Managing drug-resistant TB, never a simple endeavor, requires additional considerations in the following special situations: extrapulmonary TB, HIV, liver disease, renal failure, pregnancy, and pediatric TB.

Extrapulmonary TB

There is scant information regarding extrapulmonary drug-resistant tuberculosis (TB) in the medical literature. Many of the series of multidrug-resistant TB (MDR-TB) cases in the literature describe a proportion of cases with extrapulmonary disease without specific mention of outcomes or treatment modifications.

Many of the series from New York in the 1990s reported large proportions of HIV-infected individuals, who are known to have higher rates of extrapulmonary TB than normal 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. The indication for corticosteroids in patients with drug-resistant TB remains unclear.

• **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-infected individuals. This phenomenon is known as a “paradoxical reaction” or the immune reconstitution inflammatory syndrome (IRIS). However, if the clinical worsening is actually due to microbiologic failure associated with unrecognized (or not yet diagnosed) drug resistance, it may inappropriately be attributed to a paradoxical reaction. In this case, 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 known penetration of first-line anti-tuberculosis drugs into tissues, years of experience, and some clinical trials.** Unfortunately, much less is known regarding the penetration of second-line drugs into tissues. This is compounded by the increased rates of malabsorption and drug interactions experienced by individuals at risk for drug-resistant TB.

• **Serial cultures are often not available.** Clinical and radiographic assessments should be used to determine duration of therapy. Computed tomography is often useful in following treatment progress in these patients.
Role of Surgery

Some forms of extrapulmonary TB 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 Central Nervous System TB

Several reports detail poor outcomes of drug-resistant TB meningitis. Most of the patients in these series were HIV-infected and many developed meningitis while already receiving treatment for MDR-TB. Mortality in 2 series from South Africa, 1 in adults and 1 in children, ranged from 57% to 88%. The majority of patients were HIV-infected. Any degree of drug resistance will hinder the treatment of TB meningitis or other central nervous system (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 INH in MDR-TB meningitis, especially in the setting of low-level INH resistance.

Rifampin (RIF), rifabutin, ethambutol (EMB), para-aminosalicylate (PAS), and the aminoglycosides penetrate poorly into the CSF with non-inflamed meninges, but better with inflamed meninges. For RIF, 10% to 20% of the serum level reaches the CSF in the setting of inflamed meninges (still exceeding the minimum inhibitory concentration [MIC] of sensitive isolates). One study of RIF CSF with uninflamed meninges showed similar results, with penetration of 13% to 42% (median = 22%).

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 and cycloserine also have good CNS penetration, approaching that in serum, but a South African study evaluated CSF levels of ethionamide and concluded that doses of 20 mg/kg/day should be used in order to achieve useful levels in the CSF.

The fluoroquinolones have variable CSF penetration. Levofloxacin levels in the CSF are about 15% to 30% that of serum (level around 2 mcg/ml for a normal dose). Since higher doses are generally used to treat MDR-TB, CSF levels may be adequate to treat TB meningitis (MIC 0.5–1.0). Moxifloxacin has shown good CSF penetration in several animal studies (CSF levels approximately 50% of serum). Human data will be required to determine which fluoroquinolone will have best efficacy in the treatment of TB meningitis. There is no clinical data yet available on MDR-TB meningitis outcomes with the use of moxifloxacin.
Route of Administration

If the patient is obtunded or severely ill, consideration should be given to using drugs that can be given parenterally: INH, RIF, fluoroquinolones, and aminoglycosides.

Two recent reports of treatment of MDR-TB meningitis in non–HIV-infected individuals describe the use of intrathecal aminoglycosides and fluoroquinolones with good success and tolerability. Since most of the reports of fatal MDR-TB meningitis were in HIV-infected 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.

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.
- Patients with extrapulmonary TB are at risk of treatment failure due to poor drug penetration to the affected tissue and the lack of accessibility of tissue for serial cultures.
- Surgical resection (scrofula) and drainage (empyema, abscesses, 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 newer fluoroquinolones may improve outcome and should be evaluated prospectively.
HIV

Patients with HIV/AIDS are at increased risk of developing tuberculosis (TB) once infected compared to immunocompetent individuals. Additionally, TB increases HIV replication, promoting a vicious cycle of viral and mycobacterial proliferation. Patients with HIV 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 are less likely to have cavitary disease and more likely to have mid- and lower-lung disease than are individuals without HIV infection.

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

- Previous exposure to rifamycins
- Use of highly intermittent rifamycin treatment
- Malabsorption of drugs
- Drug-drug interactions
- Residence in congregate settings
- Co-morbid conditions, including mental health and substance abuse issues
- CD4 lymphocyte count below 100 cells/mm3

Unfortunately, HIV-infected individuals have higher mortality rates than non-infected, multidrug-resistant TB (MDR-TB) patients, 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 recent large series of HIV-infected 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 HIV-TB coinfected patients.

Treatment of drug-resistant TB in HIV-infected 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
- The fact that the immune system cannot always contribute to control of the TB disease
- Malabsorption of drugs
- Drug-drug interactions
- Paradoxical reactions where 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
To maximize care of HIV-infected patients:

- Identify all HIV-infected patients by screening all patients with TB disease for HIV.
- 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.
- Consider the best HIV regimen for immune reconstitution as well as the timing of initiation of ART treatment for antiretroviral-naïve patients. Initiation of ART therapy 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 200, it is reasonable to delay ART therapy for several months. In patients with CD4 less than 100 (or patients with extrapulmonary TB and CD4 less than 200), it is advisable to begin ART therapy as soon as TB therapy is well tolerated (usually within 1 to 2 months).
- Consider alternate drugs when interactions between TB and HIV drugs are present (e.g., rifabutin in place of rifampin).

**Consider alternate drugs when interactions between TB and HIV drugs are present (e.g., rifabutin in place of rifampin).**

- **Rifamycins are inducers of cytochrome P-450 and interact with many drugs.** Rifampin (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 rifabutin) and ART therapy should be consulted. For the updated guidelines published in 2008, see: [www.cdc.gov/TB/TB_HIV_Drugs/default.htm](http://www.cdc.gov/TB/TB_HIV_Drugs/default.htm)
- **The rifamycins and other TB drugs interact with a number of the anti-infectious agents that may be taken by HIV-infected 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.
- Intervene to avoid or treat symptomatic toxicity. Peripheral neuropathy, cutaneous reactions, gastrointestinal (GI) side effects, renal impairment, and neuropsychiatric effects may all be worse in HIV/TB patients.
- Use daily directly observed therapy (DOT).
- Closely monitor signs and symptoms of malabsorption: diarrhea, abnormal stools, abnormal nutritional studies, evidence of vitamin deficiencies, weight loss, etc.
- 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 coinfected with HIV 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.

- **HIV-infected patients can be cured of their drug-resistant TB disease,** but require special monitoring and concurrent care of their HIV disease. initiation of ART prolongs survival.

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

- **Rifamycins can be used in HIV-infected patients on ART,** but dose adjustments may be required. Rifabutin generally has fewer drug interactions than does rifampin.
Liver Disease

Many tuberculosis (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 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 PAS</td>
<td>Ethionamide and para-aminosalicylate (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. Travafloxacin has been associated with severe liver toxicity in rare cases.</td>
</tr>
<tr>
<td>Levofloxacin Ethambutol (EMB) Aminoglycosides Cycloserine</td>
<td>Not commonly associated with liver dysfunction.</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 1 patient has successfully undergone liver transplantation for toxicity of multidrug-resistant TB (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 levofloxacin, EMB, an aminoglycoside, and cycloserine should be considered, if appropriate.
- If the liver disease is not imminently life-threatening, the use of a rifamycin in the regimen is advised if the isolate is susceptible.
Summary LIVER DISEASE

- INH and PZA are the anti-tuberculosis medications most often associated with hepatotoxicity.
- Second-line anti-tuberculosis medications are less commonly associated with hepatotoxicity.

See Chapter 7, “Adverse Reactions,” for more information regarding response to hepatotoxicity encountered on 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 tuberculosis (TB) 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 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.

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 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 calculator at bottom of Table 1)
- Monitor carefully for red-green color discrimination and visual changes
Aminoglycosides (Streptomycin, Kanamycin, Amikacin) and Capreomycin

- 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 amikacin 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).

Levofloxacin

- Cleared more extensively by the kidney than is moxifloxacin.
- 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 levofloxacin 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

In one small study, moxifloxacin clearance was unaltered in the presence of renal insufficiency following single oral doses. Another recent study found that moxifloxacin 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, moxifloxacin dosage should not be altered in patients with renal disease.

Cycloserine

- 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.
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</td>
<td>No change</td>
<td>300 mg once daily, or 900 mg 3 times/week</td>
</tr>
<tr>
<td>Rifampin</td>
<td>No change</td>
<td>600 mg once daily, or 600 mg 3 times/week</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Yes</td>
<td>25–35 mg/kg/dose 3 times/week (not daily)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Yes</td>
<td>15–25 mg/kg/dose 3 times/week (not daily)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Yes</td>
<td>750–1000 mg/dose 3 times/week (not daily)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>No change</td>
<td>400 mg daily</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Yes</td>
<td>250 mg once daily, or 500 mg/dose 3 times/week*</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>No change</td>
<td>15–20 mg/kg/day (can be in divided doses)</td>
</tr>
<tr>
<td>PAS</td>
<td>No change</td>
<td>4 gm/dose twice daily</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Yes</td>
<td>12–15 mg/kg/dose 2–3 times/week (not daily)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Yes</td>
<td>12–15 mg/kg/dose 2–3 times/week (not daily)</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Yes</td>
<td>12–15 mg/kg/dose 2–3 times/week (not daily)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Yes</td>
<td>12–15 mg/kg/dose 2–3 times/week (not daily)</td>
</tr>
</tbody>
</table>

- 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.
- Dose the aminoglycosides, pyrazinamide, and ethambutol by Ideal Body Weight for obese patients.

**Ideal Body Weight (Men):** 50 kg plus 2.3 kg/inch over 5 ft

**Ideal Body Weight (Women):** 45 kg plus 2.3 kg/inch over 5 ft

**Estimated creatinine clearance calculations**

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

Table adapted from the American Thoracic Society Treatment Guidelines.

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

- Isoniazid (INH), rifampin (RIF), ethionamide, and PAS 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 cycloserine, and may be helpful for other medications as well.
Pregnancy

Treatment of drug-resistant tuberculosis (TB) during pregnancy is very challenging. All female patients of childbearing age with multidrug-resistant TB (MDR-TB) should be strongly advised to avoid pregnancy. 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 and since 2003, several small series and case reports (totaling 14 patients) have been published in which treatment for MDR-TB using second- and third-line drugs was given to pregnant women with extensive, progressive disease. One woman elected to terminate her pregnancy. Of 13 live-born infants, none had congenital anomalies. Long-term follow-up of six of these children (average age 3.7 years) 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, we generally avoid use of pyrazinamide (PZA) in the United States. In the case of drug-resistant TB, PZA should be used when the isolate is susceptible. Treatment of monodrug-resistant TB for pregnant women is the same as for nonpregnant individuals:

<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 (M. bovis)</td>
<td>INH + RIF + EMB Followed by INH and RIF</td>
<td>2 months 2 months more</td>
</tr>
<tr>
<td>RIF monoresistance</td>
<td>INH + EMB + PZA</td>
<td>At least 18 months</td>
</tr>
</tbody>
</table>

Consider addition of a fluoroquinolone or injectable drug after delivery to shorten course.
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. The regimen can be strengthened after the baby delivers. A potential regimen might include cycloserine, 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 and kanamycin 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 and capreomycin are also not recommended during pregnancy, but have been used safely in some reports.

- Ethionamide 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. Levofoxacin 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 with HIV coinfection or drug-resistant 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, cycloserine, and PAS have not been extensively studied, but animal models and anecdotal human reports have not shown toxicity.
Infection Control

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, cycloserine and ethionamide 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, the 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.

• Examination of the placenta by a pathologist is sometimes helpful. Granulomata in the placenta increases 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. For a video demonstration and complete instructions for gastric aspirate collection, refer to: www.currytbcenter.ucsf.edu/pediatric_tb. Click on the “Resources” button on the left-hand side. For young babies, gastric aspirates can be collected after the baby is NPO after a long sleep several times in 1 day, and do not necessarily need to be collected in the early morning. 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 contagious with drug-resistant TB, mother and baby should be separated until the mother is not contagious.

• If an infant whose mother has known contagious or suspected TB disease is vigorous, afebrile, and has a completely normal physical exam and chest radiograph, consideration should be given to treating the infant prophylactically, 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, the advice of a pediatric TB expert should be sought.

• 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, ethionamide, or cycloserine, 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.
• If the baby is asymptomatic and the mother has been receiving effective TB therapy and is deemed to be noncontagious, and there are no other potentially contagious source cases in the infant’s home, close monitoring without chest radiograph or prophylactic treatment is appropriate.

TST

The TST is 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 between 6 and 12 months of life for immunocompetent children.

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.
Pediatrics

Treatment of drug-resistant tuberculosis (TB) in children can be easier—and more difficult—than treating the disease in adults.

<table>
<thead>
<tr>
<th>Easier Elements</th>
<th>More Difficult Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Children with drug-resistant TB have almost always acquired it from a contagious teen or adult rather than evolving it over years of failed therapy. This means that their bodies tend to be strong and healthy when the treatment is started.</td>
<td>• Young children are more likely to develop TB meningitis.</td>
</tr>
<tr>
<td>• Children have few M. tuberculosis organisms in their diseased tissues compared to adolescents and adults, making amplification of resistance on treatment much less likely.</td>
<td>• It is difficult to obtain good clinical specimens for culture confirmation, susceptibility testing, and clinical monitoring.</td>
</tr>
<tr>
<td>• Some TB disease diagnosed in children is actually already being controlled by their own immune system.</td>
<td>• Anti-tuberculosis drugs are not sold in child-friendly formulations.</td>
</tr>
<tr>
<td>• Children tend to tolerate the second-line medications required for drug-resistant treatment better than do adults.</td>
<td>• It is more difficult to monitor children for drug toxicity.</td>
</tr>
<tr>
<td></td>
<td>• It is difficult to entice a child to take a few doses of medicines, much less 2 or more years of multiple, bad-tasting tablets crushed into sticky, sweet vehicles.</td>
</tr>
</tbody>
</table>

Cultures

• Fewer than 25% of children are treated for TB based on positive cultures.

• If drug-resistant TB is suspected, aggressively evaluate and culture the child, as well as all possible source cases to whom the child is exposed.

• Older children (older than 5 years) can sometimes produce sputum by induction with hypertonic nebulized saline and careful coaching. Sputum induction combined with suctioning the posterior oropharynx can be used in even young children.

• For very young children with pulmonary TB, aspiration of gastric contents, first thing in the morning, sometimes yields mucous for acid-fast bacilli (AFB) culture. (See www.currytbcenter.ucsf.edu/pediatric_tb. Click on the “Resources” button on the left-hand side for complete instructions for gastric aspiration.) Three specimens are usually considered to give the maximum culture yield for sputum or for gastric aspirates. The first gastric aspirate collected gives the very highest yield and should be undertaken very carefully and seriously. Unfortunately, even the best collection techniques yield less than 50% positive cultures (higher in young infants). Therefore, the culture results are only helpful if they are positive. Gastric aspirates are occasionally positive in children with TB meningitis.

• Bronchoalveolar lavage (BAL) specimens have a slightly lower yield than gastric aspirate specimens. In sick children, especially those in whom the diagnosis of TB is not certain or in whom the concern for drug resistance is very high, a BAL is frequently useful.

Note: A negative culture never rules out tuberculosis.
An older child can and should be monitored during treatment with serial sputum specimens, but serial gastric aspirates are rarely valuable due to their low yield. If the patient is sedated for another procedure, such as deep line placement or auditory brainstem response, collect a gastric aspirate at that time to avoid some discomfort.

Other specimens that can be analyzed (particularly for children suspected of having extrapulmonary TB):

- **Excisional biopsies of lymph node, bone, and other tissue are more likely to grow *M. tuberculosis* than are needle aspiration specimens.** Surgeons and operating room personnel need to be reminded to send specimen for culture in a sterile cup without formalin.
- **Cerebrospinal fluid should be collected if meningitis is suspected.** Larger volumes should be submitted in order to increase the yield of smears and cultures.
- **Blood and urine cultures for mycobacterial cultures are sometimes positive in children with disseminated TB disease** (contact your lab to obtain the proper bottles for processing the blood).

**Treatment**

There are no controlled trials for treatment of drug-resistant TB in children. Given the paucity of clinical data and the inability to fully characterize children’s TB disease, the most prudent course to treat children with drug-resistant TB is: **Use the same principles as for adults and seek expert consultation.**

Based on small series and experience in adult patients, the following regimens are recommended:

**Isoniazid (INH) Mono-Resistant TB in Children**

Six months of rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). Longer treatment (9 to 12 months) is sometimes required if the patient has slow response to therapy.

**PZA Mono-Resistant TB in Children**

Frequently caused by *M. bovis*. *M. bovis* can be transmitted from a contagious adult, but more frequently is ingested in unpasteurized milk products. The spectrum of TB disease caused by *M. bovis* is the same as that caused by *M. tuberculosis*, but there is a disproportionate frequency of adenopathy (intra-abdominal and cervical in particular). The treatment for *M. bovis* TB is 2 months of INH, RIF, and EMB, followed by at least 7 months of INH and RIF (can be twice weekly by directly observed therapy [DOT]). Duration of therapy should be extended for *M. bovis* TB if the patient experiences a sluggish clinical response.

**Multidrug-Resistant TB in Children**

There are several series published, mostly from New York and South Africa, and more recently from Peru. South African children were treated with 4 to 5 drugs (at least 2 to 3 drugs to which the presumed source case isolate was susceptible) for 9 to 12 months. No cases of disseminated disease were identified. All children were well after 30 months of follow-up. The authors from New York recommend 1 year of treatment for non-serious or non-life-threatening forms of TB, and a minimum of 18 months for serious or life-threatening forms of TB. Among the 38 Peruvian children treated for multidrug-resistant TB...
(MDR-TB), 29% had severe radiographic findings. All were treated with at least five drugs including an injectable drug for a minimum of 6 months after culture conversion and a fluoroquinolone for the duration of therapy. The total duration of therapy was 18 to 24 months. Many children experienced some side effects (42%), but all could be managed without treatment interruption for more than five days. No joint or musculoskeletal complaints were observed. Cure or probable cure was achieved in 95% of these children.

In the absence of efficacy data derived from randomized, controlled trials, the following are generally accepted principles for treatment of MDR-TB in children:

- For MDR-TB, at least 4 drugs to which the organism is susceptible should be employed, including the fluoroquinolones and injectable agents.
- At least 3 drugs should be utilized in the continuation phase, and the total duration of therapy should be at least 18 months.
- In the case of symptomatic children or children with extensive radiographic disease, treatment should be continued at least 18 months after clinical or radiographic improvement begins.
Drug Administration

Very few anti-tuberculosis drugs are available in liquid preparations or in chewable tablets appropriate for pediatric dosing. In general:

- **Approximate doses of medications are adequate.** Exact doses of pill fragments and portions of capsules are impossible to attain. If the child's dose is 100 mg and the drug comes as a 250 mg tablet, 2 tablets will supply 5 doses. Any small discrepancy in dosing will even out over time.

- **Cut tablets into approximate fragments** (freeze ethionamide in a small plastic bag before dividing into fragments); **crush fragments for smaller children.**

- **Jiggle capsules open and approximate fractions for serial doses.**

- **Mix crushed tablets or capsule contents into a small amount of vehicle.**
  - Give a small amount of plain vehicle before the medication dose, between spoonfuls and after the dose.
  - Some powder will suspend into liquid well and can pass through a syringe. A dispenser with a bigger opening, such as a medicine dropper, is better than a syringe and will deliver a greater proportion of the drug without sticking in the syringe.
  - If mixing the medicine in a vehicle before delivery, use a small amount of the vehicle. The child will not want to take many spoonfuls of the drug. Many children will prefer the crushed pills or granules delivered with a soft vehicle.
  - Alternatively, a thin layer of soft vehicle can be placed on the spoon, the powder or pill fragment layered on top, followed by another layer of soft vehicle (making a medication sandwich and preventing drug taste in the vehicle itself).

- **Immediately after the medication is given, give good untainted food or drink to clear the palate.**

- **Give lots of praise and incentives.**

- **Some drugs can be mixed in a small amount of liquid and given to babies via a special medicine-dispensing pacifier or bottle.** Some babies will reflexively suck the medication from a bottle while they sleep. Give water in a clean bottle afterwards to rinse the medicine out of the mouth.

- **Be flexible, but firm.** The child should get a few choices, but not whether or not to take the medicine.

- **The method of delivery may need to be changed throughout the course of treatment.**
Specific TB Drugs

(See Tables 1 to 8, “Pediatric Drug Dosing.”)

Ethambutol (EMB)
- Cautiously used in children because adults who were given high doses of EMB have developed optic toxicity. While it is challenging to monitor young children for signs of eye toxicity, there have not been well-documented cases of eye toxicity in children.
- EMB can and should be used to treat children with drug-resistant TB when the isolate is susceptible to EMB.
- Recommended dose of EMB for children: 15 to 25 mg/kg/day in a single daily dose. Since eye toxicity is dose-related in adults, many clinicians feel more comfortable keeping the dose closer to the 15 mg/kg dose. This is especially true when the drug is being used over the course of many months. Unfortunately, the drug is bactericidal only at the higher doses and children require higher doses than do adults to achieve the same levels.
- Instruct families to watch for any evidence of eye problems: eye rubbing or excessive blinking, sitting closer to the television, or difficulty with accurate grasping. Monitor even young children by offering them Cheerios and watching their grasp. A child whose vision has changed will not be able to grasp the small objects as accurately as he/she had previously. Monitor older children with Snellen eye charts and color vision tools.
- EMB comes in 100 mg and 400 mg white tablets, which can be crushed fairly easily into liquid or food. It can be given independent of food intake.

Ethionamide
- Better tolerated by children than adults with fewer gastrointestinal (GI) side effects.
- Dose: 15 to 20 mg/kg/day in a single dose or divided doses (maximum 1 gram).
- To ensure tolerability, start with a small dose—around 5 mg/kg once a day, and gradually increase the dose every 3 to 5 days. After a few weeks of full dose divided twice a day, the child could try the dose in a single daily dose with food.
- Ethionamide comes as a 250 mg coated tablet that is not scored. If the child needs a partial dose, the tablet can be frozen and then fractured in a small plastic bag. The fragments can be used over several doses in order to get an accurate dose in over the course of several doses.
- As with adults, children should be supplemented with additional pyridoxine when taking ethionamide, and thyroid function should be monitored.

Cycloserine
- Generally well tolerated in children, though there have been reports of central nervous system (CNS) side effects.
- Drug levels have not been as consistent as those seen in adults, but should still be monitored in order to minimize the risk of toxicity.

Fluoroquinolones
- Fluoroquinolones have generally been avoided in children because arthropathy has been observed in animal models. Many thousands of children have received courses of fluoroquinolones (generally for short periods of time) and none have been found to have arthropathy or bone abnormalities. Selected patients have been monitored for fluoroquinolone toxicity by histopathologic examination, MRI, and ultra-
sound without any detection of bone or joint damage. Case reports of more than 50 children treated with fluoroquinolones for more than 6 months have been reported without arthropathy. Rates of reversible arthralgia have been similar to those in adults.

- **National guidelines endorse the use of fluoroquinolones in the treatment of children with MDR-TB if the drug is vital to the regimen. Close observation by parents and care providers for musculoskeletal complaints is advised.**

- **Levofoxacin** has significantly better activity against TB than ciprofloxacin (which is licensed for treatment of complicated urinary tract infection in children). Levofoxacin has been studied for otitis media and community-acquired pneumonia in children. Doses of 10 mg/kg in a single daily dose for children over 5 years of age, and 15 to 20 mg/kg/day, divided twice daily for less than 5 years of age, have been proposed based on early pharmacokinetic data in children and extrapolating from the drug-resistant TB experience in adults. There are no data establishing the safety or efficacy of the fluoroquinolones in treatment of TB in children. Levofoxacin comes as unscored 250 and 500 mg tablets. An oral suspension of 25 mg/ml is available (approved based on bioequivalence data generated in adults).

- There are no published pharmacokinetic or safety data for **moxifloxacin** in children.

- Long-term use of fluoroquinolones may promote development of quinolone-resistant *Streptococcus pneumoniae* carriage. While children are not usually treated with fluoroquinolones for presumed pneumococcal disease, their older family members might be. Therefore, the possibility of fluoroquinolone-resistant pneumococcal disease must be considered.

Fluoroquinolones are not licensed for use in very young children due to arthropathy seen in animal models. Fluoroquinolone use in children should be undertaken with informed consent of the parents. Parents and all caregivers should be observant for any signs or symptoms of toxicity, including extremity pain, swelling, or range of motion limitation.

### Para-Aminosalicylate (PAS)

- PAS is marketed in a reasonably well-tolerated formulation of granules. The packets of granules contain 4 grams of PAS.

- Pediatric dose: 200 to 300 mg/kg/day in 2 to 4 divided doses (most children can tolerate the dose divided in only 2 daily doses). Maximum daily dose is 10 gm.

- **Flatten out the packet of granules so that they are spread evenly in the packet. The packet can then be cut in order to approximate the dose needed—i.e., cut into 4 quadrants for 1 gram doses.** The granules can be sprinkled on top of or mixed into a small amount of soft food and are best tolerated when taken with food. Some experts dose PAS with acidic food to enhance absorption.

### Injectable Drugs

- A cornerstone in the treatment of MDR-TB in adults, injectable drugs should be included in the treatment of children with MDR-TB.

- While some adults will elect to receive the drugs intramuscularly, most children should very quickly have a more permanent intravascular catheter placed for long-term use. Percutaneously placed catheters will work for some children; younger children will usually require a surgically placed Broviac-type catheter to last for many months of treatment.

- Children receiving aminoglycosides or capreomycin should be monitored, as are adults, with hearing and vestibular screens and renal function monitoring.
Tables 1 to 8. Pediatric Drug Dosing

The following tables are designed to help clinicians select pediatric doses based on fractions of tablets and capsules.

These are approximate doses. If a fraction of the tablet is given for one dose, and the remainder is given over subsequent doses, the exact dose will be given over a series of doses. It does not matter if each individual dose is exact; in fact, it will not be.

### TABLE 1. ISONIAZID

<table>
<thead>
<tr>
<th>Child's weight</th>
<th>Daily isoniazid dose 10-15 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>KILOGRAMS</td>
<td>POUNDS</td>
</tr>
<tr>
<td>-----------</td>
<td>--------</td>
</tr>
<tr>
<td>3–5</td>
<td>6.6–11</td>
</tr>
<tr>
<td>5–7.5</td>
<td>11–16.4</td>
</tr>
<tr>
<td>7.5–10</td>
<td>16.5–22</td>
</tr>
<tr>
<td>10–15</td>
<td>22–33</td>
</tr>
<tr>
<td>15–20</td>
<td>33–44</td>
</tr>
<tr>
<td>Over 20</td>
<td>Over 44</td>
</tr>
</tbody>
</table>

Maximum daily isoniazid dose is 300 mg

### TABLE 2. RIFAMPIN

<table>
<thead>
<tr>
<th>Child's weight</th>
<th>Daily rifampin dose generally 12-17 mg/kg/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>KILOGRAMS</td>
<td>POUNDS</td>
</tr>
<tr>
<td>-----------</td>
<td>--------</td>
</tr>
<tr>
<td>4–7.5</td>
<td>9–16</td>
</tr>
<tr>
<td>7.5–12.5</td>
<td>17–27</td>
</tr>
<tr>
<td>12.5–17.5</td>
<td>28–38</td>
</tr>
<tr>
<td>17.5–25</td>
<td>39–55</td>
</tr>
<tr>
<td>25–35</td>
<td>55–77</td>
</tr>
<tr>
<td>Over 35</td>
<td>Over 77</td>
</tr>
</tbody>
</table>

Maximum daily rifampin dose is 600 mg
## Pediatric Drug Dosing

### TABLE 3. **PYRAZINAMIDE**

<table>
<thead>
<tr>
<th>Child's weight</th>
<th>Daily pyrazinamide dose 20-40 mg/kg/dose</th>
<th>MILLIGRAMS</th>
<th>500 mg TABS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–6.25 KILOGRAMS</td>
<td>125 mg</td>
<td>1/4</td>
<td></td>
</tr>
<tr>
<td>6.25–12.5 KILOGRAMS</td>
<td>250 mg</td>
<td>1/2</td>
<td></td>
</tr>
<tr>
<td>12.5–20 KILOGRAMS</td>
<td>500 mg</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>20–27</td>
<td>750 mg</td>
<td>1 1/2</td>
<td></td>
</tr>
<tr>
<td>27–35</td>
<td>1000 mg</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>35–46</td>
<td>1250 mg</td>
<td>2 1/2</td>
<td></td>
</tr>
<tr>
<td>46–54</td>
<td>1500 mg</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>54–62</td>
<td>1750 mg</td>
<td>3 1/2</td>
<td></td>
</tr>
<tr>
<td>Over 62</td>
<td>2000 mg</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Dose obese children on lean body weight

**Maximum daily pyrazinamide dose is 2 grams**

### TABLE 4. **ETHAMBUTOL**

<table>
<thead>
<tr>
<th>Child's weight</th>
<th>Daily ethambutol dose 15-25 mg/kg/dose</th>
<th>MILLIGRAMS</th>
<th>100 mg TABS</th>
<th>400 mg TABS</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–6 KILOGRAMS</td>
<td>100 mg</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6–8</td>
<td>150 mg</td>
<td>1 1/2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8–12.5</td>
<td>200 mg</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>12.5–17.5</td>
<td>300 mg</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>17.5–22.5</td>
<td>400 mg</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>22.5–27.5</td>
<td>500 mg</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>27.5–32.5</td>
<td>600 mg</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>32.5–37.5</td>
<td>700 mg</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>37.5–55</td>
<td>800 mg</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>56–75</td>
<td>1200 mg</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Dose obese children on lean body weight

**Maximum daily ethambutol dose is 2.5 grams**
### TABLE 5. CYCLOSERINE

<table>
<thead>
<tr>
<th>Child's weight</th>
<th>Daily cycloserine dose</th>
<th>Daily cycloserine dose 10-20 mg/kg/day divided bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>KILOGRAMS</td>
<td>POUNDS</td>
<td>MILLIGRAMS</td>
</tr>
<tr>
<td>8–12</td>
<td>17–26</td>
<td>83 mg po bid</td>
</tr>
<tr>
<td>12–16</td>
<td>27–35</td>
<td>125 mg po bid</td>
</tr>
<tr>
<td>16–25</td>
<td>35–55</td>
<td>166 mg po bid</td>
</tr>
<tr>
<td>25–38</td>
<td>55–84</td>
<td>250 mg po bid</td>
</tr>
<tr>
<td>Over 38</td>
<td></td>
<td>Start with 1 capsule (250 mg) bid. If level less than 25 mcg/ml, consider total daily dose of 750 mg divided into 2 doses</td>
</tr>
</tbody>
</table>

**Maximum daily cycloserine dose is 1 gram**

### TABLE 6. ETHIONAMIDE

<table>
<thead>
<tr>
<th>Child's weight</th>
<th>Daily ethionamide dose</th>
<th>Daily ethionamide dose 15-20 mg/kg/day divided bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>KILOGRAMS</td>
<td>POUNDS</td>
<td>INITIAL DOSE</td>
</tr>
<tr>
<td>8.4–11</td>
<td>18.5–24</td>
<td>82.5 mg po qhs</td>
</tr>
<tr>
<td>11.1–16.6</td>
<td>24–36.5</td>
<td>125 mg po qhs</td>
</tr>
<tr>
<td>16.7–20</td>
<td>36.5–44</td>
<td>165 mg po qhs</td>
</tr>
<tr>
<td>25–33.3</td>
<td>55–73</td>
<td>250 mg po qhs</td>
</tr>
<tr>
<td>Over 33.3</td>
<td>Over 73</td>
<td>250 mg po qhs</td>
</tr>
</tbody>
</table>

**Maximum daily ethionamide dose is 1 gram**

### TABLE 7. CAPREOMYCIN / AMIKACIN / KANAMYCIN / STREPTOMYCIN

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capreomycin/Amikacin/Kanamycin</td>
<td>15–30 mg/kg/day up to 1 gram IV or IM</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>20–40 mg/kg/day up to 1 gram IV or IM</td>
</tr>
</tbody>
</table>

**Maximum daily dose is generally 1 gram**, but a large muscular adolescent should be treated like an adult.
Children with drug-resistant TB generally suffer fewer side effects with second-line anti-tuberculosis drugs than do adults. Dosing children with tablets and capsules requires patience and creativity. Fluoroquinolones should be used with care in young children. Children have a smaller bacillary load compared to adults. While some series report shorter courses of MDR-TB treatment, duration of treatment should generally approximate that of adults (at least 18 months).

Drug-resistant TB in children should be treated by the most experienced clinician or clinic available. Consult with a pediatric TB expert throughout the course of care.

### TABLE 8. PARA-AMINOSALICYLATE (PAS)

<table>
<thead>
<tr>
<th>Child’s weight</th>
<th>Daily PAS dose 200-300 mg/kg/day in divided doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>KILOGRAMS</td>
<td>POUNDS</td>
</tr>
<tr>
<td>8–10</td>
<td>17–22</td>
</tr>
<tr>
<td>10–15</td>
<td>22–34</td>
</tr>
<tr>
<td>15–20</td>
<td>35–44</td>
</tr>
<tr>
<td>20–30</td>
<td>45–66</td>
</tr>
<tr>
<td>30–40</td>
<td>67–88</td>
</tr>
<tr>
<td>Over 40</td>
<td>Over 89</td>
</tr>
</tbody>
</table>

**Maximum daily PAS dose is 10 grams**
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.


LIVER DISEASE


RENA L FAILURE


PREGNANCY


PEDIATRICS


