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Adverse Reactions

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SUMMARY OF KEY UPDATES (2022)

- Updated discussion of adverse events associated with newer DR-TB regimens including BPaL and BPaLM
- Expanded discussion of hematologic adverse events, especially related to linezolid
- Additional information on linezolid-associated peripheral neuropathy prevention, management, and prognosis
- New section on cardiovascular toxicity including QT prolongation monitoring and management.

Adverse reactions and toxicity should be anticipated with any treatment course for drug-resistant TB.

Introduction

Treatment of drug-resistant tuberculosis (DR-TB) requires the use of multiple medications that are frequently associated with adverse events. The response of an individual person with DR-TB, however, cannot be predicted. **Medications should not be withheld in anticipation of or because of fear of a reaction.** Even some elderly or very ill patients will tolerate complex regimens for DR-TB. By contrast, others may have serious difficulty tolerating relatively simple regimens.

Persons with DR-TB should be well informed about their anti-tuberculosis treatment regimens so that they can be recruited as partners invested in the success of their therapies. Empower them by providing information about potential adverse events and reassurance that they will be supported throughout the treatment regimen.

In recent years, treatment of DR-TB has undergone a transformation with the introduction of **new regimens** that contain drugs such as bedaquiline (BDQ), pretomanid (Pa), delamanid (DLM), linezolid (LZD) and the later-generation fluoroquinolones (levofloxacin [LFX] and moxifloxacin [MFX]). While these treatment-shortening regimens have shown remarkable success and enabled more rapid cures, they have also introduced new and sometimes serious adverse events. Some of the newer drugs developed specifically for TB treatment, such as Pa and DLM, have been poorly characterized in regard to adverse events because they have only been administered as part of multi-drug regimens.

A notable adverse event, new for TB care, is **QT prolongation**, especially when multiple QT-prolonging agents are used concurrently (e.g., BDQ and MFX). Cytopenias and peripheral neuropathy are frequently seen with LZD; treatment merits careful clinical and laboratory monitoring. Finally, while the fluoroquinolones have been used for many years, as a class they are also associated with several U.S. Food and Drug Administration (FDA) boxed warnings. Fluoroquinolones can be associated with non-specific adverse events like anorexia, dizziness, fatigue, and headache, which can make it difficult to associate with a particular drug in a multi-drug regimen. Fluoroquinolone-related adverse events may be more pronounced when treating for DR-TB (which can take many months) in contrast to bacterial infections (in which the fluoroquinolones are typically used for only 1-3 weeks). As more drugs are added or repurposed to treat DR-TB, clinicians' familiarity with recognizing and managing adverse events is also rapidly changing.

- **Prior to initiating a treatment regimen, it is essential to discuss the benefits and risks of therapy.** The person with DR-TB should understand the need for treatment, the importance of each medication in the treatment regimen, and the possible side effects and toxicities.
- Specifically, patients must understand that there are limited medication options for treating DR-TB such that replacing even one drug from the regimen because of toxicity or side effects can be problematic. Explain that inadequate treatment can lead to disease progression and transmission.
- **Assure the person with DR-TB that every attempt will be made to make treatment as easy as possible while acknowledging that having enough effective drugs in the regimen is essential to achieving a cure.** While side effects may be inevitable, emphasize that they will be addressed and treated as aggressively as possible. Ideally, persons undergoing care will be mentally prepared for likely discomfort and a long road of treatment. If possible, include family or significant others in discussions to provide awareness and support.
- **Help persons with DR-TB realize that this may be their best opportunity for cure and future treatment regimens could be more toxic and less effective.**
- Whenever possible, avoid breaks in therapy to maximize the effectiveness of treatment.

Quickly recognize and respond to symptoms when expressed. Careful assessment may allow attribution of some symptoms to causes other than medication toxicity. Most persons with DR-TB will be willing to continue medication despite side effects when: 1) they understand the benefit of the medication for themselves and others; 2) they know that many of these symptoms improve after the first several weeks; and 3) they are assured that their providers are doing their best to evaluate and address their problems. Express appreciation for their efforts to cooperate. This recognition often helps a person to continue therapy. Persons with DR-TB can be counseled that treating drug-resistant disease is more similar to cancer chemotherapy than treating a typical infection. Treatment of this life-threatening disease is a marathon, not a sprint, and there may be setbacks.

An important principle in the management of DR-TB: Do not stop a drug that leaves the person with DR-TB at risk of relapse or treatment failure without consulting an expert in the management of DR-TB. Any change in the treatment regimen — dosage adjustment, drug discontinuation, or substitution — must be assessed with a thorough risk/benefit analysis of the proposed changes. The dose of a drug should not be reduced unless it can be done without compromising the efficacy of the treatment regimen. In some cases, minor drug reactions may persist and the person on treatment may be asked to try to tolerate the discomfort to ensure the success of the regimen, especially for multidrug-resistant (MDR) or extensively-drug-resistant (XDR) TB. For example, some patients may need to weigh the benefits of continuing LZD against tolerating some neuropathy to maximize the opportunity of a lasting cure. Educate persons on treatment about the toxicities of their medications and encourage them to express their opinions about what they can tolerate.

Frequent meetings with the person with DR-TB and family to clarify goals and address symptom management can strengthen the provider-patient alliance that is so important to supporting a person through treatment.

Gastrointestinal

The most difficult side effects at the initiation of treatment often relate to **gastrointestinal (GI) upset**. Nausea and vomiting are most often reported, but abdominal cramps and increased flatulence may be equally troubling. Anorexia with or without nausea, vomiting, and/or the metallic taste caused by ethionamide (ETA) can prevent weight gain or even cause worrisome weight loss. Nausea, vomiting, and anorexia may represent possible hepatotoxicity; if these symptoms develop, liver enzymes and total bilirubin should be checked. If symptoms are significant, potentially liver-toxic medications are usually held pending laboratory results. GI symptoms during TB therapy can be due to TB medications, unrelated underlying GI conditions or a combination of the two. Factors that influence the adequacy of a given drug dose for an individual that may necessitate dose adjustments that could effect tolerance include the individual's weight, ability to adequately absorb and metabolize drugs, and concomitant medications that affect drug metabolism.

Some common causes of GI symptoms while on anti-tuberculosis therapy include:

Possibly due to TB therapy:

- Hepatitis or hepatotoxicity
- Biliary disease
- Gastritis
- Pancreatitis
- *Clostridium difficile* colitis

Not related to TB therapy:

- Peptic ulcer disease
- Inflammatory bowel disease
- Lactose intolerance
- Diabetic gastroparesis
- Pregnancy

Nausea and vomiting

Treatment of nausea and vomiting

- **First, ask the persons taking the medications. Individuals may have strong ideas about which medications are causing them problems. Their opinions must be addressed and respected.**
- Encourage the individual to continue to take the medication and provide reassurance that many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely.
- **Pregnancy** should be considered as the possible etiology of nausea and vomiting in the appropriate setting, especially if the symptoms occur after a period of initial tolerance.
- Consider that the symptoms may be due to **primary GI TB** that may be undiagnosed. These symptoms should resolve over time with TB treatment.
- With **TB meningitis**, nausea and vomiting might be signs of rising intracranial pressure rather than a drug intolerance issue. If indicated, obtain urgent imaging to evaluate for hydrocephalus, and neurosurgical consultation.

Notes on specific drugs

Fluoroquinolones: LFX and MFX may frequently cause anorexia, nausea, and vomiting. The symptoms may be vague GI upset. Do not decrease the dose of fluoroquinolones because of nausea — the bactericidal effects of fluoroquinolones are dose-dependent. Some providers find that switching from one fluoroquinolone to the other may alleviate the symptoms.

BDQ: Nausea and vomiting are usually confined to the first 2 weeks of daily therapy with improvement or resolution after the dosage interval is decreased to 3 times weekly. Most persons are able to complete the initial 2 weeks of daily therapy. The dose of BDQ should not be altered.

Rifampin (RIF): Can cause gastritis; use of a proton-pump inhibitor such as pantoprazole may help (pantoprazole does not interact with rifamycins).

LZD: May also be associated with nausea and vomiting. If the LZD dose is 1200 mg/day, reduction of the dose to 600 mg/day may be considered to improve GI tolerance and is not associated with loss of efficacy. Most reports noting efficacy at 300 mg daily were in persons who had the dose decreased after a period of time on the 600-mg dose. Consider therapeutic drug monitoring (TDM) when the dose is decreased to less than 600 mg daily; this can help confirm an adequate peak concentration is being achieved. See **Chapter 3, *Laboratory*** and **Chapter 4, *Treatment*** for more information on TDM. Some patients will require a 400- to 450-mg daily dose to achieve a therapeutic level (only available with the liquid formulation of the drug).

ETA: Frequently associated with nausea and vomiting, as well as a metallic taste. Initial "ramping" of dose may improve tolerance (see **Chapter 4, *Treatment***). If nausea improves after ETA is held, rechallenge at a lower dose with a gradual

increase to reach a minimum of 500 mg daily. Administering ETA before bedtime may help with nausea. For persons who require a higher dose of 750 mg daily, split dosing can be attempted with the higher dose of ETA taken in the evening (ETA 250 mg in the morning, 500 mg at bedtime). While giving ETA in 2 or 3 doses over the day may improve tolerance, it will significantly complicate directly observed therapy (DOT) efforts — if only one of the daily doses is administered by DOT and self-administered doses are not taken consistently, the possibility of sub-therapeutic dosing increases.

Para-aminosalicylate (PAS): Dosed at 8,000 to 12,000 mg per day divided 2-3 times per day (initiating using a dose "ramping" strategy similar to ETA), with some experts recommending a dose of 6,000 mg daily. PAS can cause both upper and lower GI symptoms, including nausea, vomiting, abdominal cramping, and diarrhea.

If symptoms improve off of PAS, the drug can be restarted at a lower dose (2,000 to 4,000 mg daily) and gradually increased over the next 2 weeks. As with ETA, PAS can be given in 2 or 3 doses over the day, but self-administered doses must be taken consistently to avoid subtherapeutic levels.

Persons with DR-TB may tolerate either ETA or PAS, but many do not tolerate both together. If ETA or PAS is suspected of causing the symptoms, hold the dose for 3 to 4 days to evaluate whether the nausea or vomiting is alleviated and determine if only one (or both sequentially) can be restarted. Many experts would preferentially use ETA if only one drug is tolerated.

Administer antiemetics or antacids prior to medication or as needed.
Note: Antacids cannot be given within 2 hours of fluoroquinolones.

The following are some specific options for GI symptom management (adult doses):

- **Ondansetron** (Zofran) 4-8 mg PO or IV 30 minutes before the dose. The dose can be repeated after 8 hours. Note that ondansetron may also prolong QT (some experts recommend starting with lower dosage, 4 mg, and repeat or increase if needed).
- **Metoclopramide** (Reglan) 10 mg PO or IV every 6 hours as needed.
- **Lorazepam** (Ativan) 0.5 mg sublingual 30 minutes before the dose; it can be helpful for persons who have developed anticipatory nausea because of its anxiolytic and anterograde amnesia effects.
- **Promethazine** (Phenergan) 12.5 to 25 mg PO, IV, or per rectum 30 minutes before the dose and every 6 hours as needed.
- Several other antiemetics are also available. It may be helpful to try another agent when the previously listed options do not work or are not available in the local pharmacy. Caution: Combining antiemetics can have sedating effects.

Some non-pharmaceutical interventions include:

- **Give a light snack** (crackers or toast, tea, a ginger drink, or soda) before medications.
- **Space the medications** during the day to lessen the pill burden. This is relatively easy when the person is hospitalized, but in the outpatient setting, DOT may only be available once daily. Video DOT can be considered to monitor adherence, because even the most adherent individuals may have difficulty taking a medication that predictably makes them feel bad.
- Try giving the responsible medication at **bedtime**; some symptoms from adverse effects may be more tolerable during sleep.

Eliminate (or at least try to minimize) alcohol consumption to lessen GI irritation and the risk of hepatotoxicity.

- **Encourage hydration.** Sports drinks with electrolytes may be helpful (but note that the glucose content of these drinks is unacceptable for most people with diabetes).
- **Treat gastritis or acid reflux.** Proton pump inhibitors or H2-receptor blockers may be helpful. Avoid using antacids or sucralfate within 2 hours of the dose of fluoroquinolones because these agents interfere with fluoroquinolone absorption.
- **Minimize use of nonsteroidal anti-inflammatory drugs (NSAIDs).** This may be difficult if the individual also has arthralgia and myalgia from other medications. Try acetaminophen with caution as it may increase the risk of hepatotoxicity from other anti-tuberculous medications.
- If the odor of a medication is contributing, try **concealing the odor** by putting the drug into a gelatin capsule that can be purchased at a pharmacy.

Additional considerations:

- Electrolytes, BUN, and creatinine should be evaluated and corrected if significant vomiting or diarrhea occurs.
- Some anti-emetics are associated with QT-prolongation which may be additive to the QT-prolongation of anti-tuberculosis drugs.
- Diagnose and treat co-existing *Helicobacter pylori* infections, although the typical treatment for *H. pylori* may exacerbate nausea, vomiting, and GI upset.

Evaluate the effects of the interventions used to decrease the nausea and vomiting. If nausea persists through much of the day and interferes with nutrition and hydration, despite employing strategies and antiemetics, the medication may need to be stopped. However, if the culprit medications are needed to achieve cure, some nausea and even vomiting may need to be tolerated, at least in the initial period of treatment.

As a last resort:

- Consider hospitalization with better access to antiemetic therapy, IV hydration, and spacing of medications before a regimen is abandoned.
- In refractory cases, as a last resort, a percutaneous endoscopic gastrostomy (PEG) tube may be effective and allow treatment to continue despite persistent symptoms.

- For persons who have developed a psychological aversion to swallowing pills, cognitive behavioral therapy may be helpful.

Consultation with an expert is especially important when regimen changes are considered.

Diarrhea

Diarrhea, along with increased flatulence and cramping, can cause significant difficulty for persons under care, but very rarely does it lead to discontinuation of medication.

- Fluoroquinolones (LFX and MFX) may cause diarrhea and increased flatulence. These usually improve after the first several weeks. Encourage persons taking the fluoroquinolones to tolerate these adverse events if symptoms are mild. As with other GI symptoms, some providers find that switching from one fluoroquinolone to the other may help.
- Diarrhea is also a common side effect of LZD and may be ameliorated with dosage reduction from 600 mg/day to 300-450 mg/day.
- PAS often causes diarrhea with the initiation of medication, which will usually improve or resolve after several weeks.

Specific interventions include:

- Lactobacillus or foods such as yogurt with active cultures (must not be given within 2 hours of the fluoroquinolone dose) may improve symptoms by replacing normal flora.
- Loperamide (Imodium) 2 to 4 mg PO can be used initially and then 1 to 2 mg as needed after each loose stool to a maximum of 8 to 16 mg/day for adults and children over 2 years old. Loperamide may be used intermittently, especially when the person being treated needs to attend social functions or return to work. It should not be used daily.

If the diarrhea is severe, other etiologies may include:

- ***C. difficile* colitis** (especially if broad-spectrum antibiotics used; e.g., fluoroquinolone, LZD)
- **Other infectious or noninfectious causes of diarrhea**
- **Parasitic disease**
- **Lactose intolerance,** especially if the individual is hospitalized and given foods not commonly part of their diet

Rarely, a drug may have to be discontinued if diarrhea is severe. Attempts to continue the medication should be based on the importance of the drug in the treatment regimen and the availability of other medications that might be substituted. A significant exception is *C. difficile* colitis which can be life-threatening and may require discontinuation of a medication.

Hepatotoxicity

Any GI complaint may signify hepatotoxicity. **If suspected, hold all anti-tuberculosis medications that are potentially hepatotoxic until laboratory results are available.** Because anti-tuberculous treatment always involves multi-drug therapy, determining the risk of hepatotoxicity of individual drugs can be challenging. The alanine aminotransferase (ALT) is the enzyme most directly associated with hepatocellular damage, although the aspartate aminotransferase (AST) is usually also elevated. Elevations in the AST may also indicate injury to the muscles, heart, or kidney. If the enzymes are normal, continue medications using the strategies previously noted to lessen nausea and vomiting.

If elevated liver enzymes and/or bilirubin are detected, in addition to drug-induced hepatotoxicity, consider other causes such as alcohol use or gallstones. These are potentially treatable causes that, if addressed, may ease the treatment of TB.

Other predisposing factors for drug-induced liver injury that are not easily treatable include underlying liver disease, pregnancy, and the post-partum period. Individuals with HIV, especially those receiving concomitant antiretroviral therapy (ART), may have a higher likelihood of developing drug-induced hepatitis. Immune reconstitution syndrome with granulomatous hepatitis from disseminated TB may be seen in persons with AIDS after starting ART. Hepatitis C, an elevated baseline serum bilirubin, low CD4 cell count, and fluconazole therapy have all been associated with drug-induced liver injury. Several reports of persons with HIV with hepatitis C noted hepatotoxicity.

The risk of liver injury from anti-tuberculosis drugs in persons with hepatitis B is variable. It appears to be increased in those with chronic active infection compared to those who are only seropositive. Consider referral to a hepatologist for initiation of concurrent hepatitis B therapy (e.g., entecavir), as appropriate.

Notes on specific drugs

Pyrazinamide (PZA): PZA is a well-documented cause of symptomatic acute liver injury that can be severe and possibly fatal.

- In DR-TB disease, PZA may be used for longer than the normal 60 doses indicated for pan-susceptible TB disease; high vigilance with monthly liver enzyme monitoring is warranted.
- In some case series, approximately 30% of individuals will not be able to tolerate PZA. Many persons with PZA-associated hepatotoxicity have prolonged and severe liver enzyme elevation, and fatalities have been reported.

Isoniazid (INH): Like PZA, INH is associated predominately with transaminitis (elevated AST/ALT). There is overlap in the pattern of liver injury caused by these anti-tuberculous drugs; individually or in combination they may contribute to hepatotoxicity.

RIF: If both bilirubin and alkaline phosphatase are elevated (cholestatic pattern), RIF may be a likely etiology of the liver injury.

- RIF may be associated with transient liver enzyme elevations in 10-20% of persons taking the drug, due to either direct toxic effect of RIF metabolites or an immunologic reaction.
- Isolated serum bilirubin increases (without associated liver enzyme abnormalities) may also be observed during the first weeks of therapy and may reflect interference with bilirubin excretion and not necessarily liver inflammation.
- As with INH and PZA, RIF-associated hepatotoxicity can progress to be severe or fatal. The same hepatotoxicity risks apply to all drugs in the rifamycin class although some experts consider rifabutin (RFB) potentially less hepatotoxic than RIF.

Fluoroquinolones: While less hepatotoxic than PZA, INH or RIF, the fluoroquinolones have been associated with hepatotoxicity. Liver enzyme elevations are usually mild, but isolated case reports have documented symptomatic liver injury and, very rarely, hepatic failure. The specific fluoroquinolone drugs used for TB treatment (MFX and LFX) are considered less likely to cause liver injury, although MFX may be potentially more hepatotoxic than LFX.

BDQ: Elevated liver enzymes have been reported in 8-12% of individuals when BDQ is part of the anti-tuberculous regimen; however, it can be difficult to sort out what degree of liver enzyme abnormalities can be attributed to BDQ given the many drugs used in multi-drug regimens for DR-TB.

- The FDA insert states BDQ should be stopped when the liver enzyme elevation reaches 8 times the upper limit of normal, although many experts will hold the anti-tuberculous regimen at lower ranges of elevation, especially if the total bilirubin is over 2 times upper limit of normal. Fatal hepatotoxicity has been reported in these situations.

Pa/DLM: Data is still emerging on hepatotoxicity associated with Pa. Liver enzyme elevations have been reported in up to 30% of individuals on multi-drug regimens that include Pa, but these regimens have also included other known hepatotoxic agents such as PZA and MFX. In general, liver enzyme abnormalities tend to be asymptomatic, mild or moderate in severity, and of limited duration. DLM has been less associated with hepatotoxicity.

ETA: Liver enzyme elevation may be transient or persistent and moderate to severe in individuals with underlying liver disease. Rare fatal cases have been reported.

Clofazamine (CFZ), cycloserine (CS), LZD and ethambutol (EMB) have not been reported to have strong associations with hepatotoxicity.

Many aspects of hepatotoxicity remain poorly understood, including the value of biochemical monitoring for predicting the progression of abnormal liver enzyme and bilirubin levels to fulminant hepatic failure.

The following recommendations represent a reasonable approach given the limitations of current knowledge.

- If the hepatocellular enzymes are less than 3 times the upper limit of normal and there is no evidence of jaundice (total bilirubin < 3.0 mg/dL):
  - Continue the medications using strategies for managing nausea and vomiting and observe carefully.
  - If symptoms continue, repeat liver enzymes to exclude hepatotoxicity.
  - If the bilirubin is increased but the hepatocellular enzymes are only mildly elevated, this may indicate hepatobiliary obstruction rather than drug-induced liver injury.
  - Evaluate causes of direct and indirect hyperbilirubinemia. If the bilirubin is greater than 3.0 mg/dL, generally, hepatotoxic medications should be stopped.
- If the enzymes are more than 3 times the upper limit of normal in the presence of symptoms consistent with hepatotoxicity or more than 5 times the upper limit of normal in the absence of symptoms:
  - Hold all potentially hepatotoxic medications.
  - If at least 3 medications remain in the treatment regimen that are not hepatotoxic (for example, EMB, the aminoglycosides, LFX, or CS), then these medications can be continued. If not, then all anti-tuberculosis medications should be held. Fluoroquinolones are rarely hepatotoxic, but MFX has occasionally been implicated.
- Monitor the liver enzymes and bilirubin weekly.
- If all TB medications have been held, begin sequential rechallenge with one potentially hepatotoxic drug (along with other medications that are not hepatotoxic) when liver enzymes fall to less than 2 times normal (some experts prefer to wait until the enzyme levels normalize or return to baseline)
  - Patience is key; sometimes liver enzymes can stay elevated for several weeks and normalize very slowly.
  - Following rechallenge with each new medication, carefully observe for clinical reactions and repeat liver enzymes and bilirubin at least twice weekly until the medication has been taken for at least one week and liver enzymes and bilirubin are stable. If the first potentially hepatoxic drug is successfully re-introduced, then the remaining potentially hepatotoxic medications can be reintroduced one at a time.
    - If reintroduction of a medication leads to clinical symptoms of hepatotoxicity and an increase in enzymes, stop that medication and eliminate it from the regimen.
    - Even if a medication is identified as causing hepatotoxicity, reintroduce each additional medication one at a time, because in some instances, more than one medication may be responsible for the hepatotoxicity.
  - Monitor liver enzymes at least monthly for the remainder of the treatment course. Frequently the liver enzymes will rise early in the treatment course, but many individuals can also experience drug-associated hepatotoxicity many months into therapy.

Dermatologic reactions

Maculopapular rash and pruritus

Maculopapular rash and pruritus are common early side effects of essentially all anti-tuberculosis drugs. These effects may resolve after the first several weeks of therapy without stopping medications. If the reaction is mild, continue treatment and treat the rash and pruritus symptomatically.

Drugs should not be continued if there are systemic symptoms, fever, urticaria, mucous membrane involvement, blistering of the skin, edema of the lips or eyes, wheezing, or compromise of the airway.

Under these circumstances, seek consultation with a TB expert, a dermatologist, and possibly an allergist for desensitization (based on availability) prior to rechallenge with any of the anti-tuberculosis medications.

For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They can be given prior to the anti-tuberculosis drug regularly once or twice a day, or as needed.

- **Antihistamines:** loratadine (Claritin) 10 mg PO daily; cetirizine (Zyrtec) 10 mg PO once daily up to 20 mg twice daily; fenofexadine (Allegra) 60 mg PO daily up to 180 mg twice per day; chlorpheniramine (Chlor-trimeton) 4 mg PO before the TB medication and then every 4 to 6 hours as needed; or hydroxyzine (Atarax) 25 mg PO or IM 4x/day (can be increased to 50 mg 4x/day).
- **Diphenhydramine** (Benadryl) 25 to 50 mg PO, IV, or IM given before the TB medications, and then every 4 to 6 hours as needed, may lessen skin irritation. If drowsiness occurs, caution against driving or operating machinery.
- Some dermatologists recommend “stacking” antihistamines (e.g., cetirizine twice daily plus fenofexadine twice daily plus Benadryl at night) for an additive effect.
- **Hydrocortisone cream** can be used topically.
- **Low-dose prednisone** (10 to 20 mg/day) for several weeks can be tried if other measures are not helpful.

Evaluate for other potential etiologies of rash and pruritus:

- Scabies and insect bites may masquerade as a drug rash.
- Herpes zoster can be differentiated by its dermatomal distribution.
- Contact dermatitis; ask about use of new lotions, soaps, perfumes, etc.
- Phototoxicity (may respond to sunscreens, but these may also cause contact dermatitis).

- Other drugs, especially newly added agents, should be evaluated as possible etiologies.
- Other dermatologic causes: psoriasis, pityriasis, atopic dermatitis, etc.
- Dry skin, especially in persons with diabetes, may be the cause of pruritus. Consider liberal use of lotions, such as petroleum jelly and lanolin (may be purchased in a feed supply store where it is less expensive). Dry skin is a common problem with CFZ.
- Hypothyroidism.
- Acneiform lesions may flare with the use of INH, ETA, CFZ, and corticosteroids. This will usually resolve after several months. Standard topical acne treatment may be helpful in the meantime.
- Skin lesions associated with HIV infection can have a broad differential diagnosis.

Flushing reactions

Flushing and/or itching reactions of the skin without a rash usually involve the face and scalp and occur 2 to 3 hours after medications. Redness and watering of the eyes may also occur. This is usually due to a rifamycin or PZA and is typically mild and resolves without therapy. If it is bothersome to the person receiving care, an antihistamine may be administered to treat or to prevent the reaction.

Patients taking INH may experience flushing and/or itching of the skin with or without a rash, as well as possible hot flashes, palpitations, or headache 2 to 3 hours after consuming tyramine-containing foods (cheese, cured meats, soy sauce, fermented foods, red wine, certain fish [tuna], and soy products). Advise individuals not to ingest foods that precipitate the reaction while they are receiving INH.

Photosensitivity and hyperpigmentation

Warn persons taking PZA, CFZ, or fluoroquinolones about the potential for photosensitivity. Caution individuals to limit sun exposure and to use sunscreens. Photosensitivity may persist for prolonged periods even after the causative drug is stopped.

Caution individuals to limit sun exposure and to use sunscreen.

- Pseudojaundice (brownish discoloration of the skin) may occur with **RFB**. The sclera is clear, and the bilirubin and other liver enzymes are normal. The pseudojaundice improves after discontinuation of the drug.
- Hyperpigmentation will frequently occur with **CFZ** and may markedly increase with sun exposure; it may be worse in dark-skinned individuals. Hyperpigmentation may be a sensitive issue in certain cultural contexts. Individuals should be educated about the importance of CFZ to the regimen and reassured that the hyperpigmentation will improve after discontinuation of the drug but may last for several months.

Lichenoid drug reactions

Pruritic, flat-topped, violaceous papules may occur anywhere, but most commonly involve the wrists, shins, and back. Mucous membranes and the scalp may also be involved. Differentiation from lichen planus can be made by a biopsy showing eosinophilic infiltration. Lesions may resolve while medication continues. Topical hydrocortisone or antihistamines may be helpful to control pruritus. Do not discontinue medication unless an equally effective drug is available for substitution. Identifying the medication responsible in a multidrug regimen may be difficult because lesions resolve slowly, and EMB, INH, streptomycin (SM), and CS have all been identified as possible causes of these lesions.

Hives and urticaria

Hives and urticaria may be caused by essentially any drug in an anti-tuberculosis treatment regimen. They are more commonly due to INH, RIF, RFB, PZA, ETA, fluoroquinolones, and EMB but can also be due to newer agents such as LZD and BDQ.

All potentially responsible drugs should be stopped until the reaction resolves. **If the initial reaction was not severe and there was *no* evidence of anaphylaxis, angioedema, or airway compromise, try to identify the responsible drug by rechallenging (restarting) each drug in the regimen one at a time (Table 1).** Usually, the most important drug in a regimen should be started first unless there is strong suspicion that it is the cause of the reaction. In this situation, consider a **desensitization attempt (Table 2).**

Tables 1 and 2, modified from the Philadelphia TB Control Program, present a possible way to rechallenge with various drugs. Following desensitization, **medications should continue to be given 7 days a week for the remainder of therapy to avoid another possibly more severe reaction.** Some providers may consider a specialty consultation to support the process (e.g., allergy/immunology).

Premedication with Benadryl 25 mg with or without a small dose of prednisone (20 mg) can be given 30 minutes prior to the first dose when using either the rechallenge approach or the desensitization process. If the initial dose is well tolerated, give 25 mg of Benadryl (but not prednisone) 30 minutes prior to the second dose. If the medication is well tolerated, the third dose should be given without premedication. The dose can be increased while using the premedication following **Tables 1 and 2**. The use of premedication makes rechallenge a bit easier for the individual and the health department when this needs to be done in the outpatient setting.

Premedication does not prevent rash nor will it prevent a serious reaction but may make the reaction less severe and may blunt associated systemic effects, especially the most serious ones. Some persons may benefit from a short course of low-dose steroids if the resulting clinical reaction is only a mildly pruritic rash.

Rechallenge should be carried out in a setting in which medical personnel have the capacity to respond if anaphylaxis occurs. A response plan should be in effect in the event a serious systemic or anaphylactic reaction does occur. This includes the immediate ability to administer intramuscular epinephrine.

TABLE 1.

Suggested drug rechallenge doses following non-anaphylactic allergic reaction*

Drug	Dose – Day 1	Dose – Day 2	Dose – Day 3
INH	50 mg	300 mg	300 mg
RIF	75 mg	300 mg	600 mg
PZA	250 mg	1,000 mg	full dose
ETA	125 mg	375 mg	500–750 mg
CS	125 mg	250 mg	500–750 mg
EMB	100 mg	500 mg	full dose
SM	125 mg	500 mg	full dose

*Philadelphia TB Program 1998

Doses for the following drugs were not supplied by the Philadelphia program, but can be assumed to be the following, based on the doses given in Table 1:			
Amikacin (AK)	125 mg	500 mg	full dose
Fluoroquinolone	50 mg	200–250 mg	full dose

If the initial reaction was severe, rechallenge should be done using a smaller dose of medication (1/10th) of the Day 1 dose listed in **Table 1**, and subsequent doses increased carefully. As previously noted, rechallenge should always be performed in a setting where a healthcare provider can respond to the reaction.

If a test dose of any drug causes a reaction, that drug should be discontinued, unless it is deemed essential to the regimen. If that is the case, desensitization can be considered (**Table 2**).

TABLE 2. **Oral desensitization for INH, RIF, and EMB**

Time from start (hour: minute)	Dose of INH* (mg)	Time from start (hour: minute)	Dose of RIF** (mg)	Dose of EMB** (mg)
0:00	0.1	0:00	0.1	0.1
0:15	0.5	0:45	0.5	0.5
0:30	1	1:30	1	1
0:45	2	2:15	2	2
1:00	4	3:00	4	4
1:30	8	3:45	8	8
2:00	16	4:30	16	16
2:30	32	5:15	32	32
3:30	50	6:00	50	50
5:30	100	6:45	100	100
7:30	150	7:30	150	200
8:30	150	11:00	300	400
17:30	150			
Early next a.m.	150 2x/day x 3 days		300 2x/day x 3 days	400 3x/day x 3 days

* Holland 1990
** Matz 1994

Oral desensitization protocols should only be implemented in a hospital or in a clinical area with the ability to monitor and respond to possible anaphylaxis, and in clinical situations when the drug is determined essential to success of therapy. Because INH and RIF are such important drugs, desensitization is most commonly attempted with these two medications.

Steroid therapy is often used with desensitization and then tapered off over 2 to 3 weeks.

Once desensitization has been successfully completed, it is essential that the medication be taken 7 days per week for the remainder of treatment to avoid another, possibly more severe, reaction.

Do not attempt desensitization protocols if anaphylaxis occurred or the reaction was severe and involved significant systemic symptoms such as fever and/or mucous membranes, as occurs with Stevens-Johnson syndrome or toxic epidermal necrolysis.

Severe drug reactions

Systemic reactions

Fortunately, anaphylaxis is rare with anti-tuberculosis medications. Anaphylaxis typically presents within minutes of medication dosing. The individual commonly has signs of airway compromise, such as stridor, wheezing, a feeling of the throat being closed, swelling of the tongue, and hoarseness. Other signs and symptoms can include urticaria, pruritus, nausea, vomiting, cramping, and diarrhea. Worrisome symptoms and signs include progression to angioedema, shock, and confusion. It is essential to identify the causative agent once the patient is stable. The use of a small challenge dose of medication may be needed and should be given in the hospital and ideally with the assistance of an allergist/immunologist. Once an agent is identified as causing anaphylaxis, **do not include this drug in the treatment regimen. Also, do not attempt desensitization to these agents.**

Anaphylaxis typically presents within minutes of medication dosing.

Stevens-Johnson syndrome is associated with systemic toxicity—high fever, widely distributed urticaria, and bullae, along with mucous membrane involvement. When there is extensive sloughing of skin, toxic epidermal necrolysis is likely. These should be distinguished from staphylococcal scalded skin syndrome, which requires antibiotic therapy. **Each of these reactions needs immediate emergency/inpatient referral, potential systemic immunosuppressive or immunomodulating therapy, and supportive care.** Request a dermatology consultation and a skin biopsy if there is any question about the diagnosis.

INH, RIF, RFB, EMB, SM, fluoroquinolones, LZD, and CS have been reported as causative agents. **If a drug is identified as responsible for one of these reactions, it should never be used again.**

Drug reaction with eosinophilia and systemic symptoms (DRESS)

The drug-induced hypersensitivity syndrome, frequently known as “drug reaction with eosinophilia and systemic symptoms” (DRESS), has been described with several of the anti-tuberculosis medications.

- The TB medications most commonly associated with DRESS are **RIF or RFB**, **INH**, and **EMB**.
- A variety of other drugs has also been implicated in DRESS, including sulfonamides, dapsone, minocycline, allopurinol, and many of the antiepileptic agents. If possible, all potential culprit medications should be stopped. Skin biopsy and liver biopsy may help to establish the diagnosis.

DRESS is rare and can be life-threatening. The syndrome includes a dramatic drug rash along with hematologic abnormalities (eosinophilia, atypical lymphocytosis), lymph node enlargement, involvement of organ systems (liver, kidney, lung) and

significant systemic symptoms. DRESS usually begins **2 to 8 weeks after the drug exposure.** Fever is often the first manifestation and may be as high as 40 degrees centigrade. Fever is accompanied by malaise, lymph node enlargement, and rash. Rash will usually start on the trunk, upper extremities, and face with subsequent progression to involve the lower extremities. The initial appearance is morbilliform, but can evolve to a diffuse, confluent eruption with infiltrative erythema. The face may become edematous, and mucous membranes are involved in up to one-third of affected individuals. The erythema may progress to vesicles, pustules, diffuse dermal edema, and eventual exfoliative dermatitis.

Lymphadenopathy is a prominent finding, present in up to 50% of persons with DRESS. Biopsy usually shows benign lymphoid hyperplasia. **Organ involvement** most frequently includes the liver, and can be asymptomatic, but may also manifest as liver enlargement with jaundice and progress to liver failure. Renal involvement may include interstitial nephritis and has been associated with co-administration of allopurinol. Pulmonary involvement may include cough, fever, and dyspnea with hypoxemia. Interstitial pneumonitis along with pleural effusion may be seen on the chest radiograph. Additional organ involvement has been rarely noted.

Laboratory abnormalities include mildly elevated ALT and/or alkaline phosphatase in over 80 percent of individuals, leukocytosis with eosinophil counts > 700 in most, and atypical lymphocytosis in 30 to 70 percent of persons with DRESS. If the kidney is involved, there may be an increase in the creatinine, low-grade proteinuria, and eosinophils in the urine.

The skin eruption and other abnormalities generally resolve slowly once the drug is withdrawn. It may take more than 2 months before complete resolution; remissions and relapses not related to drug therapy may occur. DRESS has been associated with reactivation of human herpes virus 6 (HHV-6) and cutaneous eruptions may coincide with reactivation of the virus.

Management of DRESS is based on stopping potential offending drugs and avoiding the addition of new medications until the reaction has resolved. This may not be possible with persons with TB because they require ongoing anti-tuberculous treatment, especially if their disease is infectious and if steroid therapy is required to control DRESS. Stopping and starting medications or treating with a weak regimen can lead to drug resistance and treatment failure, so the balance of preventing harm and providing treatment requires significant clinical skill and experience. **Most experts would not recommend rechallenge once a drug is identified as the causative agent.**

Consult an experienced TB clinician and a dermatologist for the management of DRESS. High potency topical corticosteroids applied 2 to 3 times daily may be sufficient, but in severe cases systemic steroids, sometimes at high dose, or other immunotherapy may be needed for an extended time.

RIF hypersensitivity reactions

A variety of reactions have been reported with rifamycin therapy. One of these is a **flu-like syndrome** that is characterized by fever, chills, headache, and bone pain.

- Symptoms begin 1 to 2 hours after the dose of medication and resolve spontaneously after 6 to 8 hours.
- The syndrome typically develops after several months of rifamycin therapy and is more common with intermittent therapy. Some individuals can tolerate a rifamycin if the dosing interval is changed from intermittent to daily.
- The combination of rifapentine (RPT) and INH used for short course intermittent latent tuberculosis therapy (LTBI) can be associated with systemic drug reactions, primarily flu-like syndrome and cutaneous reactions but rarely also associated with hypotension and syncope. Although it is not certain, it is likely that RPT or the combination of RPT and INH, as opposed to INH alone, is responsible for this spectrum of adverse reactions. Persons with mild reactions have been rechallenged successfully with the INH/RPT combination but the consensus of expert opinion is that patients with severe reactions including hypotension or syncope should not be rechallenged with INH and RPT.

Other rifamycin reactions include:

- Cutaneous vasculitis
- Red cell aplasia
- Leukopenia and agranulocytosis
- Thrombocytopenia
- Disseminated intravascular coagulation
- Hemolytic anemia
- Lupoid reactions
- Acute renal failure

In the presence of these more significant hypersensitivity reactions, stop treatment with RIF or RFB. Do not try to desensitize.

Hematologic abnormalities

Hematologic abnormalities may represent underlying disease, either a comorbid condition such as chronic renal failure, HIV, alcoholism with nutritional deficiencies leading to anemia, or a malignancy. *M. tuberculosis* can be directly responsible for hematological abnormalities if disease has spread to the bone marrow or is related to decreased bone marrow production due to chronic illness from *M. tuberculosis*. GI TB may result in anemia due to blood loss from the GI tract, and pulmonary disease associated with hemoptysis may also be associated with a significant anemia.

Hematological abnormalities due to drug toxicity can involve any cell line and can be related to most TB medications. **However, the most common causes of hematological abnormalities are associated with LZD, the rifamycins (RFB and RIF), and INH.**

Anti-tuberculous drug-related cytopenias have become a more prominent concern during DR-TB treatment, in part due to the increased use of LZD. Unlike the use of LZD for bacterial infections, which is typically short-term, there are tolerability concerns with LZD when taken for several months. While LZD has been associated with suppression of all blood cell lineages, anemia and thrombocytopenia are the most common presentations. The effect is dose-dependent and reversible, but recovery time can vary greatly and last up to several weeks. LZD-related cytopenias appear to occur most commonly in persons with existing low baseline cell counts and chronic kidney disease. **Early onset of LZD-associated cytopenias can occur but will usually be observed after duration of 14 days or more.**

More information on adverse events from LZD were highlighted by the NIX and ZeNIX trials.

- NIX results published in 2020 showed that the 6-month combination of BDQ, Pa and LZD (BPaL) with LZD dosed at 1200 mg daily (dose could be reduced, interrupted, or discontinued after 1 month) was successful in 90% of persons with DR-TB. However, nearly half developed myelosuppression. **Progression to severe anemia typically presented in months 2-3 of treatment.**
- The ZeNIX trial, published in 2022, evaluated whether decreases in LZD dosing in the BPaL regimen could decrease adverse events but maintain efficacy. The study found that LZD at a dose of 600 mg daily for 26 weeks resulted in only 2% of patients developing myelosuppression.

There are no known effective measures for prevention of LZD-induced myelosuppression.

- Use of pre-emptive pyridoxine was not associated with prevention of myelosuppression in one study of 24 individuals treated with a prolonged course of LZD.
- Many experts check LZD trough levels; adjusting the dosage to a trough <2 may help prevent or ameliorate LZD mitochondrial toxicity-related adverse events. See **Chapter 3, *Laboratory*** and **Chapter 4, *Treatment*** sections on ***Therapeutic Drug Monitoring*** and ***Specific drugs: Linezolid*** for more details.

- PK/PD modeling of NIX data suggests that a decrease in hemoglobin greater than 10% from baseline after 4 weeks of treatment had good sensitivity and specificity to predict risk for subsequent severe anemia and may be a useful guide for considering dose adjustment. In this study, trough levels (done at 2, 4 and 16 weeks) predicted risk for thrombocytopenia but not anemia.

RFB is a drug in the rifamycin class with less hepatic enzyme induction than RIF. RFB is sometimes used in place of RIF when there is concern for drug-drug interactions with RIF and an individual's chronic medications (e.g., anti-retroviral therapy, methadone, prednisone, some chemotherapies, or direct-acting oral anticoagulants).

- Much of the early safety evidence on RFB use for mycobacterial infections comes from the literature on persons with AIDS for *Mycobacterium avium*, with the FDA package insert noting that in clinical trials 9.4% of 566 participants experienced a cytopenia, including neutropenia, leukopenia, anemia, and thrombocytopenia, with 2% discontinuing due to neutropenia.
- Of 100 persons with drug-susceptible TB treated with RFB in Seattle/King County, Washington, 6 developed a cytopenia.
- In another study conducted in 221 hospitalized individuals in Taiwan where RFB was used in place of RIF, 5.9% developed neutropenia; all recovered within 5 weeks after RFB was stopped. Females were more likely to have neutropenia compared to males (10.9% vs 3.8% respectively).

In contrast to RFB, **RIF** has been less frequently associated in case reports and series with anemia, hemolytic anemia, leukopenia, and thrombocytopenia.

- In a study of tolerability of differing doses of RIF, of 50 participants dosed at 600 mg daily, only 2 needed to stop treatment due to leukopenia, and of 50 receiving 900 mg daily, 2 had to stop treatment due to thrombocytopenia.

INH has been rarely associated with various cytopenias, including agranulocytosis, aplastic anemia, hemolytic anemia, sideroblastic anemia, immune thrombocytopenia, and pure red cell aplasia.

Neurotoxicity

Peripheral neuropathy

Peripheral neuropathy is characterized by symmetrical polyneuropathy in nearly all cases. The first symptoms are tingling, prickling, and burning in the balls of the feet or tips of the toes. With further progression, loss of sensation, loss of ankle reflexes, and weakness of dorsiflexion of the toes may occur. Symptoms may progress centripetally and involve the fingers and hands. Unsteadiness of gait may develop due to proprioceptive loss. The diagnosis can usually be made clinically.

- The drugs most commonly implicated are **LZD**, **INH**, **ETA**, **CS**, fluoroquinolones, and rarely, EMB. A 2013 FDA boxed warning notes an association with fluoroquinolones and potentially irreversible peripheral neuropathy.
- One nested case-control study of 5,357 incident peripheral neuropathy cases and 17,285 matched controls showed that use of any fluoroquinolone increased the risk of peripheral neuropathy by 47%, causing an additional 2.4 cases per 10,000 patients per year of current use. Risk appeared to be greater with cumulative exposure, among men, and among those older than 60 years of age.

Neuropathy is more likely to occur in persons with diabetes, alcohol use disorder, HIV, hypothyroidism, pregnancy, poor nutrition, and with inadequate dietary intake of pyridoxine.

Pyridoxine prophylaxis (50 mg daily) should be included for all persons (including a weight-proportionate dose for children) receiving treatment for DR-TB who take high-dose INH, ETA, or CS. If symptoms develop or progress, doses of 100 mg may be tried; however, pyridoxine-related neuropathy has been reported with doses greater than 100 mg daily and some experts would not go beyond 100 mg. Doses greater than 200 mg should not be used. Pyridoxine is no longer recommended for use with LZD (see **Chapter 5, *Medication Fact Sheets***).

There are rare reports of neuropathy attributed to pyridoxine in doses of 100 mg or greater.

There are rare reports of neuropathy attributed to pyridoxine in doses of 100 mg or greater.

As previously noted, the NIX and ZeNIx studies illuminated the incidence of adverse events associated with long-term use of LZD.

- In the NIX (BPaL) trial, LZD was given at a daily dose of 1,200 mg for 6 months (dose could be reduced, interrupted or discontinued after 1 month); 81% of individuals developed peripheral neuropathy.
  - Most symptoms of neuropathy improved during post-treatment follow-up. At 24-months post-treatment: neuropathy was fully resolved in 82%, mild to moderate in 12%, and remained severe in 1% (results not available in 5%).

- The ZeNIX trial looked at BPaL with varying doses of LZD (1,200 mg for 26 weeks or 9 weeks, or 600 mg for 26 weeks or 9 weeks) with peripheral neuropathy occurring in 38%, 24%, 24%, and 13%, respectively.

LZD-associated neuropathy usually tends to occur after 12-20 weeks of therapy and is likely dose-related. Initial use of the 600 mg once-daily LZD dosing followed by a decreased dose to 600 mg 3 times weekly if toxicity develops often allows continuation of LZD in the treatment regimen.

Many experts recommend checking a LZD trough and peak levels, as a trough level greater than 2 may suggest increased likelihood of adverse events and may merit a dose adjustment. See **Chapter 3, *Laboratory*** and **Chapter 4, *Treatment*** sections on ***Therapeutic Drug Monitoring*** and ***Specific drugs: Linezolid*** for more details.

NIX study PK/PD data suggest that simple clinical screening tools identified neuropathy, and while most symptoms resolved post-treatment, model simulations did not show a substantial advantage to LZD discontinuation during treatment over LZD dose reduction. In this study, trough levels (at 2, 4 and 16 weeks) did not predict risk for neuropathy.

Individuals must be followed closely once peripheral neuropathy develops, with careful considerations for dose interruption, reduction, or discontinuation. The degree of tolerable neuropathy for an individual must be balanced against alternative medications available for treatment, the toxicities of these medications, and the opportunity for a lasting cure for DR- TB.

Additional interventions to consider:

- Correct **vitamin and nutritional deficiencies.**
- Evaluate and correct **electrolytes**.
- Address **additional medical problems** that may contribute to peripheral neuropathy.
- Identify and stop (if possible) **other medications** that may cause peripheral neuropathy.
- Consider whether the **dose of LZD, ETA or CS can be reduced** without compromising the regimen.
- **Physical therapy**
- **NSAIDs or acetaminophen**
- **Gabapentin** (Neurontin) has been helpful for many individuals. Adults should be treated initially with a single dose of 300 mg on Day 1, increased to 300 mg twice a day on Day 2, and 300 mg 3 times a day on Day 3. The dose may be titrated up to 1800 mg in 3 divided doses, as needed for relief. Gabapentin is also associated with a wide range of adverse effects, including nausea and vomiting, as well as arthralgias and CNS symptoms. The dose should be decreased in patients with renal insufficiency.
- **Pregabalin** (Lyrica) is an option for individuals who do not respond to gabapentin. The starting dose is 50 to 75 mg per day in two divided doses, with escalation to the usual effective dose of 150 to 300 mg twice daily.

- **A low dose of tricyclic antidepressant** (amitriptyline [Elavil] 25 mg PO at bedtime) **can be tried if there are no contraindications.** The dose of amitriptyline may be increased (to 150 mg maximum) if lower doses are not helpful.
    - **Note:** LZD cannot be given with tricyclic drugs or selective serotonin reuptake inhibitors (SSRIs) due to its mild monoamine oxidase (MAO) activity contributing to the risk of serotonin syndrome.
- **Carbamazepine** (Tegretol), an anticonvulsant, at 100 to 400 mg PO twice daily may be considered. Blood dyscrasias and elevated liver function may complicate therapy; a complete blood count (CBC) and liver enzymes should be routinely monitored in persons on this medication.
- **Medication may need to be discontinued.** This can be a difficult choice depending on the availability of alternative drugs and likelihood of treatment success.

Central nervous system toxicity

A variety of mild effects may occur early in therapy, including drowsiness, headaches, concentration problems, irritability, mild mood changes, insomnia, and agitation. Caution persons beginning treatment to expect these effects and explain that they typically become less intense after the initial weeks of therapy. Tolerance develops towards most of these effects and individuals learn to cope with them. These relatively mild symptoms should not lead to the discontinuation of a medication unless unusual circumstances are present.

- Give medication at a time of day that minimizes the effects; for example, at bedtime in persons who experience drowsiness (ask about timing of drug ingestion).
- Analgesics or NSAIDs may help headache.
- Limiting caffeine intake in the evenings may improve sleep disturbances.
- Exercise may be effective.

Support from caregivers and family members and acceptance of the patient's mood changes and irritability will make these side effects more tolerable.

Psychiatric effects

Depression

Depression can be relatively mild and managed with support from family and health-care providers. Some degree of situational depression is to be expected for most persons who deal with the complexities and challenges of DR-TB therapy.

Medication-induced depression is especially a problem with CS and ETA. CS-related depression may be severe and is sometimes associated with suicidal ideation. Persons on CFZ who experience hyperpigmentation from the drug have been known to develop a reactive depression due to the changes in skin coloration.

- Assess and address underlying psychological/social issues. See **Chapter 8, *Monitoring and Case Management – Resources*** for examples of screening tools.
- Assess for coexisting substance use disorders and refer to counseling if appropriate.
- Always be alert to indications of suicidal ideation in persons with depression, especially those on CS or ETA. If depression is significant or suicidal ideation is present, both CS and ETA must be stopped; observe carefully with psychological support until the person is stable.
- When depression is significant, give a trial of antidepressant therapy and/or request psychiatric consultation. **Note: tricyclic antidepressants and SSRIs should not be given to persons on LZD, because of the risk of serotonin syndrome.**
- Obtain CS levels, if levels are >35 mg/dL, hold the medication and reintroduce at a lower dose. For example, if the person was on 500 mg, try a daily dose of 250 mg (or 250 mg alternating with 500 mg daily). Obtain serum levels of CS to ensure the dose produces a level within the target range. If depression is a concern, adjust dosing to achieve levels towards the lower end of the range (peak level at 2 hours post dose target range is 20–35 mg/dL; some experts consistently aim for levels in the lower end of this range for all).
- If depression progresses or does not improve by a trial of antidepressant therapy, discontinue CS and, possibly, ETA as well.
- **CS should not usually be part of an initial treatment regimen if significant depression is present.** When no alternative drugs are available and if depression is situational related to the DR-TB or if depression is controlled on therapy, some patients may tolerate CS and ETA.
- INH has been associated with depression and reported as severe in several case reports. Withdrawal of the drug is associated with rapid recovery.

Psychosis

- **Hospitalize the patient and put under 24-hour surveillance. Obtain psychiatric consultation.**
- Hold all medications that possibly contribute until the person stabilizes.
- **The most likely drugs to cause psychosis are CS and fluoroquinolones;** INH can occasionally be implicated.
- Start antipsychotic therapy (for example, haloperidol [Haldol] PO, IV, or IM 0.5 to 5 mg) at the earliest sign of psychosis.
- If CS is part of the treatment regimen, stop CS and obtain a random CS level.
- Pyridoxine (100 mg) should be given with CS if not already part of the treatment regimen.
- **For persons already on an anti-psychotic drug, check drug-drug interactions particularly if a rifamycin is part of the anti-tuberculous regimen.** RIF is a strong hepatic enzyme inducer, and RFB is the least potent hepatic enzyme inducing agent in the class. Individuals at risk can be tipped into a psychotic break after starting a rifamycin, depending on the anti-psychotic drug.
- Consider and address all **other etiologies**, especially substance use disorders and other medical problems (meningitis, hypothyroidism, and depression).
- When symptoms resolve, the medications least likely to have contributed to the symptoms should be reintroduced first, one at a time, with careful observation.
- If no alternative drug is available, CS may be restarted at low dose. Do not increase to the previous dose without first checking a serum drug concentration. If any recurrence of psychotic behavior occurs, promptly and permanently discontinue CS.
- Once the person has stabilized with all medications successfully restarted and all symptoms resolved, taper the antipsychotic drugs under careful observation.
- Some individuals may tolerate CS with an antipsychotic drug if no other treatment options are available. This will require special observation. Utilize this therapy only after consultation with an expert in the management of DR-TB, and when the CS is determined to be essential to the regimen.

Suicidal ideation

- **Hospitalize the person and put under 24-hour surveillance. Obtain psychiatric consultation.**
- **Suicidal ideation is most often associated with CS; discontinue immediately.**
- Initiate antidepressant therapy.
- If INH or ETA are also being taken, hold these medications and only rechallenge once the person is stable. If INH is restarted, give initially 300 mg daily, if tolerated and the goal is higher-dose INH, increase dose under careful observation. ETA, if restarted, should be given initially at a dose of 250 mg once daily and then increased to 500 mg and finally 750 mg daily if the patient is stable and tolerates the dose escalation.

- If on a fluoroquinolone, check the serum drug concentration of the fluoroquinolone and lower the dose if the serum concentration is greater than the therapeutic range. Do not decrease the dose if the serum level is therapeutic.
- Keep the person hospitalized until the risk of suicide has passed.

Seizures

Immediate steps:

- **Hospitalize the person with seizures.** Ensure adequate ventilation, support cardiac output, and protect the airway while treating seizures.
- **Hold CS, fluoroquinolones, LZD, INH, imipenem (consider stopping meropenem as well), and initiate anticonvulsant therapy** (e.g., phenytonin, valproic acid). Monitor anti-epileptic drug levels as drug interactions and synergistic toxicity are possible. If the individual is on CS, obtain a random CS level because seizure activity is closely related to elevated serum CS levels.
- In cases of **INH toxicity**, treat initially with a slow intravenous bolus of pyridoxine over 3 to 5 minutes (500 mg/min) on a milligram per milligram basis equal to the INH dose (maximum 5000 mg in child). If the quantity of INH ingestion is unknown, then consider an initial intravenous bolus of pyridoxine of 5000 mg in the adult or 70 mg/kg in the child (maximum 5000 mg). If seizures continue, the pyridoxine may be repeated at the same dose. It would be rare that more than 10,000 mg of pyridoxine would be needed. The maximum safe dose for pyridoxine in INH intoxication is not known. If the individual does not respond to pyridoxine, diazepam may be administered. A benzodiazepine (e.g., lorazepam) should also be administered to support rapid control of seizure activity.
- **Evaluate for other etiologies of seizures.**
- **Check serum electrolytes, calcium, and magnesium.**

When seizures have resolved, restart medications one at a time, generally with the most effective drugs in the regimen first.

- CS generally should not be restarted.
- Continue anticonvulsant therapy during the remainder of therapy for DR-TB.

A history of prior seizures is not an absolute contraindication to the use of CS, fluoroquinolones, LZD, and INH. Do not include CS if an alternative drug is available.

Serotonin syndrome

Serotonin syndrome consists of clinical symptoms and signs that occur in the presence of excess serotonin activity. Three different mechanisms may lead to elevated serotonin levels by: 1) inhibition of serotonin metabolism (MAO inhibitor use); 2) blockade of serotonin reuptake at the presynaptic neuron (SSRI and/or tricyclic antidepressant use); or 3) increase in the release of stored serotonin (amphetamine use).

LZD is a weak, reversible, nonselective inhibitor of MAO.

- LZD alone is not potent enough to cause the serotonin syndrome, but it may occur on rare occasion when LZD is given along with other medications that increase serotonin level or with a diet that is very high in tyramine (cheese, cured meats, fermented soy products or sauce, red wine).
- Although the risk for serotonin syndrome is small when combined medications that increase the risk are used, it is important to recognize the risk. Adverse effects do not resolve unless the offending medications are withdrawn.

Serotonin syndrome can cause confusing clinical symptoms, including fever, and can present along a clinical spectrum from mild to severe, even fatal, toxicity.

Serotonin syndrome is characterized by neuromuscular findings.

Recent diagnostic criteria focus on the presence of at least one of the following:

- Clonus, seizure, myoclonus, ataxia, incoordination, jaw-trismus, rigidity, shivering, rigors, nystagmus, tremor or twitching, and hyperreflexia.
- Additional findings may include tachycardia, fever, mydriasis, diaphoresis, hyperactive bowel sounds, diarrhea, agitation, and delirium.

The syndrome typically develops soon after the introduction of the offending medication or an increase in a dose of a previously used drug.

- A physical exam should focus on assessment for clonus, deep-tendon reflexes, pupil size, mucosal dryness, bowel sounds, and diaphoresis.
- **A good drug history, including the use of any over-the-counter medications, herbal and dietary supplements, and illicit drugs (in addition to any recently prescribed drugs) is an essential part of the evaluation.**
- The differential diagnosis includes anticholinergic poisoning, malignant hyperthermia, and neuroleptic malignant syndrome. The drug history will help to identify the cause.
- Most cases have been associated with the **concomitant use of LZD and an SSRI or tricyclic antidepressant.** The half-lives of these drugs are prolonged, and if LZD therapy is planned, these agents should be withdrawn at least two weeks prior to LZD use. Observe the patient carefully; there are reports of serotonin syndrome occurring even two weeks after withdrawal of these agents.

If serotonin syndrome is identified, LZD should be discontinued.

Do not abruptly stop the SSRIs or tricyclics. When discontinued, they will continue to exert effects due to their long drug half-life. With supportive care and discontinuation of LZD, the syndrome will often resolve within 24 to 48 hours. No controlled trials are available to guide management of more severe forms of serotonin syndrome. Several drugs have been helpful, including the benzodiazepine, lorazepam. Some individuals need aggressive management of their cardiorespiratory and thermal abnormalities.

INH is also a weak MAO inhibitor and has potential for similar drug interactions.

Musculoskeletal adverse effects

Myalgias and arthralgias

Pain and tenderness of the muscles and joints are relatively common side effects associated with a variety of drugs used to treat persons with DR-TB. One or more of the following drugs may be implicated: **PZA, fluoroquinolones, RFB, INH, ETA, and BDQ.** PZA can precipitate classic gout flares with elevated serum uric acid but can also cause diffuse and debilitating arthritis and arthralgias without uric acid elevation. In general, routine checking of serum uric acid is not useful; most experts recommend symptomatic monitoring for gout signs and symptoms when on PZA. Electrolyte disturbances associated with the aminoglycosides or thyroid dysfunction may also cause muscle pain and cramping.

- **NSAIDs** are usually helpful. Monitor renal function more closely when using higher doses of NSAIDs; use caution in persons with underlying chronic kidney disease.
- If acute swelling, erythema, and warmth are present, **evaluate for the presence of infection or inflammatory disease:**
  - Aspirate joint if fluid is present.
  - Send fluid for culture for routine, mycobacterial and fungal pathogens, cell count, protein, glucose, and crystals.
- Institute treatment (often an NSAID) if the diagnosis is gout. Check uric acid level and consider discontinuation of PZA.
- Consult with a rheumatologist if evidence of inflammatory or autoimmune arthritis is present.
- **Evaluate for hypothyroidism or hyperthyroidism.**
- Draw serum electrolytes, calcium, and magnesium. Correct deficiencies.

Tendonitis and tendon rupture

Tendon rupture, commonly involving the Achilles tendon, has been reported with **fluoroquinolone use.**

In 2008, an FDA boxed warning was assigned to the fluoroquinolones regarding increased risk of tendinitis and tendon rupture. The risk was especially higher in people over age 60, patients who had received kidney, heart, or lung transplants, and people taking steroid treatment. **LFX may be more associated with tendon rupture than MFX.**

- In a study of over 1 million Medicare beneficiaries who received three different fluoroquinolones (MFX, LFX, or ciprofloxacin), only LFX exhibited a significant increased risk of tendon ruptures: 16% (HR=1.16; 95% CI 1.06 to 1.28), and 120% (HR=2.20; 95% CI 1.50 to 3.24) for rotator cuff and Achilles tendon rupture, respectively, in the ≤ 30 days window.

When tendon inflammation is **mild**:

- Administer NSAID.
- Avoid concurrent use of steroids whenever possible.
- Rest the involved joint and avoid any strenuous activity.
- Evaluate the fluoroquinolone dose and reduce if possible.

When **significant inflammation** of tendons or tendon sheaths occurs:

- Fluoroquinolones should generally be stopped.
- If the treatment regimen is likely to fail without the fluoroquinolone, inform the person of the risk of tendon rupture and the risk of treatment failure. Carefully try to continue the fluoroquinolone.

Cardiovascular toxicity and adverse reactions

QT interval prolongation

The **QT interval** is that portion of the ECG that begins at the start of the QRS complex and ends at the termination of the T wave. The QTc is a QT interval corrected for heart rate. It is calculated automatically by ECG machines but can be calculated by hand as well.

- The QTc is considered normal at <450 ms (males), and <470 ms (females).
- A **QTc interval > 500 ms is considered dangerous** for both males and females.
- An increase of 60 ms from the baseline QTc has been considered as prolonged although it can vary by up to 75 ms in the same individual at different times during the same day. **At a minimum, an increase of 60 ms indicates the need for closer follow-up.**
- To have a prolonged QTc means one is at increased risk of arrhythmias; when severe (e.g., *torsade de pointes*), arrhythmias can lead to syncope, cardiac arrest, or sudden death.

Multiple anti-tuberculosis drugs are associated with QT-prolongation including **BDQ, CFZ, DLM, MFX, LFX, ETA, and prothionamide**. Of the fluoroquinolones, MFX has been cited as potentially more QT-prolonging than LFX.

- During clinical trials, treatment with BDQ resulted in QTc prolongation that developed within the first week of treatment.
- Because of the long half-life of BDQ, persons in whom BDQ is stopped due to a prolonged QTc should have a regular ECG until the QTc normalizes.
- Despite its association with QT prolongation, there have been no reported cases to date of *torsade de pointes* with BDQ.

Not all QTc prolongation is drug-induced. **Other factors contributing to QTc prolongation include hypokalemia, hypomagnesemia, hypocalcemia, hypothyroidism, low BMI, and underlying cardiovascular disease, especially left ventricular dysfunction.** Evidence suggests that at least one risk factor is often present before drug-induced QTc prolongation occurs, and in most cases, two risk factors are present; therefore, it is very important to thoroughly assess individuals for baseline risk before attributing QTc prolongation solely to anti-tuberculosis agents.

- Obtain ECG and check QTc at baseline and at least 2, 12, and 24 weeks when taking BDQ or DLM. Some providers check at 2 and 4 weeks, then monthly if taking additional QT-prolonging agents (e.g., MFX, CFZ, others).
  - The preferred formula to calculate QT correction is the Fridericia formula, rather than the Bazett. See **Chapter 8, *Monitoring and Case Management,*** section on ***Routine toxicity monitoring/ECG*** and associated ***Resources*** for more details, online calculator tools, and an online resource site to identify QT-prolonging medications.
- **Obtain serum electrolytes at baseline;** maintain potassium, calcium, and magnesium levels in the normal range with electrolyte repletion if necessary. Consider checking thyroid function if QTc prolongation is found at baseline or on interval ECG testing.
- Drugs other than anti-tuberculosis agents can be associated with QTc prolongation. For example, anti-emetic drugs, including chlorpromazine, domperidone, droperidol, and ondansetron, have been associated with QT prolongation and possibly *torsade de pointes*. A careful assessment of the necessity of all drugs in the treatment regimen is required.

Recommendations for managing QT prolongation for persons receiving TB treatmentcan be found in the 2018 USAID/KCNV/Challenge TB *Guide for QTc monitoring and management of drug-resistant TB patients with QT-prolonging agents.* https://www.challengetb.org/publications/tools/pmdt/Guidance_on_ECG_monitoring_in_NDR_v2.pdf

If the QTc appears prolonged:

- **Confirm the QTc** by performing a manual measurement using the Fridericia correction formula and if needed, confirm with a repeat ECG (>30 minutes later).
- **Hospitalize if there are signs and symptoms concerning for arrhythmia** (e.g., palpitations, tachycardia, lightheadedness, fainting, syncope, chest pain, loss of consciousness). Hold all QT-prolonging drugs.
- If **asymptomatic with QTc >500 ms,** QT-prolonging medications should be stopped sequentially starting with ancillary medications and anti-tuberculosis agents that have the shortest half-life.
    - These medications include LFX (6-8 hours) and MFX (15-16 hours), followed by DLM (38 hours), CFZ (25 days), and then BDQ (5.5 months).
- For QTc <500 ms but >450 ms (males) and >470 ms (females), consider discontinuing first the QT-prolonging ancillary agents while managing other concomitant conditions and monitoring the ECG as previously noted.
- Check for and correct abnormal electrolytes. Evaluate for other potential contributing factors.

Once QTc stabilizes and returns to acceptable ranges, critical QT-prolonging drugs may be re-added. Consider the following adjustments, in consultation with a cardiologist if feasible:

- Consider replacing MFX with LFX (if DST confirms susceptibility).
- If previously on BDQ or DLM, restart while limiting other QT-prolonging drugs.
- Suspend CFZ permanently, if not critical to the regimen.
- Conduct weekly ECG and on an ad-hoc basis until stable. Because of the long half-life of BDQ, if the QTc is prolonged even if the drug is no longer being administered, continue ECG monitoring until the QTc normalizes.

Decisions about drug discontinuation based on QT-prolongation are among the most difficult risk/benefit decisions faced by clinicians managing persons with DR-TB. For persons with XDR-TB it may be necessary to maintain QT-prolonging drugs in a treatment regimen (with close cardiology support) even with a QTc >500 ms due to the lack of alternative effective agents. The monitoring guidelines previously proposed are recommendations that should be applied in the context of a patient's specific circumstances.

Aortic aneurysm or dissection

The FDA has issued a boxed warning regarding an association with the use of fluoroquinolones and increased risk of aortic aneurysm or dissection. The association appeared to be largely driven by **pre-existing risk factors;** individuals with existing aortic aneurysms or at increased risk for aortic aneurysm should avoid fluoroquinolones if possible. Again, this risk/benefit decision may be difficult for persons with few effective drug options.

Ophthalmic toxicity

Prevention and monitoring

The most common drug causing toxicity to the optic nerve is **EMB** and is frequently referred to as EMB-associated optic neuropathy. Although there are case reports and small series of persons who have developed sudden severe, irreversible optic nerve toxicity, most experts believe that lower and shorter doses (EMB dose at approximately 15-20 mg/kg given for less than 2 months) are rarely associated with optic neuropathy.

- **High-dose EMB (~25 mg/kg) generally should not be used for more than two months.**
- To minimize ocular toxicity, the dosing interval of EMB should be adjusted and serum drug levels considered if the creatinine clearance is <30 mL/min.
- **LZD** produces a toxic optic neuropathy that is usually reversible. If no other reasonable options exist, restarting LZD at a lower dose (300 mg) after vision returns to normal has been successfully attempted without recurrence in one published report. If visual changes are attributed to EMB, do not restart.
- **RFB** can cause a pan-uveitis that is reversible with dosage adjustment or stopping completely.
- ETA and INH are rare causes of optic nerve toxicity.
- **CFZ** toxicity produces a bull's-eye pigmentary maculopathy and generalized retinal degeneration.

When using any of these drugs:

- Conduct **baseline assessment** of visual acuity (Snellen chart) and color discrimination (Ishihara plates) at the start of treatment.
- For patients on LZD, EMB, or RFB, conduct monthly testing of visual acuity and color discrimination during treatment. Consider holding medications and referral to ophthalmology when acuity by testing worsens by two or more lines on Snellen chart, or if new deficits occur on color discrimination tests on repeat testing.
- Educate persons starting treatment to report any change in visual acuity or red-green color discrimination, scotomata, change in visual fields, erythema, or eye pain.
- For individuals with baseline visual abnormalities or who have difficulty with Snellen and Ishihara tests (e.g., due to dementia or cognitive impairment), some experts recommend monthly screening with an ophthalmology exam.
- **Improve diabetic control.**
- Correct nutritional deficiencies. Consider a multivitamin for individuals with malnutrition (wait until they are tolerating TB therapy before starting the multivitamin; remember to dose 2 hours before or after fluoroquinolone drugs if the multivitamin contains iron or other divalent cations).
- **Whenever a question about visual toxicity arises, immediately discontinue the likely offending medication and refer the individual to an ophthalmologist.** RFB may be continued if the dose can be decreased. Evaluate potential nutritional deficiencies, especially of the B-complex vitamins and folate.

Retrobulbar neuritis

Often presenting as a unilateral process, **symptoms of eye pain and/or changes in vision while on EMB** should be evaluated by ophthalmology for potential retrobulbar neuritis due to drug-associated inflammation of the optic nerve. If symptoms are present:

- Stop EMB and refer to an ophthalmologist.
- Do not restart EMB unless another cause of the neuritis or vision problem is definitely identified.
- Rare cases of toxicity due to LZD, ETA, INH and CFZ have been reported; stop their use when these drugs are implicated.

Gradual improvement in vision is noted in many patients after the offending medication is stopped. This is more common when toxicity is recognized early and medication is discontinued quickly after symptoms develop. However, some series report fairly abrupt vision loss that is permanent.

Uveitis

RFB, especially in doses greater than 300 mg daily (or given along with medications that decrease clearance, i.e., protease inhibitors, antifungal azoles, and macrolides), can cause pan-uveitis. RFB-induced uveitis is generally considered a rare, dose-related event.

- Uveitis typically presents with erythematous, painful eyes, and blurring of vision.
- **Hold RFB and consult an ophthalmologist.**
- Once symptoms have resolved, RFB can be reinstituted at a lower dose. A lower dose is usually needed when combined with drugs that cause decreased clearance of the RFB, i.e., protease inhibitors, azoles, and macrolides. If the dose is lowered, check drug levels to ensure it is still therapeutic.
- Consider other etiologies, especially in individuals with HIV; exclude bacterial and viral infection.
- Use topical steroid drops if ocular infection is ruled out.
- Some individuals may improve even when RFB treatment is continued. If recurring uveitis is a problem, stop RFB.

Ototoxicity (eighth nerve toxicity)

All the aminoglycosides are toxic to the eighth cranial nerve and can cause both vestibular and auditory toxicity.

- Higher doses increase the risk of toxicity. However, even patients with serum drug levels that are always in the therapeutic range may develop both auditory and vestibular toxicity.

Vestibular toxicity

- Assess vestibular toxicity at least monthly if using aminoglycosides. [See **Chapter 8, *Monitoring and Case Management*** for instructions.]
- Ask the individual about tinnitus and dizziness and observe closely for unsteadiness.

Fullness in the ears may be an early symptom of vestibular toxicity. When this is reported, it is sometimes possible to both limit toxicity and continue the injectable agent for another month or more by decreasing the dosing interval to 2 or 3 times a week.

Watch the patient carefully. **Toxicity is related to the total dose and is cumulative.** It is impossible to predict for an individual what dose will be tolerated. A degree of disequilibrium can be caused by CS, fluoroquinolones, ETA, INH, or LZD. Prior to stopping the injectable agent, evaluate whether these and/or other medications are causing the symptoms. All drugs can be held for several days to see if the symptoms improve. Symptoms of vestibular toxicity generally do not improve rapidly after holding medication, although some improvement may occur over time, particularly if the injectable is stopped before significant toxicity occurs.

If tinnitus and unsteadiness develop and these are attributed to vestibular toxicity caused by the aminoglycoside, stop the injectable agent. If the injectable agent is continued or an attempt is made to substitute one injectable for another, persistent vertigo, unsteadiness, tinnitus, and ataxia will develop. **Drug-induced vestibular toxicity may not be reversible.**

Auditory toxicity

Prevention and monitoring

Hearing loss is a direct effect of injectable aminoglycoside toxicity to the eighth cranial nerve. Some degree of hearing loss occurs in up to 50% of those treated for MDR-TB with a regimen that includes an aminoglycoside. High-frequency loss usually occurs first, but this rarely affects conversational speech. With continued treatment, the effects are cumulative. Hearing loss may be reversible or permanent.

- Perform a **baseline audiogram and repeat monthly.** Monitor the ability of the patient to participate in normal conversation.
- After 3-4 months of daily aminoglycoside treatment, and once the cultures are negative, consider decreasing to 3 times a week.
- **Avoid loop diuretics** because they increase eighth nerve toxicity.
- Resistance to SM is common and should be excluded before substituting it for another injectable aminoglycoside.

Nephrotoxicity

Prevention and monitoring

All the aminoglycosides (and capreomycin, which is no longer recommended) can cause nephrotoxicity. Ongoing assessment of renal function is critical.

- Perform serum creatinine with calculated glomerular filtration rate (GFR) prior to therapy and monitor the serum creatinine weekly for the first several weeks, and then at least monthly.
- If there are concerns about the accuracy of the serum GFR or if baseline GFR is marginal, perform a 24-hour creatinine clearance and then repeat as necessary to accurately monitor renal function. The GFR determined using 24-hour urine creatinine clearance is a more accurate determination of GFR than the calculated value from serum.
- Encourage adequate hydration.
- Check drug levels.
  - Some experts have obtained excellent therapeutic benefits while limiting toxicity by adjusting the dose of aminoglycosides to target peak levels of approximately 25 mcg/mL at 1 hour after intravenous administration or 2 hours after intramuscular injection.
  - Aminoglycoside trough levels should be less than 5 mcg/mL or undetectable prior to the next dose.
- For adults over 59 years of age, many experienced clinicians prefer to decrease the dose of the injectable drugs to 10 mg/kg and monitor drug concentrations. Target levels should be the same as for younger individuals.
- With effective oral drugs now available, most persons with decreased renal function should not receive an aminoglycoside. If the injectable is used as a salvage regimen, a 12-15 mg/kg dose 2 to 3 times per week is recommended (see **Chapter 7, *Co-Morbidities and Special Situations,* Renal Failure, Table 1,** for creatinine clearance calculations).

- **Monitor serum drug concentrations and adjust the medication dose accordingly.** Trough drug levels are especially helpful when there is evidence of renal insufficiency.

See **Chapter 3, *Laboratory*** and **Chapter 5, *Medication Fact Sheets*** for more details. **A trough before the next dose should be less than 5 mcg/mL or undetectable. Increasing the interval between doses may offer the best approach to ensure an adequate peak level while keeping the trough concentration below 5.**

For decreased renal function that develops during treatment:

- Ensure **adequate hydration.**
- Hold the injectable agent for 1 to 2 weeks to allow renal function to stabilize.
- Check **serum electrolytes** and correct if needed.
- Evaluate other drugs the individual is taking and adjust dose and/or dosing interval if needed. If creatinine clearance is less than 30 mL/minute, adjust the doses of EMB, PZA, some fluoroquinolones, CS and the injectable drug (only in the most desperate cases should the aminoglycoside be continued when renal or auditory toxicity due to the drug are significant).
  - For a creatinine clearance between 50 and 70 mL/min, some patients may tolerate 3-times-a-week aminoglycoside dosing at 12 to 15 mg/kg.

- **Monitor peak and trough drug concentrations.**
  Important: Obtain a therapeutic peak and ensure that trough concentrations are less than 5 mcg/mL before giving another dose of the drug.

- Follow renal function carefully

Electrolyte loss

All the aminoglycosides can cause electrolyte disturbances due to renal tubular wasting of potassium, magnesium, and calcium salts. Chloride and hydrogen losses may also occur with resulting alkalosis. A defect in renal tubular resorption of chloride may be seen. Nausea, vomiting, and diarrhea may also contribute to electrolyte abnormalities. Electrolyte disturbances with these medications may precipitate serious, even fatal cardiac arrhythmias.

- Conduct baseline assessment and at least monthly follow-up of potassium, calcium, and magnesium during injectable drug treatment.
- Replace electrolytes as needed.
- Assess renal function when replacing electrolytes.
- **If an isolated potassium value is low, also check the calcium and magnesium.**
- A low serum calcium is most commonly due to hypoalbuminemia. If the calcium is low, check albumin and free calcium to obtain the corrected value.
- Hypomagnesemia, if present, must be treated to correct hypocalcemia and hypokalemia.

For **severe** electrolyte abnormalities, hospitalize and monitor.

- Perform an electrocardiogram.
- Hold medications that may contribute to prolongation of the QT interval (fluoroquinolones, CFZ, BDQ). See section: ***Cardiovascular toxicity and adverse reactions, QT interval prolongation***
- Hold medications (digoxin, tricyclic antidepressants) that may precipitate arrhythmias.

Miscellaneous adverse reactions

Hypothyroidism

Hypothyroidism may develop with either **PAS or ETA**; when both drugs are used the incidence of hypothyroidism may be 40% or greater.

- Assess baseline thyroid function prior to start of PAS or ETA and correct if needed. Assess thyroid function every 1 to 2 months unless clinical assessment indicates the need to evaluate more often. Conduct monthly clinical assessments for hypothyroidism, although these may lag behind laboratory findings.
- When thyroid stimulating hormone (TSH) begins to increase, evaluate for clinical evidence of hypothyroidism. Begin to monitor more frequently.
- When TSH rises to more than 1.5 times the upper limit of normal, begin thyroid hormone replacement:
  - Most adults will require 100 to 150 mcg of levothyroxine daily.
  - Young healthy adults can be started on 75 to 100 mcg of levothyroxine daily.
  - Older individuals should begin treatment with 50 mcg daily.
  - **Individuals with significant cardiovascular disease should start at 25 mcg daily.** Increase thyroid hormone slowly in persons with significant cardiovascular disease.
  - Be aware that thyroid dysfunction can also contribute to risk for arrhythmia, particularly if there's a potential for QT-prolongation due to anti-TB drugs (e.g., BDQ, CFZ, fluoroquinolones).
- Repeat the TSH level after 1 to 2 months of treatment, adjust dose if needed, and continue to monitor monthly while on treatment. Hormone treatment can be stopped once treatment with the associated medication is stopped.
- **Adjust thyroid hormone replacement until theTSH is within the normal range.** Thyroid function will return to normal after PAS or ETA are discontinued. Hormone treatment should be stopped once treatment with the associated medication is stopped and follow-up normalization of TSH is documented.

Metallic taste

Metallic taste is reported as an adverse reaction when taking **ETA**. Fluoroquinolones may also cause changes in taste. Encourage those on treatment to tolerate this side effect. Sucking on lemon drops or other hard candy or chewing gum can be helpful. Normal taste returns when treatment is stopped.

Gynecomastia

Breast enlargement can be a troublesome side effect of **ETA** therapy, especially for males. **Galactorrhea** has also been reported. Encourage individuals to tolerate this side effect. Resolution occurs after treatment is stopped.

Alopecia

Hair loss can occur with either **INH** or **ETA**. In the first months of treatment, there can be significant thinning of the hair, but this is temporary and not progressive during treatment. Significant cosmetic change has not been reported with **ETA**, but rare cases have been reported due to **INH**.

Superficial fungal infection

Vaginal or penile candidiasis may occur. This is most common with **fluoroquinolone** and **LZD** therapy and is more likely to occur in persons with diabetes. Cutaneous candidiasis in skin folds may also occur. Topical antifungal agents or short-course oral antifungal drugs are helpful; be mindful of the drug interaction between rifamycin drugs and oral antifungal azoles. Exclude other diseases if response to treatment is not prompt.

Black hairy tongue

Elongation of the filiform papillae with yellowish to brown discoloration of the tongue can be an infrequent consequence of antibiotic use (e.g., **LZD**). Benign and generally asymptomatic, the condition can be treated by increasing oral hygiene, including soft-bristle brushing or scraping of affected areas.

Non-specific numbness

Transient numbness, especially around the mouth, occurs with **SM**. Unlike vestibular or auditory toxicity, these symptoms associated with **SM** are not progressive, and **SM** does not always have to be discontinued. If the symptoms are particularly difficult to tolerate and the treatment regimen would not be compromised, consider a reduction in dose to alleviate the symptoms. However, ensure that the serum drug levels remain therapeutic. Another option: if the daily dose has produced therapeutic levels, use this same dose 2 or 3 times a week.

Hypo-/Hyperglycemia

Several cases of hypoglycemia have been reported due to **LZD** documented by rechallenge. Hypoglycemia was more often associated with diabetes. Later-generation **fluoroquinolones** have been reported to cause both hypo- and hyperglycemia, especially in older persons and persons with diabetes. Gatifloxacin (no longer available in the U.S.) has been most frequently implicated, but **MFX and LFX** may also cause dysglycemia.

SUMMARY

- Common adverse effects of DR-TB treatment may involve almost any organ system and may include:
  - Gastrointestinal adverse effects
  - Cardiovascular adverse effects
  - Dermatologic reactions
  - Systemic hypersensitivity reactions
  - Hematologic abnormalities
  - Neurotoxicity
  - Ototoxicity
  - Ophthalmic toxicity
  - Nephrotoxicity
  - Musculoskeletal reactions
  - Endocrine adverse effects
- Anticipate adverse reactions and toxicity with any treatment course for DR-TB. Persons with DR-TB must be well-informed so that they will know what to expect and can be partners in their treatment plans.
- Paying close attention to toxicity and reports of discomfort is essential in maintaining goodwill and cooperation with the regimen.
- In many cases, some toxicity may need to be tolerated (although it should be treated and minimized).
- In some cases, offending drugs crucial to the regimen cannot be permanently discontinued without negatively affecting the chance for a lasting cure. This should be discussed with the person undergoing treatment. WHO guidelines note that persons with DR-TB are the ultimate decision makers regarding the degree of toxicity that they are willing to tolerate.

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