid (PAS)**; it is thought to have poor CNS penetration and should not be relied upon as active treatment for CNS TB.
- **Streptomycin (SM) and the other aminoglycosides** have poor or variable penetration to the CSF, although 20% or more of serum concentrations may be achieved particularly with inflamed meninges (CSF concentrations of 1-9 mcg/mL in most patients). Successful use of intrathecal administration has been described in at least one case of CNS MDR-TB (see ***Route of Administration***).

Drugs with limited data for use in CNS TB:

Data on the CNS penetration of clofazimine (CFZ), bedaquiline (BDQ), pretomanid (Pa), and delamanid (DLM) are limited. In addition, drug levels in CSF may not parallel drug concentrations in brain tissue or meninges.

- A study from 2019 evaluated the distribution of DLM and its metabolite in the brain and CSF of rabbits and in the CSF of 3 patients receiving DLM as a multidrug regimen for extensively drug-resistant (XDR-) TB meningitis. Although CSF drug levels were low, DLM concentrations in the brains of rabbits were 5-fold higher than in plasma and free-drug levels in the CSF may still be sufficient.
- A recent animal study using 18-fluorine-radiolabeled-pretomanid positron emission tomography (PET) revealed excellent penetration of Pa into brain tissues, although BPaL appeared to be inferior to standard treatment based on measurements of bacterial burden throughout treatment, likely due to low penetration of BDQ and LZD in the brain tissues.
- A case report of a patient receiving BDQ for MDR CNS TB/meningitis described undetectable BDQ CSF levels despite therapeutic serum levels. However, a pharmacokinetic study of BDQ in CSF in patients with pulmonary TB (presumably intact blood-brain barrier; study also used CSF collection process optimized to improve measurement of highly protein-bound drug) determined that BDQ and the M2 metabolite penetrated the CSF and was found at concentrations similar to the estimated unbound fraction in plasma.

Further clinical studies are needed.

Route of administration

If the patient is obtunded or severely ill, medications given via naso/orogastric tubes can be effective, but many experts would consider using drugs that can be given parenterally (INH, RIF, fluoroquinolones, LZD, and aminoglycosides) given potential for impaired absorption. One study showed high-dose RIF administered IV improved outcomes.

Two reports of treatment of MDR-TB meningitis in individuals without HIV 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 people with HIV, it is hard to compare the outcomes of intrathecal vs. systemic administration of second-line anti-TB drugs. However, for patients not responding quickly to systemic treatment, intrathecal administration may be an option.

SUMMARY: EXTRAPULMONARY TB

- Data regarding treatment of extrapulmonary DR-TB are limited.
- In general, extrapulmonary involvement other than meningitis is not a risk factor for treatment failure in DR-TB.
- Surgical resection and/or drainage may decrease bacterial burden and improve outcomes in some presentations of extrapulmonary disease. Full medical treatment is still indicated.
- DR-TB meningitis is challenging to treat due to the incomplete CSF penetration of many second-line drugs. Because of favorable CNS penetration and clinical experience, many experts use fluoroquinolones and LZD in regimens to treat CNS DR-TB.

HIV

People 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. People with HIV 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 with a normal 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 without HIV.

People with HIV/AIDS are more likely to have atypical presentations of TB

TB progresses much more rapidly among persons with severe immunodeficiency. When treating persons with advanced HIV disease who have risk factors for infection with a drug-resistant strain of *mycobacterium (M.) tuberculosis*, prioritize use of rapid molecular diagnostics for drug-susceptibility testing (DST), and use a lower threshold to consider regimens with expanded coverage for drug resistance.

Factors that increase the risk for exposure to or development of drug-resistant (DR) TB in people with HIV/AIDS include:

- Previous exposure to rifamycins (e.g., the use of rifabutin [RFB] to prevent or treat disseminated *Mycobacterium avium intracellulare* disease)
- Use of highly intermittent rifamycin treatment
- Malabsorption of drugs
- Drug-drug interactions (e.g., inadequate rifamycin dosing with antiretroviral coadministration, typically rifampin [RIF] or rifapentine [RPT] co-administration with protease inhibitors, efavirenz, or integrase inhibitors)
- Residence in congregate settings
- Co-morbid conditions, including those that may interfere with adherence (e.g., substance use disorders)
- CD4 lymphocyte count below 100 cells/mm^3

Unfortunately, people with HIV with multidrug-resistant (MDR-) TB have higher mortality rates than MDR-TB patients without HIV, 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 DR-TB, the patients had advanced AIDS, and MDR-TB was not recognized initially—therefore, drug therapy was inadequate.

A large series from Thailand of TB patients with HIV showed that early detection and optimal treatment of MDR-TB improved survival, as did antiretroviral therapy (ART). ART should be initiated in all patients with HIV and TB with special attention paid to drug interactions and overlapping toxicities.

Fortunately, recent trials of shorter regimens included many patients with HIV. A multi-site trial (n=109) of an all-oral regimen for extensively drug-resistant (XDR-) TB or treatment intolerant/non-responsive MDR-TB containing bedaquiline, pretomanid, and linezolid (BPaL) showed favorable outcomes in 90% of participants. This trial included 56 (51%) participants with HIV/AIDS receiving ART with CD4 > 50.

Overall rates of unfavorable outcomes, death, and serious adverse events were similar among those with and without HIV.

Treatment of DR-TB in people with HIV/AIDS is complicated by:

- Overlapping drug side effects or toxicity of medications used to treat TB, HIV, or other opportunistic infections
- High pill burden for medicines that must be taken for both conditions
- The fact that the immune system cannot always contribute to control of the TB disease
- Malabsorption of drugs
- Drug-drug interactions
- Complex social, mental health, and substance use 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
- Paradoxical reactions (TB disease appears to worsen when immune reconstitution occurs)

To maximize care of people with HIV/AIDS:

Screen all patients with TB disease for HIV.

- Identify people with HIV by screening all patients with TB disease for HIV.
- Use 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.
- Understanding drug-drug interactions is essential for proper treatment. Consult a clinical pharmacist and/or a drug interaction tool such as Liverpool HIV Interactions (see ***Resources*** at the end of this chapter) to check for potential drug-drug interactions.
- **It is critically important to appropriately treat the HIV infection** as well as the DR-TB. Consider optimizing the HIV regimen based on CD4 count, HIV RNA, HIV genotype, HLA-B*5701 status, and presence of co-morbidities as well as the timing of initiation of ART for antiretroviral-naive patients. See ***Resources*** for a link to current ART recommendations.

- Initiation of ART in people with HIV who are treatment-naïve is associated with increased drug toxicity and the phenomenon of immune reconstitution; however, clinicians should weigh the growing body of evidence supporting early initiation of ART, in general and specifically in patients with HIV-TB co-infection. Immune reconstitution may exacerbate clinical symptoms of TB by stimulating an inflammatory response. Prednisone therapy during the first 4 weeks after ART initiation in patients with HIV with CD4<100 may reduce the risk of TB-related immune reconstitution inflammatory syndrome (IRIS).
- **In patients with CD4 lymphocyte counts of 50 or higher, start ART within 8 weeks of TB therapy.**
- **In patients with CD4 less than 50, begin ART as soon as possible, ideally within 2 weeks. The exception is 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. Expert consultation for CNS TB is recommended; many experts would consider early initiation of ART if monitoring of CNS adverse events and drug-drug interactions is possible.
- In patients with CD4 less than 100, low-dose prednisone therapy started within 4 weeks of ART initiation may reduce the risk of IRIS.

Consider alternate HIV or TB drugs when interactions occur.

- **Rifamycins are inducers of cytochrome P-450 and interact with many drugs.** Use of RIF is not recommended for patients receiving protease inhibitors (boosted or unboosted), elvitegravir (EVG), etravirine (ETR), rilpivirine (RPV), or tenofovir alafenamide (TAF). Increased antiretroviral (ARV) doses are needed when RIF is used with dolutegravir (DTG), raltegravir (RAL), or maraviroc (MVC). 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 several of the anti-infectious agents that may be taken by patients with HIV**, including the macrolide drugs, cidofovir, anti-fungal drugs, and others.

- Concurrent use of efavirenz (EFV) and bedaquiline (BDQ) may result in reduced BDQ exposure. Although the clinical significance of this interaction remains unclear, most experts avoid using EFV in patients receiving BDQ, and instead favor ART regimens containing integrase inhibitors.
- Avoid BDQ use with cobicistat, as cobicistat is a strong CYP3A4 inhibitor and may increase BDQ exposure and the risk of adverse reactions.
- Use of lopinavir/ritonavir alters the metabolism of BDQ and leads to higher serum levels and effects of BDQ.

- Efavirenz increases the clearance of para-aminosalicylate (PAS) by approximately 50%.
- Knowledge about the metabolism of the traditional second-line drugs (ethionamide [ETA] and cycloserine [CS]) 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.
- Delamanid (DLM) appears to have few clinically significant drug interactions, and does not significantly impact systemic exposure to tenofovir, efavirenz, lopinavir, or ritonavir when co-administered with these drugs.
- Second-line injectable drugs are primarily renally excreted unchanged and should not have interactions with antiretrovirals.
- Fluoroquinolones are unlikely to have significant interactions with antiretrovirals (low quality evidence exists for potential interactions between levofloxacin (LFX) or moxifloxacin (MFX) and rilpivarine or atazanavir, as well as MFX and efavirenz, etravirine, or ritonavir; use *Liverpool HIV Interactions* or another drug interaction tool).
- 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.
- 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 DR-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 use disorder clinics, and mental health facilities.
- Involve the patient's social support system, as appropriate.

SUMMARY: HIV

- MDR-TB patients with HIV have higher mortality rates, particularly when they are profoundly immunocompromised (CD4 lymphocyte count less than 100) and when an optimal TB regimen is not initiated early in the course of disease. Expert consultation is advised.
- Antiretroviral therapy is a critical part of the treatment of DR-TB in people with HIV.
- Patients with HIV can be cured of their DR-TB disease but require special monitoring and concurrent care of their HIV disease. Early initiation of ART increases survival.
- All-oral 6-month therapies are appropriate for some TB patients with HIV.
- Malabsorption and drug interactions increase risk of DR-TB as well as complicate its treatment.
- Rifamycins can be used in patients with HIV on ART, but dose adjustments may be required. RFB generally has fewer drug interactions than does RIF.

Diabetes mellitus

The association of diabetes mellitus 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.** The 2011 publication of the *Collaborative Framework for the Care and Control of Tuberculosis and Diabetes* solidified a rising global awareness that outcomes for patients who have both TB and diabetes are poorer than for TB patients without diabetes. The role of diabetes in furthering drug resistance has remained controversial, but some evidence is accumulating that diabetes may increase the risk of drug-resistant (DR-) TB.

Outcomes for patients who have both TB and diabetes are poorer than for TB patients without diabetes.

One mechanism for poorer outcomes and acquired drug resistance has been linked to **suboptimal drug levels**, particularly of rifampin (RIF). This was first described in patients with diabetes in an Indonesian cohort and associated with the higher body mass index of patients with TB and diabetes. A publication from Virginia 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. **Patients with diabetes were 6.3 times more likely to have a slower response to therapy** when adjusted for age, gender, country of origin, prior TB cavitary disease, HIV, and alcohol and tobacco use. Researchers found that 82% of these slow responders had low levels of either isoniazid (INH) or rifampin (RIF), with statistically significantly lower serum RIF levels.

A 2011 study from Taiwan followed 192 patients (60 with TB and diabetes, 132 with TB only) who were treated for a full course of anti-TB medication and prospectively followed for over one year. Those with TB and diabetes 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 those with TB-only. After one year, 3 persons with TB and diabetes (5.0%) and one person with TB-only (0.8 %) had multidrug-resistant (MDR-) TB.

Once persons with TB and diabetes have MDR-TB, there is evidence that **outcomes of treatment are also poorer.** A 2013 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 patients (17%). Patients with MDR-TB and diabetes had a significantly lower treatment success rate than those without diabetes (36.0% vs. 47.2%). Diabetes was a significant predictor of poor long-term sur-

vival in multivariate analyses. Newer data suggests that metformin specifically may improve efficacy of TB treatment when used in patients with TB and diabetes.

Patients with diabetes and MDR-TB may be at **increased risk of adverse events** because many of the anti-TB drugs have side effects that place patients with diabetes at special risk. Patients with long-standing diabetes may have underlying **renal impairment** that can be worsened by second-line injectable drugs. **Neuropathy** is a common complication of diabetes that can also 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.

Consider **pharmacologic effects** when administering TB and diabetes medications. Linezolid (LZD), fluoroquinolones, and para-aminosalicylate (PAS) may enhance the hypoglycemic effects of insulin, metformin, thiazolidinediones, GLP-1 receptor agonists, DDP-4 inhibitors, sulfonylureas, and SGLT1 inhibitors. RIF can decrease the effectiveness of sulfonylureas, thiazolidinediones, DDP-4 inhibitors, and SGLT1 inhibitors. In addition, fluoroquinolones have been associated with glucose homeostasis abnormalities that can lead to both hypo- and hyperglycemia.

In patients with poorly controlled diabetes and TB who require dual or triple diabetes therapy, consider the risk and benefit of multiple oral medications. Some patients may benefit from early insulin therapy for tighter glucose control, decrease in pill burden, and avoiding additional GI side effects associated with multiple oral diabetic medications.

Side effects of both TB medications and TB disease (initial low body weight, anorexia or other GI side effects, and increasing weight as TB disease is treated) may impact the ability to maintain optimal dosing of diabetes medications. In patients with drug-drug interactions, close monitoring of glucose and titration of diabetes medications are recommended.

Recommendations when treating patients who have MDR-TB and diabetes

- Treat and monitor diabetes to achieve optimal glucose control.
- Follow renal function carefully and avoid injectables or use intermittent dosing 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 (particularly if extensive disease, uncontrolled diabetes, gastroparesis, or renal dysfunction) to be sure that adequate blood levels are being obtained, and adjust doses if levels are low. This also applies to RIF and/or other drugs used for INH mono-resistance.

SUMMARY: DIABETES

- Diabetes increases risk of progression from LTBI to active TB disease and adversely affects treatment outcomes for TB.
- Blood levels of anti-TB medications may be lower and sub-therapeutic in patients with diabetes and therapeutic drug monitoring should be considered.
- Patients with diabetes are at increased risk of adverse reactions to anti-TB drugs.

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-TB drugs used for treatment of drug-resistant (DR-) disease have a lower risk of hepatotoxicity. **Table 1** is a list of anti-TB medications and their effects on the liver.

TABLE 1 **Anti-TB medications and their effects on the liver**

Drug	Effect on liver
Isoniazid (INH)	INH is most likely to cause hepatitis. In patients 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.
Rifampin (RIF)	RIF more commonly causes a cholestatic jaundice but can potentiate the hepatocyte damage caused by INH.
Pyrazinamide (PZA)	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.
Ethionamide (ETA) **Para-aminosalicylate (PAS)**	ETA and PAS have also been implicated in hepatotoxic drug reactions.
Fluoroquinolones	Moxifloxacin (MFX) has been associated with occasional cases of liver damage. However, levofloxacin (LFX) is thought to have less hepatoxicity and has been used in “liver-sparing” regimens following hepatotoxicity (both LFX and MFX have been successfully used with close monitoring).
Pretomanid (Pa)	There is uncertainty about the effect of Pa on the liver. Early trials of regimens including Pa and other liver-toxic medications like PZA showed some hepatotoxicity. Studies using BDQ and LZD have found rare hepatotoxicity.
Bedaquline (BDQ)	Not associated with hepatotoxicity in most observational studies. The BDQ package insert states that because it has not been studied in patients with severe liver disease, it should be used with caution and only when risks outweigh benefits in these patients.
Aminoglycosides **Clofazimine (CFZ)** **Cycloserine (CS)** **Ethambutol (EMB)** **Linezolid (LZD)**	Not commonly associated with liver dysfunction.

Treatment of DR-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.** Consider LFX, EMB, an aminoglycoside, and CS, if appropriate. LZD, BDQ (precautions noted in **Table 1**), and CFZ are additional alternatives.
- If the liver disease is not imminently life-threatening and is Child Pugh classification A or B, the use of one or two hepatotoxic drugs can be considered in a TB regimen. Because of the efficacy of rifamycin, **consider a rifamycin challenge** (before other hepatotoxic drugs) if the isolate is susceptible, e.g., for INH mono-resistance.

SUMMARY: LIVER DISEASE

- INH and PZA are the anti-TB medications most often associated with hepatotoxicity.
- Second-line anti-TB medications are less commonly associated with hepatotoxicity.
- See **Chapter 9, *Adverse Reactions***, for more information regarding response to hepatotoxicity encountered during TB therapy.

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 (DR) TB in particular.

Data regarding clearance of anti-TB drugs are best documented for patients with creatinine clearance less than 30 mL/minute, or for those undergoing hemodialysis. For patients with mild renal failure or undergoing peritoneal dialysis, data are less available. In addition to the effects on drug clearance, the diseases that cause renal failure and their concomitant treatments can also impact drug levels (by altering absorption or through drug interactions). **Table 2** 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 2. **Dosing recommendations for adult patients with reduced renal function and for adult patients receiving hemodialysis**

Drug	Change in frequency?	Recommended dose and frequency for patients with creatinine clearance < 30 mL / min or patients receiving hemodialysis
Isoniazid (INH)	No change	300 mg once daily
Rifampin (RIF)	No change	600 mg once daily
Pyrazinamide (PZA)	Yes	25–35 mg/kg/dose 3x/week (not daily)
Ethambutol (EMB)	Yes	15–25 mg/kg/dose 3x/week (not daily)
Levofloxacin (LFX)	Yes	750 –1000 mg/dose 3x/week (not daily) for creatinine clearance <50 mL/min
Moxifloxacin (MFX)	No change	400 mg daily
Cycloserine (CS)	Yes	250 mg once daily, or 500 mg/dose 3x/week*
Ethionamide (ETA)	No change	15–20 mg/kg/day (can be in divided doses)
Para-aminosalicylate (PAS)	No change	4,000 mg/dose twice daily
Linezolid (LZD)	No change	600 mg daily
Clofazimine (CFZ)	No change	100–200 mg daily
Amikacin (AK)	Yes	12–15 mg/kg/dose 2–3x/week (not daily)
Capreomycin (CM)	Yes	12–15 mg/kg/dose 2–3x/week (not daily)
Kanamycin (KM)	Yes	12–15 mg/kg/dose 2–3x/week (not daily)
Streptomycin (SM)	Yes	12–15 mg/kg/dose 2–3x/week (not daily)

Note: Bedaquiline (BDQ) and Pretomanid (Pa) need no change with mild to moderate renal dysfunction but should be used with caution in severe renal disease. Delamanid (DLM) is not recommended in patients with 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 are not currently 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, PZA, and EMB in obese patients.

Table adapted from the ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-susceptible Tuberculosis 2016.

* The appropriateness of the 250 mg daily dose has not been established .

Estimated creatinine clearance calculations

Men: Ideal Body Weight (kg) X (140 – age) / 72 X serum creatinine (mg/dL)

Women: 0.85 X Ideal Body Weight (kg) X (140 – age) / 72 X serum creatinine (mg/dL)

Creatinine clearance calculator: https://reference.medscape.com/calculator/51/crcl-cockroft-gault

While there are some recommendations for giving large doses before dialysis and supplementary 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 patients with renal failure.

Specific TB drugs

Bedaquiline (BDQ)

- Mainly eliminated in feces; urinary excretion of BDQ was < 0.001% of dose in clinical pharmacokinetic studies
- Creatinine clearance may not impact pharmacokinetics of BDQ; however, no patients with end-stage renal disease were included in primary clinical studies
- A small number of patients with renal failure have been reported in the published literature to have received BDQ; no adverse drug events associated with BDQ were reported

Ethambutol (EMB)

- Up to 80% cleared by the kidney
- Incompletely dialyzed
- Dose should be adjusted as shown in **Table 2**, 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-TB drug dosing for patients on continuous ambulatory peritoneal dialysis (CAPD) and no guidelines currently exist; 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***, at the bottom of **Table 2**)
- Monitor carefully for red-green color discrimination and visual acuity changes

Delamanid (DLM)

- Renal excretion is less than 5% unchanged
- Primarily metabolized in plasma by albumin and to a lesser extent by CYP3A4.

Aminoglycosides (Streptomycin [SM] and Amikacin [AK])

- Cleared nearly entirely by the kidneys and only about 40% of the dose is removed by dialysis.
- There may be some accumulation of the 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 2**).
- For patients with creatinine clearance less than 30 mL/min or those receiving hemodialysis, 12-15 mg/kg 2 to 3x/week is recommended. Some experts would recommend considering 3x/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 3x/week (not daily) is recommended for treatment of TB if creatinine clearance <50 mL/min. 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 were 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 ATS/CDC/IDSA 2016 guidelines recommend using the usual daily dose and dosing after dialysis. (Note: 2019 ATS/CDC/ERS/IDSA guidelines did not address renal dosing of drugs.) There are few data regarding use of PAS in patients with renal failure not yet on dialysis, but no clear evidence of toxicity.

Pretomanid (Pa)

- Pretomanid is metabolized by multiple oxidative and reductive pathways; it is estimated that CYP3A4 is responsible for 20% of metabolism. Although renal metabolism is not thought to a play an important role, the safety, effectiveness, and pharmacokinetics are unknown in persons with severe renal disease.

SUMMARY: RENAL FAILURE

- **INH, RIF, BDQ, Pa, MFX, ETA, PAS, LZD, DLM**, and **CFZ** are not cleared by the kidney, and their dosing does not require adjustment for renal failure. Most other anti-TB 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 and contraception

Treatment of drug-resistant tuberculosis (DR-TB) during pregnancy is challenging. All patients with childbearing potential with multidrug-resistant (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. Most medications currently used to treat DR-TB are not known to be teratogenic but full safety profiles for use in pregnancy remain unknown. For these reasons, there has been reluctance in the past to aggressively treat pregnant MDR-TB patients. However, this view has changed, particularly as standard MDR-TB regimens no longer default to use of aminoglycosides, and successful outcomes have been documented.

Contraception

If a person is receiving rifamycins, anticipate drug interactions that decrease effectiveness of most hormonal birth control methods (including combo pills, mini pills, implantable contraception, the patch, and the ring), and counsel the person to use a backup method of contraception. Contraceptive methods that retain their effectiveness with rifamycin use include barrier methods (male and female condoms, cervical cap, diaphragm, spermicide) and IUDs (both copper-containing and levonorgestrel-releasing).

Consider depot medroxyprogesterone (DMPA) with caution as a contraceptive method when used with rifamycins; in a study of 42 women with HIV receiving rifampin (RIF) for TB treatment as well as DMPA, approximately10% of women had sub-therapeutic DMPA levels by week 12, but no ovulation or pregnancy occurred.

In discussing pregnancy and TB-related outcomes with persons who are or wish to become pregnant, it is important to advise them that data on treatment and pregnancy outcomes among MDR-TB patients are limited and come from international settings. Several studies might be worth discussing:

- One case series on MDR-TB in pregnancy included 38 pregnant patients with MDR-TB in Peru, with TB treatment outcomes comparable to those of non-pregnant patients. Pregnancy outcomes were described as similar to those of the general population; of the 38 pregnancies, 5 ended in spontaneous abortions, and 1 child was stillborn.
- Another study described long-term follow-up of 6 children exposed to MDR-TB drugs while *in utero*, the majority of whom were exposed to both an injectable agent and a fluoroquinolone. 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.

- In a South African retrospective review of pregnant MDR/RIF-resistant (RR) TB patients including 108 patients, most with co-morbid HIV, favorable maternal treatment outcomes were reported in 67% of women, without a comparison to outcomes for non-pregnant women during a similar time frame. There were 8 maternal deaths after childbirth, 4 of which were attributed to MDR-TB; all 8 infants survived. Pregnancy outcomes included 91% of fetuses that survived to birth, among which 52% had a "favorable pregnancy outcome", with unfavorable outcomes driven by low birth weight. Among the live births, 84% were healthy and had normal development at 12 months. The authors stratified by bedaquiline (BDQ) exposure (median duration of *in utero* BDQ exposure was 77 days, with only a few instances of first trimester exposure). They found similar pregnancy outcomes in BDQ-exposed and unexposed; although a higher proportion of newborns exposed to BDQ had low birthweight, 88% of BDQ-exposed infants had normal growth and development at 12 months.
- In another retrospective review of 35 pregnant women treated for MDR/RR-TB, pregnancy outcomes were available for 20 of 35 (57.1%) women. Overall, 13 of 20 (65.0%) of the women with known pregnancy outcomes had an adverse pregnancy outcome, including 11 preterm births, 1 miscarriage, and 1 neonatal death.

Key recommendations for DR-TB care during pregnancy include:

- **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.
- **Current U.S. guidelines favor treatment of MDR-TB during pregnancy because the benefits of treatment to mother and child likely outweigh the harms. However, the full range of options includes:**
  - Treatment of DR-TB during pregnancy should start with the best possible MDR-TB combination, avoiding the known (potential) teratogens: the aminoglycosides and ethionamide (ETA). The regimen can be strengthened after the baby is delivered.
  - A potential regimen should include at least four active drugs, and might include BDQ, cycloserine (CS), para-aminosalicylate (PAS), and ethambutol (EMB) or pyrazinamide (PZA) if still susceptible. Experience with the fluoroquinolones and linezolid (LZD) during pregnancy is limited, but small series have not shown teratogenicity, thus many experts are comfortable with use of these drugs during pregnancy.
  - Short-course MDR-TB therapies such as BPaL [BDQ, Pretomanid (Pa) and LZD] have not been studied in pregnancy. Although there is limited data to suggest BDQ and LZD may be used safely in pregnancy, there is no published data regarding pregnancy outcomes with Pa. Pa was associated with testicular atrophy and impaired fertility in male rats; but subsequent data in humans has been reassuring. An analysis of hormone levels from >800 male patients enrolled in four clinical trials of Pa-containing regimens showed no evidence of testicular toxicity.
- If options are severely limited, using known teratogens such as injectable agents or ETA, guided by susceptibility testing, may be considered. It is essential to discuss the potential risks and benefits with the patient and family prior to beginning such a regimen. Other options, less often used, include:

- No treatment at all for very stable disease pending delivery of the baby. An example might be an asymptomatic patient identified during screening who has a small infiltrate, is smear-negative, and is within a month or two of delivery.
- Termination of the pregnancy can be considered, particularly if the mother's life is at risk without use of known teratogens, or potential risk of drug exposure to the fetus is unacceptable to the patient.

Teratogenicity

- **Aminoglycosides** are the only TB drugs that have well-documented teratogenicity with mild to severe bilateral congenital deafness (eighth nerve toxicity) in up to 17% of pregnancies. For that reason, **amikacin (AK)** and **streptomycin (SM)** (and capreomycin [CM] which is no longer used) are 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.
- **BDQ** is not a known teratogen, and animal studies suggest it is safe for use in pregnancy. There are limited studies of BDQ in pregnant human subjects. A 2017 case report of a woman receiving BDQ for extensively drug-resistant (XDR-)TB in her third trimester noted no fetal toxicities 2 years after delivery, and a retrospective review of 108 pregnant women treated for MDR/RR-TB noted that although more babies exposed to BDQ were of low birth weight, over 80% had gained weight and were developing normally at 1 year. The potency of BDQ and absence of known harm to the fetus make it a reasonable option for treating MDR-TB in pregnancy.
- **Fluoroquinolones** have historically been avoided during pregnancy due to the observation of arthropathy in puppy models and adverse events in monkeys receiving norfloxacin. However, observational data suggest that fluoroquinolone exposure, even in the first trimester, is not associated with adverse fetal outcomes. **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. Fluoroquinolone drugs have been used in the treatment of MDR-TB in pregnancy and have not been associated with identified teratogenicity.
- **LZD** use in pregnancy was not teratogenic in animal studies, although fetal toxicities were seen at high doses of the drug. There are inadequate human data, with a 2017 case report of a woman receiving LZD for XDR-TB in her third trimester noting no fetal toxicities 2 years after delivery.
- **PZA** was historically avoided in the TB regimens of most pregnant women with drug-susceptible TB in the U.S. 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 U.S.), and toxicity to the fetus has not been documented. **For women with HIV or DR-TB disease, PZA should be included in the TB regimen if the isolate is susceptible.**
- **Isoniazid (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.

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 pregnant patients will receive obstetrics (OB) care.
- If the patient is anticipated to still be infectious at the time of delivery, make plans for delivery well in advance. Arrange for a negative pressure birthing room and appropriate personal protective equipment (PPE) for healthcare workers. It is not 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 two major issues:

1. Is the baby already infected with TB (congenital TB)?
2. What can be done to prevent the baby from becoming infected with TB?

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 findings frequently include:
  - 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, but granulomata can have a wide variety of causes. 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 (approximately 90% each) in cases of congenital TB. See **Chapter 6, *Pediatrics***, for details on obtaining gastric aspirates. Perform lumbar puncture for cell count, pro-

tein, glucose, bacterial and acid-fast bacilli (AFB) smear and culture for a child with suspected congenital TB. Mycobacterial culture of blood, skin lesions, and ear drainage are also sometimes helpful.

Given the rarity of congenital TB, consider also evaluating the sick newborn for neonatal sepsis and other congenital infections.

Treatment of suspected congenital TB

If a newborn is suspected of having active or congenital TB, initiate treatment for TB disease as soon as the previously mentioned 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 DR-TB, mother and baby should be separated until the mother is not infectious or the baby is on effective window treatment. However, mother-infant bonding is important and there are trade-offs to be considered when making decisions about separating newborns and mothers. 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, the baby should also receive 6.25 mg (or one-fourth of a 25-mg tablet) of 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.
- In the rare event that separation of the mother and infant is not possible, and no practical prophylactic regimen is available, the Bacille Calmette-Guérin (BCG) vaccine can be considered for administration. Note: BCG can be difficult to procure in the U.S. (contact local/state TB program for support). 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. (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 a negative TST result 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. IGRAs may be less reliable than the TST in children under age 2 but may be used on a case-by-case basis.

Breastfeeding

Most TB drugs cross into the breast milk at low levels. Note: The doses of TB drugs that babies receive via breast milk are insufficient to treat or prevent TB in the infant.

Past expert recommendations (without notable supporting data) suggested breastfed infants should be supplemented with vitamin B6 (pyridoxine) if mothers were receiving INH, CS, LZD, and/or ETA, and the utility of this practice is unclear. Recent LTBI clinical recommendations (National TB Controllers Association/National Society of TB Clinicians 2021) do not support the need for vitamin B6 supplementation for breastfed infants if the mother is taking INH. In addition, the suggested mechanism for most adverse effects due to LZD does not implicate a role for vitamin B6. Because of uncertainty around this issue and low toxicity of vitamin B6, some experts would still recommend its use in these circumstances.

Small amounts of fluoroquinolones have been detected in human breast milk and concerns have been raised about the risk of arthropathy in immature animal models. 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.

SUMMARY: PREGNANCY and CONTRACEPTION

- Guidelines support treatment of DR-TB during pregnancy, with documented beneficial outcomes. Newer drug options reduce potential toxicity compared with past treatment practice.

- Expert consultation is recommended to address:
  - Risk of teratogenicity of anti-TB drugs
  - Infection control risks during OB care
  - Risk of transmission to the infant

- During pregnancy, PZA is avoided in drug-susceptible TB but is recommended for use in DR-TB.

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 an SOT is associated with a mortality of 6%-22%, which is substantially higher than the 5% mortality among all TB patients in the U.S.

TB can occur in a person who has received a SOT for the following reasons:

1. Reactivation of latent TB infection (LTBI)
2. Relapse of previously treated TB
3. TB transmitted by the transplanted organ (donor-derived TB)
4. New transmission of TB after organ transplantation
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, most 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 an 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 multidrug-resistant (MDR-)TB in a person who has received an SOT can be complicated, primarily because of **interactions between TB medications and immuno-suppressive medications.** Treatment of MDR-TB in a person who has received an 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 3**. Due to these potential interactions, MDR-TB treatment will require **close monitoring and close coordination with pharmacy and transplant teams** during treatment initiation, treatment change/holds, and treatment discontinuation (expert consultation is recommended).

TABLE 3. **Interactions between immunosuppressants and commonly used DR-TB medications**

Immunosuppressant	Rifampin (RIF)*	Isoniazid (INH)	Bedaquiline (BDQ)	Pretomanid (Pa)	Cycloserine (CS)	Clofazamine (CFZ)	Moxifloxacin (MFX) or Levofloxacin (LFX)	Linezolid (LZD)
Corticosteroids	Decreased serum concentration of corticosteroids with potential increased risk for organ rejection	May decrease the serum concentration of INH	None	None	Overlapping toxicity: caution and close monitoring recommended for neurologic (mood, psychiatric) changes	None	Increased risk of tendonitis	None
Cyclosporine A	Decreased cyclosporine serum levels with potential increased risk for organ rejection	May increase serum concentration of cyclosporine	None	None	None	May increase serum concentration of cyclosporine	May increase cyclosporine levels (usually LFX only)	None
Tacrolimus	Decreased serum concentration of tacrolimus with potential increased risk for organ rejection	May increase serum concentration of tacrolimus.	Increased risk and enhancement of QTc prolongation	None	None	Increased risk and enhancement of QTc prolongation; may increase serum concentration of tacrolimus.	None	None
Rapamycin/ sirolimus	Decreased serum concentration of sirolimus with potential increased risk for organ rejection	May increase serum concentration of sirolimus.	None	None	None	May increase serum concentration of sirolimus	None	None
Mycophenolate mofetil (CellCept®)	Decreased serum concentration of active metabolite, mycophenolic acid with potential increased risk for organ rejection	None	None	May increase the serum concentration of mycophenolate	None	None	May decrease mycophenolate level	None
Azathioprine	None	None	None	None	None	None	None	May increase risk of bone marrow suppression

* Given the predicted significant decrease in levels of multiple immunosuppressants with RIF, leading to increased risk for organ rejection, most experts would not use RIF in combination with these agents. Some experts may consider using rifabutin (RFB), in very close coordination with ID pharmacy and transplant providers

Resources

Guidelines for Use of Antiretroviral Agents in Adults and Adolescents with HIV.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. "Considerations for Antiviral Use in Patients with Coinfections: TB/HIV Coinfection". Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new-guidelines
Accessed October 20, 2022.

Pretomanid information

https://www.tballiance.org/sites/default/files/assets/Pretomanid_Full-Prescribing-Information.pdf
Accessed October 20, 2022.

University of Liverpool. HIV Drug Interaction Database.

https://www.hiv-druginteractions.org/
Accessed October 20, 2022.

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.

http://www.merck.com/product/usa/pi_circulars/b/bcg/bcg_pi.pdf
Accessed October 20, 2022.

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EXTRAPULMONARY TB

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