Drug-Susceptible Tuberculosis Therapy Guideline

This document serves to provide guidance on recommended treatment doses, duration, and important patient counseling points in the treatment of tuberculosis (TB). Consultation with Pediatric Infectious Diseases and LPCH Stanford Infection Prevention and Control is recommended in evaluation and treatment of TB infection and TB disease.

A. Dosing, Duration, and Monitoring Recommendations

Treatment of Tuberculosis Infection

[Note, "tuberculosis infection" is the newer, preferred term for latent tuberculosis infection or LTBI]

Drug(s)	Duration	Population	Dose	Frequency	Total Doses	Treatment Completion
Isoniazid (INH)[a] and Rifapentine (RPT)[b]	3 months	Children 2–11 years	**INH**: 25 mg/kg (max 900 mg/dose) **RPT:** 10 to 14 kg: 300 mg 14.1 to 25 kg: 450 mg 25.1 to 32 kg: 600 mg 32.1 to 49.9 kg: 750 mg ≥ 50 kg: 900 mg	Once weekly[c]	12	Using 12 doses in 16 weeks is strongly preferred. In situations where 12 doses cannot be completed, a minimum of 11 doses within 16 consecutive weeks can be considered complete. Give doses at least 72 hours apart.
		Children ≥12 years and Adult	**INH:** 15 mg/kg (max 900 mg/dose) **RPT:** as above			
Rifampin (RIF)[d]	4 months	Children	15-20 mg/kg (max 600 mg/dose)	Daily	120	Complete doses within 6 consecutive months
		Adult	10 mg/kg (max 600 mg/dose)			
Isoniazid (INH)[a]	6 months	Children	10 -20 mg/kg[e] (max 300 mg/dose)	Daily	180	Complete doses within 9 consecutive months[f]
		Adult	5 mg/kg (max 300 mg/dose)			
	9 months	Children	10-20 mg/kg[e] (max 300 mg/dose)	Daily	270	Complete doses within 12 consecutive months
		Adult	5 mg/kg (max 300 mg/dose)			
Isoniazid (INH)[a] and Rifampin (RIF)[d]	3 months	Children	**INH:** 10-20 mg/kg (max 300 mg/dose) **RIF:** 15-20 mg/kg (max 600 mg/dose)	Daily	90	Complete doses within 4 consecutive months
		Adult	**INH:** 5 mg/kg (max 300 mg/dose) **RIF:** 10 mg/kg (max 600 mg/dose)			

Adapted from CDC Table: https://www.cdc.gov/tb/topic/treatment/ltbi.htm

a. Isoniazid (INH) is formulated as 100 mg and 300 mg tablets and as a 10 mg/mL syrup. Although a liquid preparation is available, solid dosage forms are preferred. When using tablets, please round doses to the nearest 50 mg. Concomitant pyridoxine may be considered in patients at risk for isoniazid-induced neuropathy. See discussion in Section B below.
b. Rifapentine (RPT) is formulated as 150 mg tablets. Tablets are dispensed in blister packs and should be sealed until use.
c. Intermittent regimens (i.e., <7 days per week dosing) may be administered by directly observed therapy (DOT) or self-administered therapy (SAT) at the clinician's discretion.
d. Rifampin (RIF) is formulated in 150 mg and 300 mg capsules. An extemporaneous compounding recipe is available for an oral suspension, but not all pharmacies are equipped to supply the compounded formulation. Although a liquid preparation is available from LPCH, solid dosage forms are preferred (liquid is poorly tolerated). When possible, utilize capsules, which can be opened, and contents mixed with soft food (preferred) or liquid.
e. The American Academy of Pediatrics recommends an INH dosage of 10–15 mg/kg for the daily regimen.
f. If gap(s) are ≥ 2 months, patients should be re-evaluated for signs and symptoms before resuming treatment

Monitoring for TB Infection

The CDC recommends monthly visits to assess medication adherence and signs or symptoms of drug toxicity. No laboratory tests are routinely needed for follow-up visits unless there is a clinical indication and/or concern for drug toxicity.

Owners: L Puckett, H Schwenk, L Bio, D Vu, L Kushner
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Window Prophylaxis

Window prophylaxis is the practice of treating a patient who has been exposed to a potentially infectious source case but who has no current evidence of TB disease or infection (by negative TST/IGRA and normal 2-view CXR and exam). Children < 5 years of age and/or significantly immunocompromised individuals who have been in contact with an infectious adult or teen in the past 8 weeks should begin early treatment to potentially abort early infection or prevent rapid transition from early infection to TB disease in vulnerable hosts.

- If there is no evidence of TB disease, window prophylaxis should be continued until 8-10 weeks since the last exposure to the source case, or since the source case has become non-infectious if contact is ongoing.
- **Treatment:** Drug regimens for window prophylaxis are the same as those used for treatment of TB infection (i.e., LTBI). See table above for recommendations on treatment regimens and dosing.
- **Duration:**
    - For children with intact immune systems (and at least 6 months of age), if the follow-up TST or IGRA remains negative (after the 8- to 10-week window period as defined above), window prophylaxis can be stopped.
    - For young infants and for children who are immunocompromised, a full TB infection course should be administered, as the TST/IGRA may not be sufficiently sensitive to rule out infection.
- **Monitoring:**
    - Patients receiving window prophylaxis should be monitored regularly during treatment. For patients on therapy, monitoring for medication adherence and signs or symptoms of drug toxicity should be performed regularly, as is done for patients receiving treatment for TB infection. No laboratory tests are routinely needed unless there is a clinical indication and/or concern for drug toxicity.
    - Patients should be monitored for new or worsening symptoms of TB disease, as some patients develop TB disease despite TB infection treatment or window prophylaxis.
    - Patients who are not receiving TB infection treatment or window prophylaxis and are in contact with a known source should be monitored for signs and symptoms of TB disease so that early evaluation and treatment can be initiated if they develop disease. Perform a clinical exam and symptom review every 3 to 6 months for 2 years (with CXR as indicated). If findings are suggestive of TB disease, proceed with TB work-up and consider initiation of TB regimen.

Treatment of Tuberculosis Disease

[Note, "tuberculosis disease" is the newer, preferred term for active tuberculosis]

RIPE TB treatment regimen consists of: rifampin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB). RIPE regimens for treatment of TB disease have an intensive phase of 2 months, followed by a continuation phase of either 4 or 7 months (total of 6 to 9 months of treatment). See CDC Guideline for recommendations of scenarios where a total 9 months of treatment is preferred.

Regimen	Intensive Phase		Continuation Phase		Comments[d]
	Drugs[a]	Interval and Dose (Minimum Duration)	Drugs	Interval and Dose (Minimum Duration)[b]	
1	RIF INH PZA EMB	7 days/week (8 weeks) OR 5 days/week (8 weeks)[c]	RIF INH	7 days/week (18 weeks) OR 5 days/week (18 weeks)[c]	Preferred regimen for patients with newly diagnosed pulmonary tuberculosis.
2	RIF INH PZA EMB	7 days/week (8 weeks) OR 5 days/week (8 weeks)[c]	RIF INH	**3 times weekly** (18 weeks)[c,e]	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.

a. Other combinations may be appropriate in certain circumstances; additional regimens can be found in the ATS/CDC/IDSA TB Guidelines.

b. Based on expert opinion, patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week) continuation phase.

c. Although there are no studies that compare 5 with 7 daily doses, extensive experience indicated that this would be an effective practice. Regimens where drugs are administered <7 days per week require directly observed therapy (DOT).

d. Pyridoxine (vitamin B6), 25-50 mg/day, is given with INH to all persons at risk of neuropathy (e.g., pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.

e. Dosing less frequently than daily (once-, twice-, thrice- weekly) may have different dosing recommendations, which may not be available for pediatric patients. For dosing with meds given < 7 days/week, refer to the CDC Guidelines.

Owners: L Puckett, H Schwenk, L Bio, D Vu, L Kushner
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Doses[a-c] of Antituberculosis Drugs for Adults and Children for TB Disease

See General Tips for Administering Oral TB Drugs in Children below on recommendations around administering partial capsules/tablets. Information on all listed TB therapies except Amikacin can be found in the Therapeutic Drug Monitoring section below.

<table>
<tr><th>Drug</th><th>Formulations</th><th>Population</th><th>Daily Dosing[a]</th></tr>
<tr><td colspan="4">First-line drugs</td></tr>
<tr><td rowspan="2">Ethambutol
(EMB)</td><td rowspan="2">Tablet: 100 mg, 400 mg

Suspension: 50 mg/mL (not prepared at LPCH)</td><td>Children</td><td>15-25 mg/kg (max 1 g/day)

<table>
<tr><th rowspan="2">Weight (kg)</th><th rowspan="2">Dose (mg)</th><th colspan="2">Weight-banded Dose</th></tr>
<tr><th>100 mg TAB</th><th>400 mg TAB</th></tr>
<tr><td>4 – 6</td><td>100</td><td>1</td><td>0</td></tr>
<tr><td>6.1 – 8</td><td>150</td><td>1.5</td><td>0</td></tr>
<tr><td>8.1 – 12.5</td><td>200</td><td>2</td><td>0</td></tr>
<tr><td>12.6 – 17. 5</td><td>300</td><td>3</td><td>0</td></tr>
<tr><td>17.6 – 22.5</td><td>400</td><td>0</td><td>1</td></tr>
<tr><td>22.6 – 27.5</td><td>500</td><td>1</td><td>1</td></tr>
<tr><td>27.6 – 32.5</td><td>600</td><td>0</td><td>1.5</td></tr>
<tr><td>32.6 – 37.5</td><td>700</td><td>3</td><td>1</td></tr>
<tr><td>37.6 – 55</td><td>800</td><td>0</td><td>2</td></tr>
<tr><td>56 – 75</td><td>1200</td><td>0</td><td>3</td></tr>
<tr><td colspan="4">Dose obese[a] children based on lean body weight.</td></tr>
</table>

Note: AAP recommends 1000 mg as a maximum daily ethambutol dose for children. TB pharmacologist suggest dosing based on lean body weight. Max daily dose might exceed 1000 mg for a muscular teen.</td></tr>
<tr><td>Adult</td><td>40 to 55 kg: 800 mg (14.5 to 20 mg/kg)
56 to 75 kg: 1200 mg (16 to 21.4 mg/kg)
76 to 90 kg: 1600 mg (17.8 to 21.1 mg/kg)</td></tr>
<tr><td rowspan="2">Isoniazid
(INH)

± Pyridoxine (see section B below)</td><td rowspan="2">Tablet: 50 mg, 100 mg, 300 mg

Suspension: 50 mg/5mL

IV not routinely stocked</td><td>Children</td><td>10-15 mg/kg (max 300 mg/day)

<table>
<tr><th rowspan="2">Weight (kg)</th><th rowspan="2">Dose (mg)</th><th colspan="2">Weight-banded Dose</th></tr>
<tr><th>100 mg TAB</th><th>300 mg TAB</th></tr>
<tr><td>3-5</td><td>50</td><td>½</td><td>0</td></tr>
<tr><td>5.1-7.5</td><td>75</td><td>¾</td><td>0</td></tr>
<tr><td>7.6-10</td><td>100</td><td>1</td><td>0</td></tr>
<tr><td>10.1-15</td><td>150</td><td>0</td><td>½</td></tr>
<tr><td>15.1-20</td><td>200</td><td>2</td><td>0</td></tr>
<tr><td>>20</td><td>300</td><td>0</td><td>1</td></tr>
</table></td></tr>
<tr><td>Adult</td><td>5 mg/kg (max 300 mg/day)</td></tr>
<tr><td rowspan="2">Pyrazinamide
(PZA)</td><td rowspan="2">Tablet: 500 mg

Suspension: 100 mg/mL
(LPCH compounded)</td><td>Children</td><td>30-40 mg/kg (max 2000 mg/day)

<table>
<tr><th>Weight (kg)</th><th>Dose (mg)</th><th>Weight-banded Dose
500 mg TABS</th></tr>
<tr><td>3 – 4.2</td><td>125</td><td>¼</td></tr>
<tr><td>4.3 – 5.9</td><td colspan="2">Consult ID and TB control*</td></tr>
<tr><td>6 – 8.9</td><td>250</td><td>½</td></tr>
<tr><td>9 – 12.5</td><td>375</td><td>¾</td></tr>
<tr><td>12.6 – 17</td><td>500</td><td>1</td></tr>
<tr><td>17.1 – 25</td><td>750</td><td>1.5</td></tr>
<tr><td>25.1 – 33.3</td><td>1000</td><td>2</td></tr>
<tr><td>33.4 – 41. 5</td><td>1250</td><td>2.5</td></tr>
<tr><td>41.6 – 50[c]</td><td>1500</td><td>3</td></tr>
<tr><td>≥50.1[c]</td><td>2000</td><td>4</td></tr>
<tr><td colspan="3">Dose obese[a] children on lean body weight</td></tr>
<tr><td colspan="3">*Patients may have dose drawn up with suspension if available.</td></tr>
</table></td></tr>
<tr><td>Adult[c]</td><td>40 to 55 kg: 1 g (18.2 – 25 mg/kg)
56 to 75 kg: 1500 mg (20 – 26.8 mg/kg)
76 to 90 kg: 2000 mg (22.2 – 26.3 mg/kg)</td></tr>
</table>

<table>
<tr>
<td rowspan="2">Rifampin
(RIF)</td>
<td rowspan="2">Capsule: 150 mg, 300 mg

Suspension:

25 mg/mL (LPCH compound)

Outside compounded: strength may vary
• Recipe for 25 mg/mL from Nationwide Children's if needed

IV available</td>
<td>Children</td>
<td>Neonates (<28 days of age): 10 mg/kg/day
Infants and Toddlers: 20-30 mg/kg/day
Children and Adolescents: 15-20 mg/kg (max 600 mg/day)
Children and Adolescents with disseminated disease: 20-30 mg/kg/day

<table>
<tr><th colspan="4">Standard RIF for TB infection in all ages and non-severe/non-extensive TB in older children (outside the infant/toddler age group)</th></tr>
<tr><th rowspan="2">Weight (kg)</th><th rowspan="2">Dose (mg)</th><th colspan="2">Weight-banded Dose</th></tr>
<tr><th>150 mg CAP</th><th>300 mg CAP</th></tr>
<tr><td>Neonates <28 days</td><td>10 mg/kg</td><td colspan="2">Use Suspension</td></tr>
<tr><td>Infants >28 days and <3.75 kg</td><td>20-30 mg/kg</td><td colspan="2">Use Suspension</td></tr>
<tr><td>3.75 – 6</td><td>75</td><td>½</td><td>0</td></tr>
<tr><td>6.1 – 10</td><td>150</td><td>1</td><td>0</td></tr>
<tr><td>10.1 – 15</td><td>225</td><td>1.5</td><td>0</td></tr>
<tr><td>15.1 – 20</td><td>300</td><td>0</td><td>1</td></tr>
<tr><td>20.1 – 30</td><td>450</td><td>1</td><td>1</td></tr>
<tr><td>>30 kg</td><td>600</td><td>0</td><td>2</td></tr>
</table>

<table>
<tr><th colspan="4">Higher RIF dosing for infants and toddlers or for children of any age with severe or extensive TB disease</th></tr>
<tr><th rowspan="2">Weight (kg)</th><th rowspan="2">Dose (mg)</th><th colspan="2">Weight-banded Dose</th></tr>
<tr><th>150 mg CAP</th><th>300 mg CAP</th></tr>
<tr><td>Neonates < 28 days</td><td>10 mg/kg</td><td colspan="2">Use Suspension</td></tr>
<tr><td><5 kg and ≥ 28 days</td><td>20-30 mg/kg</td><td colspan="2">Use Suspension</td></tr>
<tr><td>5 – 7.5</td><td>150</td><td>1</td><td>0</td></tr>
<tr><td>7.6 – 10</td><td>225</td><td>1.5</td><td>0</td></tr>
<tr><td>10.1 – 15</td><td>300</td><td>0</td><td>1</td></tr>
<tr><td>15.1 – 20</td><td>450</td><td>1</td><td>1</td></tr>
<tr><td>>20 kg</td><td>600</td><td>0</td><td>2</td></tr>
</table>
</td>
</tr>
<tr>
<td>Adult</td>
<td>10 mg/kg (max 600 mg/day)</td>
</tr>
<tr>
<td colspan="4">Select Second-line drugs</td>
</tr>
<tr>
<td rowspan="2">Ethionamide
(ETA)</td>
<td rowspan="2">Tablet: 250 mg</td>
<td>Children</td>
<td>15-20 mg/kg total (div into 1-2 daily doses) (max 1000 mg/day)

<table>
<tr><th>Weight (kg)</th><th>Initial Dose</th><th>Dose Size (initial) (250 mg TAB)</th><th>Final Dose*</th><th>Dose Size (final) (250 mg TAB)</th></tr>
<tr><td>6 – 11.9</td><td>125 mg</td><td>½</td><td>125 mg</td><td>½</td></tr>
<tr><td>12 – 18</td><td>125 mg</td><td>½</td><td>250 mg</td><td>1</td></tr>
<tr><td>18.1 – 25</td><td>250 mg</td><td>1</td><td>375 mg</td><td>1.5</td></tr>
<tr><td>>25.1</td><td>250 mg</td><td>1</td><td>500 mg</td><td>2</td></tr>
<tr><td colspan="5">*Gradually increase dose every 3 to 5 days. It may take a few weeks to reach full dose. For those experiencing nausea, daily doses could be divided BID if DOT allows. For severe extrapulmonary TB (ex. meningitis), may push to daily max of 1000 mg/day if tolerated.</td></tr>
</table>
</td>
</tr>
<tr>
<td>Adult</td>
<td>15 – 20 mg/kg total (usually 250 - 500 mg once or twice daily)</td>
</tr>
<tr>
<td rowspan="3">Amikacin
(AK)</td>
<td rowspan="3">IV/IM only</td>
<td>Children</td>
<td>15 – 20 mg/kg</td>
</tr>
<tr>
<td>Adult</td>
<td>15 mg/kg - Some clinicians prefer 25 mg/kg 3 times weekly. Recommend TDM, especially in patients with decreased renal function.</td>
</tr>
<tr>
<td>TDM</td>
<td>Timing:
• Peak: once during 1st week of therapy and after as clinically indicated
• Trough: concentration may be obtained just prior to a scheduled dose weekly for 4 weeks, followed by every 2 weeks once stable

Target concentrations refer to Aminoglycoside Guideline.</td>
</tr>
</table>

Levofloxacin (LFX)	**Tablet:** 250 mg, 500 mg, 750 mg *IV available*	Children	15 – 20 mg/kg (max 1000 mg/day)
		Adult	500 – 1000 mg

a. Dosing based on actual weight is acceptable in patients who are not obese. For obese patients (>20% above ideal body weight [IBW] or above the 95th percentile for children and teens of the same age and sex), dosing based on IBW may be preferred for initial doses. Some clinicians prefer a modified IBW (IBW + [0.4 x (actual weight -IBW)] as is done for initial aminoglycoside doses. Because tuberculosis drug dosing for obese patients has not been established, therapeutic drug monitoring may be considered for such patients.

b. Dosing less frequently than daily (once-, twice-, thrice- weekly) may have different dosing recommendations, which may not be available for pediatric patients. For dosing recommends < 7 days/week, refer to the CDC Guidelines.

c. For purposes of this document, pediatric doses are recommended up to age 14 years OR until their weight-based dose equals the adult dose (whichever comes first). For pyrazinamide and patients weighing >40 kg, please review dosing with TB control.

Monitoring TB Disease: RIPE therapy[1]

Monitoring Parameter	Monitoring Frequency	Associated Medication
Weight	Baseline, Weekly, and Monthly PRN[2]	All
Height	Baseline, Weekly, and Monthly[3]	All
CBC	Baseline and Monthly[4] or PRN	RIF
LFTs	Baseline and Monthly[5] or PRN	RIF, INH, PZA
Uric acid	Baseline and Monthly or PRN	PZA
Vision testing (visual acuity and color discrimination)	Baseline and Monthly	EMB

ETH, ethambutol; INH, isoniazid; PYR, pyrazinamide; RIF, rifampin

[1]Monitoring used for second line agents can be found through Lexicomp monographs and through Curry TB Center Medication Fact Sheets.

[2]Weight should be assessed at start of treatment, weekly until stable, and then monthly throughout. Dose should be adjusted based on weight gain.

[3] Height should be assessed at start of treatment for all patients (to be able to assess lean body weight or BMI); then monthly for children (to assess growth).

[4] Baseline and then monthly if baseline abnormalities or as clinically indicated

[5]Liver function tests only at baseline unless there were abnormalities at baseline, symptoms consistent with hepatotoxicity develop, on other hepatotoxic medications, viral hepatitis or history of liver disease, HIV, or prior drug-induced liver injury

B. Adverse Reactions, Administration, Clinical Pearls, and Counseling

AMIKACIN (AK)	
Adverse Reactions	• Electrolyte abnormalities: hypokalemia, hypocalcemia, hypomagnesemia • Nephrotoxicity • Neurotoxicity – muscle twitching, numbness, seizure, tingling of skin • Ototoxicity – auditory and vestibular
Administration	• Injectable – PICC strongly preferred over IM for long-term tolerability
Pearls and Counseling	• Based on risk of side effects (nephrotoxicity, ototoxicity, vestibular toxicity, complications of central line use), use should be limited for when oral drugs are not available. • Hospitalized patients with severe disease may benefit from transient use of AK until preferred oral agents are available. • Patients should be monitored with hearing and vestibular screens and renal function monitoring periodically • AK should be initiated at 5-7 days per week, with reduction to intermittent dosing (3x/week) after culture conversion or clinical/radiographic improvement is shown • Placement of PICC is strongly preferred to IM administration for tolerability – if IM injection is used, appropriate site should be selected and injection site rotated with each injection. Large muscle mass (e.g., ventrogluteal)

ETHAMBUTOL (EMB)	
Adverse Reactions	• **CNS**: confusion, dizziness, hallucination, headache, malaise, peripheral neuritis • Fever • **GI upset**: abdominal pain, anorexia, nausea/vomiting • **Hematologic effects:** eosinophilia, leukopenia, lymphadenopathy, neutropenia, thrombocytopenia • **Hepatotoxicity** • **Hyperuricemia/gout flare** • **Ocular**: Decreased visual acuity, red-green color blindness, optic neuritis (dose related and irreversible) • **Respiratory:** pneumonitis, pulmonary infiltrates (with/without eosinophilia) • **Skin**: Dermatitis, erythema multiforme, exfoliative dermatitis, pruritis, rash
Administration	• **Tablets can be cut/crushed** • Can be given with or without food

Pearls and Counseling	• Contraindicated in pts with pre-existing optic neuritis or those with visual changes on EMB
	• Optic toxicity
	  ○ Has been observed in adults, usually when higher doses of EMB are used. It is challenging to monitor for optic toxicity in young children; however, there have been no well-documented cases of optic toxicity in children.
	  ○ Drug is bactericidal only at higher doses and children require higher dose than adults (15 to 25 mg/kg/day in children) to achieve the same levels. Some providers use doses closer to 25 mg/kg in the initial phase of treatment when bacillary loads are highest, then decrease to doses closer to 15 to 20 mg/kg for long-term management.
	• Optic toxicity in children
	  ○ Older children can be monitored with Snellen eye charts and color vision tools.
	  ○ For children unable to be assessed with Snellen testing:
	  ▪ Potential signs of optic toxicity include eye rubbing or excessive blinking, sitting closer to screens, difficulty with accurate grasping of objects.
	  ▪ Offering small items (ex. Cheerios, rice puffs) to young children and watching their grasp. Children with vision changes may have trouble grasping the small objects as accurately as they had previously.

ETHIONAMIDE (ETA)	
Adverse Reactions	• **CNS:** depression, dizziness, drowsiness, headache, metallic taste, peripheral neuritis, psychiatric disturbance, restlessness • **Endocrine/metabolic**: goiter, gynecomastia, hypoglycemia, reversible hypothyroidism, pellagra-like syndrome, weight loss, menstrual irregularity • **GI upset:** abdominal pain, anorexia, diarrhea, nausea, vomiting • **Hematologic effects**: purpuric disease, thrombocytopenia • **Hepatotoxicity** • **Ophthalmic:** blurred vision, diplopia, optic neuritis • Skin photosensitivity, rash • Metallic taste

Administration	• Tablet can be cut/crushed
	• Give at bedtime or with a main meal to reduce nausea
	• Start with smaller dose and titrate up as tolerated (see pearls below)
	• Giving partial tablets:
	  ○ 250 mg tablet is coated and not scored – to administer partial dose, outside compounding pharmacies can create a suspension or tablet can be fractured in small plastic bag and fragments administered.
	  ○ Freezing tablet prior to breaking may help. Giving fragments from single tablet over several dose helps to achieve an accurate dose over several days.
	• Children should be supplemented with pyridoxine when taking ETA and thyroid function should be monitored

Pearls and Counseling	• Better tolerated by children than adults with few GI side effects. Tolerability can be improved by ramping up the drug dose – starting with small dose (around 5 mg/kg daily) then gradually increasing every 3-5 days. After a few weeks of divided dosing, children may be able to try receiving the entire dose as a single dose with food.

<table>
<tr><th colspan="2">ISONIAZID (INH)</th></tr>
<tr><td>Adverse Reactions</td><td>

CNS effects: peripheral neuropathy (supplement B6), psychosis, seizure, paresthesia, optic neuritis, encephalopathy
GI upset: diarrhea, epigastric distress, nausea, vomiting
Hematologic effects: anemia (sideroblastic, hemolytic, aplastic), eosinophilia, thrombocytopenia
Hepatoxicity (both asymptomatic elevations of LFTs and up to fatal hepatitis)
Hypersensitivity reactions
Lupus-like syndrome

</td></tr>
<tr><td>Administration</td><td>

Administration on empty stomach preferred (bioavailability decreased with food)

For upset stomach, can take with snack. Avoid large fatty meals.

Tablets may be crushed and mixed in soft food/liquid
Do not take any antacid within 1 hour of the dose

</td></tr>
<tr><td>Pearls and Counseling</td><td>

May be given with pyridoxine (vitamin B6) to prevent neuropathy.

DOSE:

Infants and Children: 1 – 2 mg/kg once daily (max 50 mg/day)

<table>
<tr><th rowspan="2">Weight (kg)</th><th rowspan="2">Dose (mg)</th><th colspan="2">Weight-banded Dose</th></tr>
<tr><th>25 mg CAP</th><th>50 mg CAP</th></tr>
<tr><td><3 kg</td><td colspan="3">1-2 mg/kg daily</td></tr>
<tr><td>≥3 – 6.2</td><td>6.25</td><td>¼</td><td>0</td></tr>
<tr><td>6.3 – 12.4</td><td>12.5</td><td>½</td><td>0</td></tr>
<tr><td>12.5 – 18.7</td><td>25</td><td>1</td><td>0</td></tr>
<tr><td>18.8 – 24.9</td><td>37.5</td><td>1.5</td><td>0</td></tr>
<tr><td>>25</td><td>50</td><td>0</td><td>1</td></tr>
</table>

Adolescent and Adults: 25 – 50 mg once daily

Persons at risk for neuropathy: pregnant/breastfeeding women, breastfeeding infants, persons with HIV, diabetes, alcoholism, malnutrition, chronic renal failure, advanced age.
Persons already with peripheral neuropathy can have dose increased to 100 mg/day (expert opinion)

Suspension: contains high quantities of sorbitol → causes nausea or diarrhea at volumes >5mL or when taken on empty stomach. Consider crushing tablets and mixing with small amount of food or liquid.
Weak MAOI – if patients are experiencing flushing, sweating, or headaches, ask if they are eating foods high in tyramine (i.e., smoked/cured meats, aged cheeses, pickled/fermented food, pickled or fermented foods, soy containing foods) as well as if they started new medication/supplements.

</td></tr>
<tr><th colspan="2">LEVOFLOXACIN (LFX)</th></tr>
<tr><td>Adverse Reactions</td><td>

Aortic aneurysm/aortic dissection
Arthropathy/arthralgia
CNS effects/neuroexcitation: dizziness, restlessness, confusion, agitation, insomnia, drowsiness, hallucinations, suicidal ideation
Glucose dysregulation (hyper/hypoglycemia)
Hepatotoxicity
Peripheral neuropathy, including Guillain-Barre syndrome
Phototoxicity
QT prolongation
Tendinopathy/tendon rupture

</td></tr>
<tr><td>Administration</td><td>

Tablets are unscored and coated – can be crushed but discouraged (bitter taste). For patients unable to swallow tablets, suspension is recommended and is commercially available.
Should be taken with or without food – drink with plenty of beverages.
Should not be administered by mouth within 2 hours of ingestion of milk-based products, antacids, or other medicines with divalent cations (iron, magnesium, calcium, vitamins).

</td></tr>
<tr><td>Pearls and Counseling</td><td>

Parents and caregivers should observe for any signs or symptoms of toxicity, including extremity pain, swelling, or a decrease in range of motion.

Note that no cases of irreversible arthropathy or bone abnormalities have been reported in literature at this time. Rates of reversible arthropathy with fluoroquinolone use are similar to those reported in adult patients. Rare cases of Achilles tendon rupture in adolescents have been reported.

Associated with QTc prolongation – check baseline QTc and monitor in patients on other QTc prolonging medications.
May cause sun sensitivity – patients should use sunscreens

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PYRAZINAMIDE (PZA)	
Adverse Reactions	• **Hyperuricemia** → asymptomatic hyperuricemia to acute gouty arthritis • **Hepatotoxicity** • **GI upset**: anorexia, nausea, vomiting • Transient morbilliform rash and dermatitis • Photosensitivity (rare)
Administration	• May be taken with or without food • Tablets can be split/crushed – if crushing, rounding to 125 mg increments (1/4 tab) is preferred
Pearls and Counseling	• May cause rash after sun exposure – limit sun exposure
RIFAMPIN (RIF)	

Adverse Reactions	• **Dermatologic**: Rash, pruritis
	• **GI upset**: Abdominal cramps, anorexia, diarrhea, epigastric discomfort, heartburn, nausea, flatulence, vomiting
	• **Hematologic effects:** eosinophilia, hemolysis, hemolytic anemia, leukopenia, thrombocytopenia
	• **Hepatotoxicity**
	• **Hypersensitivity reactions**
	  ○ Immediate (urticaria, angioedema, anaphylaxis) and delayed (rash, fixed drug eruption, EM, DRESS, SJS/TEN)
	  ○ Flu-like syndrome
	• **Pulmonary toxicity:** interstitial pulmonary disease, pneumonitis, eosinophilic pneumonitis, pulmonary infiltrates, ARDS, bronchiolitis obliterans organizing pneumonia, pulmonary fibrosis
	• **Red-orange metabolites** → **red-orange coloration** of ALL bodily secretions (and tooth staining)

Administration	• Available in solid and liquid dosage form. Suspension is very dilute – it is preferred to open a capsule when possible and sprinkle onto food if patient is unable to swallow capsules. • Best taken on empty stomach to improve absorption; if it bothers patients' stomach, can be taken with small amount of food or at bedtime to improve tolerability.
Pearls and Counseling	• Enormous number of drug-drug interactions: Include warfarin, methadone, antiepileptics, oral contraceptives. Run drug-drug interaction check prior to initiation and with any new medications or supplements prior to beginning. • Red-orange discoloration: Will stain urine, saliva, sputum, sweat, teeth, tears reddish-orange to reddish-brown color. Avoid wearing soft contacts while taking rifampin. • Warning – since rifampin will stain urine, counseling to look for dark urine may not be effective method to monitor for hepatotoxicity.
RIFAPENTINE (RPT)	
Adverse Reactions	• **GI upset:** anorexia, diarrhea, dyspepsia, nausea, vomiting • **Dermatologic:** rash and pruritis • **Hematologic effects:** eosinophilia, hemolysis, hemolytic anemia, leukopenia, thrombocytopenia • **Hepatotoxicity** • Hypersensitivity reactions • **Red-orange metabolites** → **red-orange coloration** of ALL bodily secretions (and tooth staining)
Administration	• Patients prone to GI upset – taking with food may improve tolerability ○ Administration with fatty meal preferred to improve absorption • Tablets may be cut/crushed and given with small amount of semi-solid food.
Pearls and Counseling	• Enormous number of drug-drug interactions, including: warfarin, methadone, antiepileptics, oral contraceptives • Red-orange discoloration: Will stain urine, saliva, sputum, sweat, teeth, tears reddish-orange to reddish-brown color. Avoid wearing soft contacts while taking rifampin • Warning – since rifapentine will stain urine, counseling to look for dark urine may not be an effective method to monitor for hepatotoxicity.

ARDS, acute respiratory distress syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms (DRESS); SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis (TEN)

C. Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) is not routinely required for patients receiving therapy for TB disease. However, it may be considered in patients with the following conditions or situations: poor response to treatment despite adherence; severe gastrointestinal abnormalities (severe gastroparesis, short bowel syndrome, chronic diarrhea with malabsorption); drug-drug interactions; impaired renal clearance; HIV infection; diabetes mellitus; treatment using second-line drugs; and/or, obesity[1].

All serum testing are send-out labs and have roughly a 2-week turnaround time. Any TDM should be done in conjunction with Pediatric ID and County TB Prevention and Control. Additional information required regarding medication dose and timing can be found on the National Jewish Health Website.

Medication	Serum Goals		Collection and Preparation	How to perform TDM
	C_{max} (µg/mL)	Predicted T_{max} (h)		
Ethambutol EMB	2 – 6	2 – 3	**Collection[1]:** Collect blood in 8-10mL plain red top tube. If collecting more than 1 serum level with the same drawn, please contact the lab to see if more than 1 tube is needed. **Specimen Preparation:** Separated plasma/serum should be aliquoted into polypropylene or similar plastic tube after centrifugation. Separate tubes should be used for each test order. Preferred volume: 2mL of serum/plasma Minimum volume (serum/plasma): • RIF, PRY, EMB, LFX: 0.5 mL • INH: 1mL • ETA: 0.25 mL If minimum volume cannot be obtained, contact reference laboratory. **PK Requisition**: Information needed for lab assay include drug dose amount, frequency, method, and date and time of last dose prior to draw. **Turnaround time**: Within 10 business days	Serum levels should be drawn 2 hours after administration, with an additional 6hr serum level recommended if there are concerns for malabsorption. Levels should be repeated as needed with consideration for the following; • Change in clinical status (e.g. change in renal function and/or severity of gastrointestinal abnormalities)[2] • New drug-drug interactions • Suspected toxicity (e.g., hepatotoxicity with pyrazinamide, ocular toxicity with ethambutol) • Continued clinical worsening despite treatment adherence
Ethionamide ETA	2 – 5	2		
Isoniazid INH	3 – 6	1 – 2		
Levofloxacin LFX	8 – 13	1 – 2		
Pyrazinamide PYR	20 – 60	1 – 2		
Rifampin RIF	8 – 24	2		

[1]Samples are shipped via overnight delivery and can be received Monday through Friday. Do not collect Friday or Saturday.

[2]Renal dosage adjustment is only needed for ethambutol, levofloxacin, and pyrazinamide.

D. General Tips for Administering Oral TB Drugs in Children

1. **Solid dosage forms are preferred, even for patients unable to swallow tablets/capsules**
    a. Few anti-TB drugs are commercially available in liquid preparations.
    b. Most compounded liquid preparations are of low concentration and poorly tolerated.
2. **General tips for administering partial tablets/capsules**
    a. Approximate doses are adequate:
        i. Exact doses can be nearly impossible to attain from tablet fragments or approximation of capsule contents. Example: A 500 mg tablet of pyrazinamide can provide 4 doses of 125 mg. When given over 4 days, any small discrepancy in dosing will even out over the week.
    b. Opening, cutting, and crushing medication:
        i. See "administration" in counseling section for recommendations on solid dosage form manipulation.
    c. Mixing crushed tablets/capsule contents with food or liquid:
        i. Give a small amount of plain food/liquid before, between spoonfuls with medication, and after the dose.
        ii. Take care not to mix with too much food or liquid at once to ensure that all of the dose is consumed.
        iii. **Mixing with liquid:** Does not typically work well with crushed tablets, as the taste is noticeable, and the tablet fragments will sink to the bottom of thin liquids. For open capsules, the powder contents can be suspended in liquid and pass through a syringe. Use of a device with a large opening, like a medicine dropper, allows for more drug to pass through without sticking to the syringe.
            1. **For infants:** Mix capsule contents and crushed tablets in small amount of liquid, which can include formula or breastmilk. Use of special medicine dispensing pacifier or bottle allows for better chances of entire dose being taken instead of mixing into entire bottle. Babies may reflexively suck on the medication while they sleep. Some water should be given after medication doses to rinse any remaining medicine out of the mouth.
        iv. **Mixing with food (for older infants or children who are consuming solids):**
            1. Many children prefer crushed pills or granules delivered with soft food.
            2. Example soft foods for administration: yogurt, pudding, applesauce or other pureed fruit, oatmeal, ice cream, nut butters (i.e., peanut butter).
            3. Give a small amount of plain food before the dose, between spoonfuls containing medication, and after the dose.
            4. Use a small amount of food when mixing with medication. The child may not want many spoonfuls of the drug. Medicine can either be mixed with soft food or prepared as a "medication sandwich" (ex. A thin layer of food on the spoon, the powder or pill fragment, then another layer of food on top). The sandwich method may lessen the drug taste in the food itself.
    d. Administer immediately after preparation in food and then give food or drink after to clear the palate.
3. **Caregiver counseling**
    a. **Be flexible, but firm:** The patient can be given a few choices on how to take the medicine, but whether or not to take the medicine should not be one of them.
    b. **Incentivize medication compliance** (i.e., with sticker charts or other reward systems)

Key Revisions:

12/2023: Revision to LPCH available rifampin suspension concentration.

1/2024: Therapeutic drug monitoring section added. TB window prophylaxis recommendations added. Aminoglycoside monitoring guideline linked.

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