

# Adverse Reactions

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

## Introduction

Treatment of drug-resistant tuberculosis (TB) requires the use of multiple medications and most patients will experience some difficulty tolerating them. The response of an individual patient, 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 drug-resistant TB. By contrast, others may have serious difficulty tolerating relatively simple regimens.

Patients should be well informed about their anti-tuberculosis treatment regimens so that they can be recruited as partners invested in the success of their therapy.

- **Prior to initiating a treatment regimen, it is essential to discuss the benefits and risks of therapy.** The patient should understand the need for treatment, the importance of each medication in the treatment regimen, and the possible side effects and toxicities.
- **Assure patients that every possible attempt to make their treatment as easy as possible will be made, but emphasize that having enough effective drugs in the regimen is essential to achieving a cure.** Patients should know that while side effects may be inevitable, they will be addressed and treated as aggressively as possible. Patients should be mentally prepared for likely discomfort and should brace themselves for the long road ahead.
- **Help patients realize that this may be their last opportunity for cure and future treatment regimens could be more toxic and less effective.**
- Breaks in therapy should be avoided whenever possible to maximize the effectiveness of treatment.

Quickly recognize and respond to the symptoms a patient expresses. Careful assessment may allow some symptoms to be attributed to causes other than medication toxicity. Most patients will be willing to continue medication despite side effects when: 1) they understand the benefit of the medication; 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 the patient's efforts to cooperate. This recognition often helps a patient to continue therapy.

**Do not stop a drug that leaves the patient at risk of relapse or treatment failure without consulting an expert in the management of drug-resistant TB.** Likewise, do not reduce the dose of a drug unless this can be done without compromising the

efficacy of the treatment regimen. In some cases, minor drug reactions and discomfort may persist and will have to be tolerated to ensure the success of the regimen. In some instances, serious adverse events will need to be tolerated in order to cure multidrug-resistant (MDR) or extensively-drug-resistant (XDR) TB. For example, some patients with severe disease and extensive resistance may need an aminoglycoside to ensure cure. These patients should be informed that hearing loss may be inevitable in order to ensure the patient does not fail treatment or die of TB.

Patients can be counseled that treating drug-resistant TB is more like cancer chemotherapy than treating a typical infection. Treatment of this life-threatening disease is a marathon, not a sprint, and there may be setbacks. Adverse effects are likely on the way toward the goal of a durable cure. Frequent family meetings to clarify goals and address symptom management can strengthen the provider-patient alliance so important to supporting patients 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 are also consistent with possible hepatotoxicity, so if these symptoms develop, liver enzymes and total bilirubin should be checked.

### Common causes of GI symptoms include:

- **Gastritis**
- **Hepatitis or hepatotoxicity**
- **Biliary disease**
- **Pancreatitis**
- **Peptic ulcer disease**
- **Inflammatory bowel disease**
- ***Clostridium difficile* colitis**
- **Lactose intolerance**
- **Acute renal failure or nephrotoxicity**
- **GI TB, if early in the course**
- **Diabetic gastroparesis**
- **Pregnancy**

## Nausea and vomiting

### Treatment of nausea and vomiting:

- **First, ask the patient. Patients may have strong ideas about which medication is causing them problems. Their opinions must be addressed and respected (even if no change can be made).**

- Encourage patients to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely. Offer ancillary treatment for symptoms.
- **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.
- If the patient has TB meningitis, nausea and vomiting might be signs of rising intracranial pressure rather than a drug intolerance issue. Obtain urgent imaging to evaluate for hydrocephalus, and neurosurgical consultation if indicated.

**The following are specific interventions that can be attempted, depending on the drug:**

**ETA** tends to cause more upper GI symptoms such as nausea and vomiting, and **para-aminosalicylate (PAS)** more lower GI symptoms, such as abdominal cramping and diarrhea, though there is often overlap. Patients may tolerate one of these two drugs, 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 this helps to alleviate the nausea or vomiting. Advise the patient that this is a test to determine which drug is causing side effects and that the drug will be reintroduced at a lower dose and slowly increased to a therapeutic dose.

If the patient improves off of the medication, 1 drug at a time can be restarted at a lower dose (ETA 250 mg, PAS 2 to 4 grams) to identify if the lower dose is better tolerated. The dose of medication can be gradually increased over the next 2 weeks. Both medications can be given in 2 or 3 doses over the day, which may improve tolerance. Many patients tolerate the higher dose of ETA better in the evening (ETA 250 mg in a.m., 500 mg at bedtime; or may only tolerate 500 mg at bedtime). The goal should be to increase the ETA dose to at least 500 mg daily and the PAS dose to at least 6 to 8 grams daily. In some situations it may be best to dose ETA at 500 mg daily or PAS at 6 grams daily if the patient tolerates this, rather than to increase to a dose that cannot be tolerated. This will depend on the patient and the patient's weight. Serum drug levels should be obtained to document whether the level is therapeutic.

**Linezolid (LZD)** may also be associated with nausea and vomiting. If the LZD dose is 600 mg/day, reduction of the dose to 300 mg/day may be considered to improve GI tolerance and is not generally associated with loss of efficacy. Most reports noting efficacy at 300 mg daily were in patients who had the dose decreased after a period of time on the 600 mg dose. A therapeutic level should be documented if the dose is decreased. Some patients require a 400-450 mg daily dose to achieve a therapeutic level. These doses are only available with the liquid formulation of the drug.

**Fluoroquinolones, clofazimine (CFZ), and bedaquiline (BDQ)** may also cause nausea or vomiting. The dose of fluoroquinolones such as **levofloxacin (LFX)** or **moxifloxacin (MXF)** should not be decreased because of nausea. The fluoroquinolones are crucial drugs in the treatment regimen and the bactericidal effects are dose-dependent. If GI toxicity is present and the dose of **CFZ** is more than 100 mg daily, it should be reduced to 100 mg daily. **BDQ** may also be associated with nausea and vomiting. There is no information currently about the impact of BDQ dose reduction on the severity of GI side effects or the efficacy of the drug. The dose of BDQ should not be changed.

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):**

- **Promethazine** (Phenergan) 12.5 to 25 mg PO, IV, or PRN 30 minutes before the dose and every 6 hours as needed.
- **Ondansetron** (Zofran) 8 mg PO 30 minutes before the dose. The dose can be repeated after 8 hours.
- **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 patients who have developed anticipatory nausea because of its anxiolytic and anterograde amnesia effects.
- A number of other antiemetics are also available. Trying another agent may be helpful in some patients when the previously listed options do not work or are not available in your pharmacy.
- Try giving the responsible medication at **bedtime**; some symptoms from adverse effects may be more tolerable during sleep.
  - This is relatively easy when the patient is hospitalized, but in the outpatient setting, directly observed therapy (DOT) may only be available once daily. It may be necessary to allow the patient to self-administer the evening dose. Video DOT can be considered to monitor adherence, because even the most adherent patients may have difficulty taking a medication that predictably makes them feel bad.
- **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 can easily be done during hospitalization, but may represent a challenge in the community setting.
- **Treat gastritis or acid reflux.** Proton pump inhibitors or H<sub>2</sub>-receptor blockers may be helpful. Avoid using antacids or sucralfate within 2 hours of the dose of fluoroquinolones because these agents may interfere with fluoroquinolone absorption.
- **Minimize use of nonsteroidal anti-inflammatory drugs (NSAIDs).** This may be difficult if the patient also has arthralgia and myalgia from other medications. Try acetaminophen with caution as it may increase the risk of hepatotoxicity from other antituberculous medications.
- Diagnose and treat co-existing *Helicobacter pylori* infections.
- **Encourage hydration.** Sports drinks with electrolytes may be helpful (but note that the glucose content of these drinks is unacceptable for most diabetics).
- 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.
- Electrolytes, BUN, and creatinine should be evaluated and corrected if significant vomiting or diarrhea occurs.

Evaluate the effects of the interventions you have used to decrease the nausea and vomiting. If the patient still has daily nausea that persists through much of the day and interferes with nutrition and hydration, despite employing strategies along with antiemetics,

the medication may need to be stopped. This is an easier choice if an adequate regimen can be designed without the medication, but if it leaves the patient with a regimen likely to fail, some nausea and even vomiting may need to be tolerated, at least in the initial period of treatment.

- 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 patients who have developed a psychological aversion to swallowing pills, cognitive behavioral therapy may be helpful.
- In most instances, treatment should include at least 4 active drugs likely to be effective.
- **Consultation with an expert is especially important when regimen changes are considered.**

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

## Diarrhea

Diarrhea, along with increased flatus and cramping, can cause significant difficulty for patients, but very rarely does it lead to discontinuation of medication.

- PAS often causes diarrhea with the initiation of medication. Inform patients that diarrhea usually resolves or improves considerably after several weeks.

- **Always start PAS at a low dose and then increase gradually over the next 2 weeks to minimize this problem as much as possible.** See Figure 3, “Dose Escalation (Drug Ramping)” in **Chapter 4, Treatment**.

- Fluoroquinolones and LZD may also cause loose stools or diarrhea, along with increased flatulence. This usually improves after the first several weeks, but may persist in part for the duration of therapy.
  - Lactobacillus or foods such as yogurt (not given within 2 hours of the fluoroquinolone dose) with active cultures may improve symptoms by replacing normal flora.
  - Loperamide (Imodium) 2 to 4 mg PO can be used initially and then 1 to 2 mg after each loose stool to a maximum of 8 to 16 mg/day for adults. Loperamide is approved for use in children over 2 years old. This may be used intermittently, especially when patients need to attend social functions or return to work. It should not be used daily.
  - Encourage patients to tolerate some degree of loose stools and flatulence and remind them that the fluoroquinolone and LZD are key drugs in the treatment regimen.
- Diarrhea is one of the most common side effects of LZD, and as with nausea and vomiting, may be ameliorated with LZD dosage reduction from 600 mg/day to 300-450 mg/day.

### If the diarrhea is severe, other etiologies may include:

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

## Hepatotoxicity

- Any GI complaint may represent hepatotoxicity. **If hepatotoxicity is suspected, hold all anti-tuberculosis medications that are potentially hepatotoxic until laboratory results are available.** The alanine aminotransferase (ALT) is the hepatocellular enzyme most directly associated with hepatocellular damage. If the enzymes are normal, continue medications using the strategies previously noted to lessen nausea and vomiting.
- The ALT is more specific for hepatocellular injury than the aspartate aminotransferase (AST). Elevations in the AST may also indicate injury to the muscle, heart, or kidney. However, elevation of either the AST or ALT should raise concerns about drug-induced hepatotoxicity. Once that possibility is excluded, other causes of the elevated hepatic enzymes, such as alcohol use, should be pursued.
- **If elevated liver enzymes and/or bilirubin are detected, in addition to drug-induced hepatotoxicity, consider other causes such as gallstones or viral hepatitis. These are potentially treatable causes that, if addressed, may make treatment of the TB easier.**
- 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 again 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. An evaluation for causes of direct and indirect hyperbilirubinemia should be done. If the bilirubin is greater than 3.0 mg/dl, generally, hepatotoxic medications should be stopped.
- If both bilirubin and alkaline phosphatase are elevated (cholestatic pattern), rifampin (RIF) is the most likely etiology of the liver injury. If the liver injury is predominately transaminitis (elevated AST/ALT), PZA and isoniazid (INH) are the most likely causes of liver injury. However, there is overlap in the pattern of liver injury caused by these drugs, and all individually or in combination may contribute to hepatotoxicity.
- 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 even in the absence of any symptoms, hold all potentially hepatotoxic medications. If at least 3 medications remain in the treatment regimen that are not hepatotoxic (for example, ethambutol [EMB], the aminoglycosides, LFX, or cycloserine [CS]), then these 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, when liver enzymes fall to less than twice normal (some experts prefer to wait until the enzyme levels normalize or return to baseline), one potentially hepatotoxic drug (along with other medications that are not hepatotoxic) can be restarted.
- If the first potentially hepatotoxic drug is successfully re-introduced, then the remaining potentially hepatotoxic medications should be reintroduced one at a time.
- Carefully observe for clinical reactions and repeat liver enzymes and bilirubin at least twice weekly until the medication has been taken for at least a week and liver enzymes and bilirubin are stable. The next medication can then be added to the regimen and monitored. All remaining medications should be reintroduced in this manner.
- If reintroduction of a medication leads to clinical symptoms of hepatotoxicity and enzymes increase, 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.

Patients with underlying liver disease are at increased risk of drug-induced liver injury. HIV-positive individuals, especially those receiving concomitant antiretroviral therapy (ART), have had an increased incidence of hepatitis in some studies. Several reports of HIV-positive persons with hepatitis C noted hepatotoxicity in over 20% of cases.

ART may be associated with drug-induced hepatitis, with the incidence depending on the individual drugs utilized. Immune reconstitution syndrome with granulomatous hepatitis from disseminated TB may be seen in patients with AIDS after starting ART. Hepatitis C, an elevated baseline serum bilirubin, low CD4 cell count and fluconazole therapy have all been associated with hepatitis. The risk of liver injury from anti-tuberculosis drugs in patients with hepatitis B is variable. It appears to be increased in those with chronic active infection compared to those who are only seropositive.

**If at least 3 medications remain in the treatment regimen that are not hepatotoxic, then these can be continued in the face of elevated liver function tests.**

# 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, or 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 or as needed.
- **Diphenhydramine** (Benadryl) 25 to 50 mg PO, IV, or IM given before the medication, and then every 4 to 6 hours as needed, may lessen skin irritation. If patients become drowsy, caution them not to drive or operate machinery.
- **Other antihistamines:** chlorpheniramine (Chlor-trimeton) 4 mg PO before the medication and then every 4 to 6 hours as needed; hydroxyzine (Atarax) 25 mg PO or IM QID (can be increased to 50 mg QID); or loratadine (Claritin) 10 mg PO before the medication.
- **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 other potential etiologies of rash and pruritus:

- Scabies and insect bites may masquerade as a drug rash.
- Contact dermatitis. Question patient about use of new lotions, soaps, perfumes, etc.
- Phototoxicity (may respond to sunscreens, but these may 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 diabetic patients, 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.
- Unusual skin lesions may be associated with HIV infection.

## 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 RIF or PZA and is usually mild and resolves without therapy. If it is bothersome to the patient, 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 patients not to ingest foods that precipitate the reaction while they are receiving INH.**

## Photosensitivity and hyperpigmentation

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

Pseudojaundice (brownish discoloration of the skin) may occur with rifabutin (RFB). The sclera is clear and the bilirubin and other liver enzymes are normal.

Hyperpigmentation, often worse in dark-skinned individuals, can also occur with CFZ and may markedly increase with sun exposure. The hyperpigmentation improves after discontinuation of the drug.

*Caution patients to limit sun exposure and to use sunscreen.*

## 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. Medication should not be discontinued 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 causing 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, 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.**

**The patient can be premedicated with Benadryl 25 mg with or without a small dose of prednisone (10–20mg) 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 pre-medication following the tables below. The use of premedication makes rechallenge a bit easier for the patient and the health department when this needs to be done in the outpatient setting.**

**Premedication does not prevent a rash but typically makes the reaction less severe and may blunt associated systemic effects, especially the most serious ones. Some patients may benefit from a short course of low-dose steroids if the resulting clinical reaction is only a mildly pruritic rash.**

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       |              |
| RIF  | 75 mg        | 300 mg       | 600 mg       |
| PZA  | 250 mg       | 1 gram       | 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    |
| PAS  | 1 gram       | 4 gram       | 6–8 grams    |
| 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 |
| Capreomycin (CM)                                                                                                                                          | 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. Rechallenge should always be accomplished 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<br>(hour:minute) | Dose of INH*        | Time from start<br>(hour:minute) | Dose of RIF**       | Dose of EMB**       |
|----------------------------------|---------------------|----------------------------------|---------------------|---------------------|
| 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 bid<br>x 3 days |                                  | 300 bid<br>x 3 days | 400 tid<br>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 patient take medication 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, but does occur. Anaphylaxis typically presents within minutes of medication dosing. The patient classically has signs of airway compromise, such as stridor, wheezing, a feeling of the throat being closed, swelling of the tongue, and hoarseness. Additional signs and symptoms include shock, urticaria, angioedema, confusion, and pruritus. Nausea, vomiting, cramping, and diarrhea may also occur. 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.**

Reactions associated with systemic toxicity—high fever, widely distributed urticaria, and bulla, along with mucous membrane involvement—are characteristic of Stevens-Johnson syndrome. 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 therapy, usually with systemic steroids and supportive care.** A dermatology consultation and a skin biopsy should be requested if there is any question about the diagnosis. INH, RIF, EMB, SM, ofloxacin, 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.**

*Anaphylaxis typically presents within minutes of medication dosing.*

### Hypersensitivity syndrome (DRESS)

The drug-induced hypersensitivity syndrome has been described with several of the anti-tuberculosis medications. Recently many of the patients with this group of reactions are identified as having “drug reaction with eosinophilia and systemic symptoms” (DRESS).

- The TB medications most commonly associated with DRESS are **RIF, INH** and **EMB**.
- Some persons experiencing DRESS may be receiving treatment with both allopurinol and first-line antituberculous medications. Allopurinol has been used to decrease the elevated uric acid which is characteristically seen in persons taking **PZA**. Although most patients with elevated uric acid do not need treatment other than adequate hydration, if there is a need to address elevated uric acid levels, allopurinol should not be used.
- A variety of other drugs has also been implicated, including sulfonamides, dapsone, minocycline, and many of the antiepileptic agents. 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, often the first manifestation, may be as high as 40 degrees centigrade and is accompanied by malaise, lymph node enlargement, and rash. The rash begins as a morbilliform eruption, but progresses to a diffuse, confluent eruption with infiltrative erythema. Rash usually starts on the trunk, upper extremities, and face. The face may become edematous, facial involvement is symmetrical and associated with erythema that is persistent. The mucous membranes are involved in up to one-third of patients. The rash usually progresses to involve the lower extremities and often involves more than half of the body. The erythema may progress to vesicles, pustules, diffuse dermal edema and eventual exfoliative dermatitis.

Lymphadenopathy is a prominent finding and is present in up to 50% of patients. Biopsy usually shows benign lymphoid hyperplasia. Organ involvement most frequently includes the liver but may less frequently involve the kidneys or lungs. Liver involvement may manifest as liver enlargement with jaundice but most often is asymptomatic. If the offending drug is discontinued, the abnormalities are usually mild and resolve quickly. Severe involvement may occur and progress to liver failure. Renal involvement is manifested as interstitial nephritis and has been associated with co-administration of the drug allopurinol. Pulmonary involvement may include cough, fever, and dyspnea with hypoxemia. Interstitial pneumonitis along with pleural effusion may be seen on the chest radiograph. Rare cases of multiple additional organ involvement have been noted.

Laboratory abnormalities include mildly elevated ALT and/or alkaline phosphatase in over 80 percent of patients, leukocytosis with eosinophil counts > 700 in most, and atypical lymphocytosis in 30 to 70 percent of patients. 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 the patient experiences 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 TB patients because they need to be treated for TB, especially if infectious and if steroid therapy is required to control DRESS. It is sometimes not possible to distinguish a reaction as due to the addition of a new drug or due to a flare of the underlying reaction. 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.**

An experienced TB clinician should be consulted in addition to a dermatologist. High potency topical corticosteroids applied 2 to 3 times daily are preferred to systemic steroids, but can be used for only 1 to 2 weeks. Systemic steroids, sometimes in high dose, may be needed for an extended period of time.

## RIF hypersensitivity reactions

A variety of reactions have been reported with RIF 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. Typically the syndrome develops after several months of therapy and is more common with intermittent therapy. Many patients are able to tolerate RIF if the dosing interval is changed from intermittent to daily.

For most other hypersensitivity reactions, treatment with RIF should be stopped. Do not try desensitization. Many patients require steroid therapy to control the reactions.

### Reactions include:

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

## 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 such as seen with disseminated TB involving the bone marrow directly or related to decreased bone marrow production due to chronic illness from *M. tuberculosis*. Gastrointestinal 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 of the medications. However, the most common causes of hematological abnormalities are related to INH, RIF and LZD, any of which may cause abnormalities in all cell lines. Most TB medications can occasionally be associated with hematologic abnormalities. See Table 3.

TABLE 3.

## Hematologic Abnormalities Associated with Anti-Tuberculosis Drugs

| Drug         | WBC ↓ | WBC ↑ | PMN ↓ | Plt ↓ | Plt ↑ | Pan ↓ | Red cell aplasia | DIC or Coag abnl | Hgb ↓ | Hemolytic anemia | Eos ↑ | Aplastic anemia |
|--------------|-------|-------|-------|-------|-------|-------|------------------|------------------|-------|------------------|-------|-----------------|
| Amikacin     |       |       |       |       |       |       |                  |                  |       |                  | X     |                 |
| Amox/clav    | X     |       | X     | X     | X     |       |                  |                  | X     | X                | X     |                 |
| Capreomycin  | X     | X     |       |       |       |       |                  |                  |       |                  | X     |                 |
| Clofazimine  | X     |       |       |       |       |       |                  | X                | X     |                  | X     |                 |
| Cycloserine  |       |       |       |       |       |       |                  |                  | X     |                  |       |                 |
| Ethambutol   | X     |       | X     |       |       |       |                  |                  |       |                  | X     |                 |
| Ethionamide  | X     |       |       | X     |       |       |                  |                  |       |                  |       |                 |
| Imipenem     | X     | X     | X     | X     | X     | X     |                  | X                | X     | X                | X     |                 |
| Isoniazid    | X     |       | X     | X     |       | X     | X                | X                | X     | X                | X     | X               |
| Kanamycin    |       |       |       |       |       |       |                  |                  |       |                  |       |                 |
| Levofloxacin | X     | X     |       | X     |       |       |                  |                  | X     | X                | X     | X               |
| Linezolid    | X     |       |       | X     |       | X     | X                |                  | X     |                  |       |                 |
| Moxifloxacin | X     | X     | X     | X     | X     |       |                  | X                | X     | X                | X     |                 |
| PAS          |       |       | X     | X     |       |       |                  |                  |       |                  |       |                 |
| Pyrazinamide |       |       |       | X     |       |       |                  |                  | X     |                  |       |                 |
| Rifabutin    |       |       | X     | X     |       |       |                  |                  |       |                  |       |                 |
| Rifampin     | X     | X     | X     | X     |       |       | X                | X                | X     |                  |       |                 |
| Streptomycin | X     |       |       | X     |       | X     |                  | X                |       | X                | X     |                 |

# 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 also 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 **INH**, **ETA**, **CS**, and **LZD**. Fluoroquinolones and EMB have rarely been associated with the development of neuropathy, although neuropathy has recently been added as a “black box” warning for the fluoroquinolones.

**Neuropathy is more likely to occur in patients with diabetes, alcoholism, HIV infection, hypothyroidism, pregnancy, poor nutrition, and with inadequate dietary intake of pyridoxine.**

Pyridoxine prophylaxis (50 mg daily for patients with drug-susceptible TB under a standard treatment regimen) is usually adequate. If symptoms develop or progress, the dose can be increased to 100 mg daily.

Pyridoxine prophylaxis (100 mg daily) should be included for all patients (including a weight-proportionate dose for children) receiving treatment for MDR-TB who take INH, ETA, CS, or LZD. If symptoms develop or progress, doses of 150 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.

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

Neuropathy associated with LZD usually tends to occur after 4 months of therapy and is likely dose-related. Initial use of the 600 mg once-daily LZD dosing followed by a decreased dose of 300 to 450 mg daily (or alternatively 600 mg 3 or 4 times weekly if toxicity develops) usually allows continuation of LZD in the treatment regimen. Patients must be followed closely once peripheral neuropathy develops, as symptoms may not improve or may even progress when LZD is discontinued. The degree of tolerable neuropathy for an individual patient must be balanced against alternative medications available for treatment, the toxicities of these medications, and the opportunity for a lasting cure of drug-resistant TB.

### Additional interventions should include:

- **Correct vitamin and nutritional deficiencies.**
- **Address additional medical problems.**
- **Evaluate and correct electrolytes.**
- **Identify and stop (if possible) other medications that may cause peripheral neuropathy.**
- **Consider whether the dose of ETA or CS can be reduced without compromising the regimen.** Monitor serum drug concentrations if doses are lowered.

- **Physical therapy may be helpful.**
- **NSAIDs or acetaminophen may be helpful.**
- **Gabapentin** (Neurontin) has been helpful for many patients. Adults should be treated initially with a single dose of 300 mg PO 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) may be tried in patients 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. However, 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 the serotonin syndrome.
- **Carbamazepine** (Tegretol), an anticonvulsant, at 100 to 400 mg PO BID, can be tried. Blood dyscrasias and elevated liver function may complicate therapy; a complete blood count (CBC) and liver enzymes should be routinely monitored in patients on this medication.
- **Rarely, medication may be discontinued, but only if an alternative drug is available or the regimen is not compromised.**

## 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 patients to expect these effects and understand that they typically become less problematic after the initial weeks of therapy. **Tolerance develops towards most of these effects and the patient learns 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 patients who experience drowsiness. Consult the patient as to 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 supportive attention from family and healthcare providers. Some degree of situational depression is to be expected for most patients who deal with the complexities and challenges of drug-resistant 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. Patients on CFZ who experience hyperpigmentation from the drug have been known to develop a reactive depression due to the changes in skin coloration.

*CS should not usually be part of an initial treatment regimen if significant depression is present.*

- Assess and address underlying psychological/social issues.
- Assess patients for coexisting substance abuse and refer to counseling if appropriate.
- Always be alert to indications of suicidal ideation in patients with depression, especially those on CS or ETA. If depression is significant or suicidal ideation is present, both CS and ETA must be stopped, and the patient observed carefully with psychological support until they are 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 patients on LZD, because of the risk of serotonin syndrome.**
- Obtain CS levels. Reduce the dose if levels are >35 mg/dl. Adjust dosing to achieve levels toward the lower end of the target range (peak level at 2 hours post dose target range is 20–35 mg/dl).
- Reduce the dose of CS and ETA from 750 mg daily to 500 mg daily to see if depression is lessened.
- If depression progresses or is not improved 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 depression is controlled on therapy, some patients may tolerate CS and ETA.
- INH has been associated with depression, reported as severe in several case reports. Withdrawal of the drug is associated with rapid recovery.

### Psychosis

- If psychosis is present, hospitalize the patient and put him/her under 24-hour surveillance.
- Obtain psychiatric consultation.
- Hold all medications that possibly contribute until the patient stabilizes.
- **The most likely drugs to cause psychosis are CS and fluoroquinolones; INH can occasionally be implicated.**
- Pyridoxine (100–150 mg) should be given if not already part of the treatment.
- 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.

- 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.
- When the patient has stabilized, all medications have been successfully restarted, and all symptoms have resolved, taper the antipsychotic drugs with careful observation of the patient.
- Consider and address all other etiologies, especially illicit drugs, alcohol, and medical problems (meningitis, hypothyroidism, and depression).
- Some patients may tolerate CS with an antipsychotic drug if no other treatment options are available. These patients require special observation. Utilize this therapy only after consultation with an expert in the management of drug-resistant TB, and when the CS is determined to be essential to the regimen and no alternative is available.

### Suicidal ideation

- **Hospitalize the patient and put under 24-hour surveillance.**
- Discontinue CS.
- Obtain psychiatric consultation.
- Initiate antidepressant therapy.
- If the patient is also on INH or ETA, hold these medications and only rechallenge once the patient is stable. INH, if restarted, is given at 300 mg daily. 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 the patient is 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 patient in the hospital until the risk of suicide has passed.

### Seizures

Immediate steps:

- Hospitalize patient. 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 (phenytoin, valproic acid). Monitor anti-epileptic drug levels as drug interactions and synergistic toxicity are possible. If the patient is on CS, obtain a random CS level as seizure activity is closely related to elevated serum CS levels.
- In cases of INH toxicity: If the dose of INH is known, the patient should be treated initially with a slow intravenous bolus of pyridoxine, over 3 to 5 minutes, on a gram per gram basis, equal to the INH dose. If the quantity of INH ingestion is unknown, then consider an initial intravenous bolus of pyridoxine of 5 grams in the adult or 80 mg/kg in the child. If seizures continue, the dosage of pyridoxine may be repeated. It would be rare that more than 10 grams of pyridoxine would need to be given. The maximum safe dose for pyridoxine in INH intoxication is not known. If the patient does not respond to pyridoxine, diazepam may be administered.

- 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 drug in the regimen first.

- CS should not be restarted unless it is absolutely essential to the regimen. This will not often be the case.
- Continue anticonvulsant therapy during the remainder of therapy for drug-resistant 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: 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.

Although LZD alone is not potent enough to cause the serotonin syndrome, it may occur when LZD is given along with medications that increase the serotonin level or when a diet is very high in tyramine (cheese, cured meats, fermented soy products or sauce, red wine). Although this is a rare occurrence, it can be severe and even fatal. Because the syndrome does not resolve unless the offending medications are withdrawn, recognition is imperative.

The clinical picture varies from mild to severe 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 its 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.**

The SSRIs or tricyclics cannot be abruptly stopped and even if discontinued 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 patients need aggressive management of their cardiorespiratory and thermal abnormalities.

## Ototoxicity (eighth nerve toxicity)

**All of the aminoglycosides and CM 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

- At least monthly, assess vestibular toxicity. [See **Chapter 8, Monitoring and Case Management** for instructions.]
- Ask the patient about tinnitus and dizziness, and observe the patient 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 patient what dose is 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 after time if the injectable is stopped before significant toxicity occurs. Stopping the injectable should be done only after carefully excluding other causes of the symptoms.

If tinnitus and unsteadiness develop and these are attributed to vestibular toxicity, stop the injectable agent. This is one of the few adverse reactions that often may cause permanent intolerable toxicity and necessitate discontinuation of a class of agents. 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 is frequently not reversible.**

## Auditory toxicity

### Prevention and monitoring

Hearing loss is a direct effect of injectable medication toxicity to the eighth cranial nerve. Some degree of hearing loss occurs in nearly all patients treated for MDR-TB. High-frequency loss usually occurs first but this rarely has an effect on 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.
- Consider change of the injectable to 3 times a week, after 3 to 4 months of treatment, and once the cultures are negative.
- Avoid loop diuretics because they increase eighth nerve toxicity.
- SM has less auditory toxicity than the other injectables, but has more vestibular toxicity.
- One retrospective study suggested that CM might be less toxic than AK.
- Resistance to SM is common and should be excluded before substituting it for another injectable.

Some patients must tolerate significant hearing loss in order to achieve a cure of their drug-resistant TB. The decision to continue therapy with an injectable when significant hearing loss occurs should be discussed with the patient and with an expert in the management of drug-resistant TB.

## Nephrotoxicity

### Prevention and monitoring

All of the aminoglycosides and capreomycin can cause nephrotoxicity. Ongoing assessment of renal function is important.

- Perform a 24-hour creatinine clearance at baseline if there are any concerns about renal function abnormality and monitor the serum creatinine weekly for the first several weeks, and then at least monthly.
- Encourage adequate hydration.
- Check drug levels.
  - The authors have obtained excellent therapeutic benefits while limiting toxicity by adjusting the dose to target peak levels of approximately 25 mcg/mL at 1 hour after intravenous administration or 2 hours after intramuscular injection.
  - 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.
- For patients with creatinine clearance less than 30 mL/min or those receiving hemodialysis, 12-15 mg/kg 2 to 3 times per week is recommended. Some experts would recommend considering 3 times per week dosing for patients with creatinine clearance of 50-70 mL/min, and twice-weekly dosing if less than 50 mL/min. (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 5, Medication Fact Sheets, and Chapter 3, Laboratory, for more details. A trough concentration before the next dose should be less than 5 mcg/mL. Decreasing the dose to achieve concentrations of less than 20 mcg/mL may not be effective.**

For decreased renal function that develops during treatment:

- If there is a decrease in renal function, repeat a 24-hour creatinine clearance.
- 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 patient is taking and adjust dose and/or dosing interval if needed. If the clearance is less than 30 mL/minute, adjust the doses of EMB, PZA, some fluoroquinolones, CS, all of the aminoglycosides, and CM.
- **For a creatinine clearance between 50 and 70 mL/min, the patient may tolerate 3-times-a-week aminoglycoside dosing at 12 to 15 mg/kg.**
- **For a creatinine clearance between 30 and 50 mL/min, twice-weekly aminoglycoside dosing at 12 mg/kg should be tried.**

- **Monitor peak and trough drug concentrations.**

It is especially important that a therapeutic peak be obtained and that trough concentrations be less than 5 mcg/mL before another dose of the drug is given.

- Follow renal function carefully.

## Electrolyte loss

All of the aminoglycosides and CM can cause electrolyte disturbances due to renal tubular wasting of potassium, magnesium, and calcium salts. These effects are most pronounced with CM. Chloride and hydrogen losses may also occur with resulting alkalosis. A defect in renal tubular resorption of chloride may be caused by these drugs. 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 caused by hypoalbuminemia. If the calcium is low, check albumin and free calcium to obtain the corrected value.
- Hypomagnesemia, if present, must be treated in order to correct hypocalcemia and hypokalemia.

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

- Perform an electrocardiogram.
- Hold medications that may contribute to prolongation of the QT interval (fluoroquinolones, CFZ, BDQ). See **Miscellaneous adverse reactions: QT interval prolongation**.
- Hold medications (digoxin, tricyclic antidepressants) that may precipitate arrhythmias. Consider change of CM to AK, as CM has been associated with more severe electrolyte losses.

## Ophthalmic toxicity

### Prevention and monitoring

The most common drug causing toxicity to the optic nerve is **EMB**. Although there are case reports and small series of patients who have developed sudden severe, irreversible optic nerve toxicity, most experts believe that EMB doses of 15 mg/kg given for less than 2 months are rarely associated with toxic changes to the optic nerve. Patients receiving prolonged or high-dose EMB are at greater risk of optic nerve toxicity. High-dose EMB (25 mg/kg) generally should not be used for more than 2 months. The dosing interval of EMB should be adjusted if the creatinine clearance is <50 mL/min to minimize ocular toxicity.

LZD produces a toxic optic neuropathy that is usually reversible. If no other reasonable options exist, restarting LZD at a lower dose (300 mg) has been successfully used without recurrence in one published 2012 study from Korea.

ETA and INH are also rare causes of optic nerve toxicity.

CFZ toxicity produces a bull's-eye pigmentary maculopathy and generalized retinal degeneration.

Visual loss due to RFB is part of a pan-uveitis that is reversible with RFB dosage adjustment.

### When using any of these drugs:

- Conduct baseline assessment of visual acuity (Snelling chart) and of color discrimination (Ishihara plates) at the start of treatment.
- Conduct monthly testing of visual acuity and color discrimination during treatment.
- Educate patients to report any change in visual acuity or red-green color discrimination, scotomata, change in visual fields, erythema, or eye pain.
- 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 exists, immediately discontinue the likely offending medication and refer the patient to an ophthalmologist.** RFB is an exception to this rule and may often be continued, especially 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.
- Refer the patient 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 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. Patients typically present with erythematous, painful eyes, and blurring of vision.

- Hold RFB until symptoms have resolved and then reinstitute at a lower dose. A lower dose is usually needed with some drugs that cause decreased clearance of the RFB, i.e., protease inhibitors, azoles, and macrolides. If the dose is lowered ensure it is still therapeutic if the drug is depended on for treatment.
- Consult an ophthalmologist.
- Consider other etiologies, especially in HIV-positive individuals; exclude bacterial and viral infection.
- Use topical steroid drops if ocular infection is ruled out.

Some patients may improve even when RFB treatment is continued. If recurring uveitis is a problem, stop RFB.

# 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 drug-resistant TB patients. One or more of the following drugs may be implicated: **PZA, fluoroquinolones, RFB, INH, ETA, and BDQ**. Electrolyte disturbances associated with the aminoglycosides and CM may also cause muscle pain and cramping. Thyroid dysfunctions may also contribute.

- Do not discontinue medications.
- NSAIDs are usually helpful. Monitor renal function more closely when using higher doses of NSAIDs; use caution in patients 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 ibuprofen) 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, mostly commonly involving the Achilles tendon, has been reported with **fluoroquinolone use**. Rupture is more common when new physical activities are undertaken and in older patients, diabetics, and patients on steroids.

When tendon inflammation is **mild**:

- Administer nonsteroidal anti-inflammatory agents.
- Rest the involved joint and avoid any strenuous activity.
- Evaluate the fluoroquinolone dose and reduce if possible. Serum drug concentrations may help to direct fluoroquinolone therapy.

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 patient of the risk of tendon rupture and the risk of treatment failure. Carefully try to continue the fluoroquinolone.

# 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. **BDQ** guidelines instruct clinicians to monitor for hypothyroidism, but clear causation by the drug has not been documented.

- Assess baseline thyroid function prior to start of these medications and correct if needed. Assess thyroid function every 1 to 2 months unless clinical assessment indicates the need to evaluate sooner. 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 synthroid daily.**
  - **Young healthy adults can be started on 75 to 100 mcg of synthroid daily.**
  - **Older patients should begin treatment with 50 mcg daily.**
  - **Patients with significant cardiovascular disease should start at 25 mcg daily.**
- 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 offending medication is stopped.

- **Adjust thyroid hormone replacement until the patient's TSH is within the normal range.**

- Increase thyroid hormone slowly in patients with significant cardiovascular disease.

## QT interval prolongation

During clinical trials, treatment with **BDQ** resulted in prolongation of the QT interval on the electrocardiogram (ECG). QT prolongation was found to develop within the first week of treatment and may persist several months even after drug discontinuation. Despite its association with QT prolongation, there have been no reported cases of *torsade de pointes*.

Monitoring of ECG and serum electrolytes is recommended before and during therapy with **BDQ** (with need for continued ECG monitoring until QT normalizes if prolongation persists after drug discontinuation). Potassium and magnesium should be maintained in the normal range with electrolyte repletion. The fluoroquinolones, especially **MXF**, can also result in prolongation of the QT interval. Guidelines issued by the CDC recommend that ECG be monitored weekly in patients who take **BDQ** along with other medications that may prolong the QT interval. There are no consensus guidelines on the concomitant use of **BDQ**, along with **MXF** and/or **CFZ**.

**Delamanid (DLM)**, although not yet approved in the United States, is also associated with QT prolongation.

## Metallic taste

**Metallic taste** is reported as an adverse reaction in patients taking **ETA** and **clarithromycin (CLR)**. Fluoroquinolones may also cause changes in taste. Encourage the patient 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 male patients. **Galactorrhea** has also been reported. Encourage patients 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 also is more likely to occur in diabetics. 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.

## 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**. These were documented by dechallenge and 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 diabetic patients. **Gatifloxacin (GFX)** (no longer available in the United States) has been most frequently implicated, but **MFX** and **LFX** may also cause dysglycemia.

## Summary

- Adverse reactions and toxicity should be anticipated with any treatment course for drug-resistant TB. Patients must be well-informed so that they will know what to expect and can be partners in their therapy.
- Close attention to toxicity and reports of discomfort are essential in maintaining the patient's good will and cooperation with the regimen.
- In many cases, some toxicity will have to be tolerated (although it should be treated and minimized). In many cases, offending drugs crucial to the regimen cannot be permanently discontinued; patients and staff need to understand that the treatment goal to achieve a cure might fail if an aggressive multidrug regimen is not maintained.
- Common side effects include:
  - **Gastrointestinal** (nausea, vomiting, diarrhea, abdominal pain, anorexia, taste perturbation, and hepatotoxicity)
  - **Dermatologic reactions** (rashes, flushing, phototoxicity, alopecia, superficial fungal infections, and hypersensitivity)
  - **Systemic hypersensitivity reactions**
  - **Hematologic abnormalities** (leukopenia, thrombocytopenia, anemia, red cell aplasia, coagulation abnormalities, and eosinophilia)
  - **Neurotoxicity** (peripheral neuropathy, CNS toxicity—depression, psychosis, seizures, and suicidal ideation)
  - **Ototoxicity** (hearing loss and vestibular disturbance)
  - **Ophthalmic toxicity** (visual loss, loss of color discrimination, uveitis, retrobulbar neuritis)
  - **Nephrotoxicity** (renal impairment, electrolyte loss)
  - **Musculoskeletal** (myalgias, arthralgias, tendonitis, and tendon rupture)
  - **Endocrine** (hypothyroidism, gynecomastia)

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