Adverse Reactions

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Adverse reactions and toxicity accompany essentially all treatment courses for drug-resistant TB.

Introduction

Treatment of drug-resistant tuberculosis (TB) involves 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 because of fear of a reaction. Even some elderly or very ill patients will readily tolerate medications. By contrast, others may have serious problems tolerating relatively simple regimens.

Patients should be well-informed and recruited as partners in 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 stress that having enough effective drugs in the treatment is essential to achieving a cure. While side effects 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.

Pay close attention to the reported side effects of each patient. Most patients will be willing to continue medication despite symptoms when they understand the benefit of the medication, know that many of these symptoms improve after the first several weeks, and 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, a drug dose should not be reduced unless it can be done without compromising its activity in the regimen. In some cases, minor drug reactions and discomfort may persist and will have to be tolerated for the sake of the success of the regimen. In some instances, very serious adverse events will need to be considered as necessary in order to save a life. For example, some patients with extensive 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 die of TB.
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 are equally troubling to some patients. Anorexia from nausea, vomiting, and/or the metallic taste caused by ethionamide can prevent weight gain or even cause worrisome weight loss. Pregnancy should be considered as the possible etiology of nausea and vomiting, especially if the symptoms occur after a period of initial tolerance. All female patients with multidrug-resistant TB (MDR-TB) should strongly consider contraception/pregnancy avoidance. Many providers do monthly laboratory screening to detect pregnancy early. When symptoms consistent with possible hepatotoxicity occur, drug-induced hepatitis should be considered, and liver enzymes and a total bilirubin checked.

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

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 the patient 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.

The following are specific interventions that can be attempted, depending on the drug:
- If the drug suspected of causing the symptoms is ethionamide or para-aminosalicylate (PAS), decrease the dose (ethionamide 250 mg, PAS 2 to 4 grams) to see if the lower dose is better tolerated. Advise the patient that this is a test to determine which drug is causing side effects and that the drug dose will be increased back to therapeutic dose in a manner that will be 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 ethionamide better in the evening (ethionamide 250 mg in a.m., 500 mg at bedtime; or may only tolerate 500 mg at bedtime). The goal should be to increase the ethionamide dose to at least 500 mg daily and the PAS dose to at least 6 to 8 grams daily.
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 (adult doses):

- **Promethazine** (Phenergen) 12.5 to 25 mg PO, IV, or PRN 30 minutes before the dose and every 6 hours as needed
- **Metoclopramide** (Reglan) 10 to 20 mg PO or IV every 4 to 6 hours as needed
- **Ondansetron** (Zofran) 8 mg PO 30 minutes before the dose and again 8 hours after the dose; for refractory nausea 24 mg 30 minutes before the dose can be tried

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 to separate the responsible medication from other drugs by several hours or give it before bedtime to allow most of the adverse effects to occur during sleep.
- This is relatively easy if 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 of medications or a dose later in the day. This can be problematic either way. If the medication is taken along with others and all medications are vomited, nothing is gained; alternatively, if the medication is essential to the regimen, even the most compliant patients may have difficulty taking a medication that predictably makes them feel bad.

- Give a light snack (crackers or toast, tea or soda) before medications.
- Space the medications out during the day to lessen the pill burden.
- Treat gastritis or acid reflux. Proton pump inhibitors or H2-receptor blockers may be helpful in many patients. Use of a drug such as sucralfate interferes with absorption of fluoroquinolones if used within 2 hours of the dose.
- Minimize use of nonsteroidal anti-inflammatory drugs (NSAIDs). This may be difficult if the patient also has arthralgias and myalgias from medications. Try acetaminophen, although it has been reported to increase isoniazid (INH) hepatotoxicity.
- Diagnose and treat co-existing *Helicobacter pylori* infections.
- Encourage hydration. Sports drinks such as Gatorade or PowerAde may be helpful as they also replace electrolytes. However, the glucose content of these drinks would be 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.

Eliminate (or at least try to minimize) alcohol consumption to lessen GI irritation and the risk of hepatotoxicity.
• Consider hospitalization with better access to antiemetic therapy, IV hydration, and spacing of medications, especially before a regimen is abandoned.
• In most instances, treatment with less than 4 active drugs to which the patient is susceptible should not be given.
• Consultation with an expert is especially important in this situation.

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 3, “Treatment.”

• Fluoroquinolones can also cause loose stools or diarrhea, along with increased flatulence. This can improve, 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 is a key drug in the treatment regimen.

If the diarrhea is severe, other etiologies may include:

• *C. difficile* colitis (especially if broad spectrum antibiotics used; e.g., fluoroquinolones)
• Other infectious diarrheas
• Parasitic disease
• Lactose intolerance, especially if patient 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 medication should be based on the importance of the drug in the treatment regimen and the availability of other substitute agents.
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 ALT or SGPT 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 (SGPT) is more specific for hepatocellular injury than the AST (SGOT). Elevations in the AST may indicate abnormalities in the muscle, heart, or kidney. If the ALT is elevated more than the AST, this is consistent with liver inflammation. When the AST is elevated more than the ALT, the possibility of alcohol-related elevation of the transaminase should be considered.

- If elevated liver function tests (LFTs) are detected, in addition to 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, consider repeating liver enzymes again to exclude hepatotoxicity. If the bilirubin is increased but the hepatocellular enzymes are only mildly elevated, this could still represent significant drug-induced liver injury. An evaluation for causes of direct and indirect hyperbilirubinemia should be done, and if the bilirubin is > 3.0 mg/dl, generally, hepatotoxic medications should be stopped.

- If the enzymes are more than 3 times the upper limit of normal, 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, levofloxacin, or cycloserine), then these can be continued. If not, then all anti-tuberculosis medications should be held.

- Monitor the LFTs weekly.

- When liver enzymes fall to less than twice normal (some experts prefer to wait until the enzyme levels normalize or return to baseline), the remaining potentially hepatotoxic medications should be reintroduced one at a time. If other non-hepatotoxic medications were also held, they should be restarted along with the first possibly hepatotoxic drug. Carefully observe for clinical reactions and repeat liver enzymes twice weekly until the medication has been taken for at least a week and enzymes 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 1 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-infected individuals treated with first-line anti-tuberculosis drugs have had an increased incidence of hepatitis in some studies. Several reports of HIV-infected persons with hepatitis C noted hepatotoxicity in over 20% of cases. Antiretroviral therapy (ART)
may be associated with drug-induced hepatitis, with the incidence depending on the individual drugs utilized. 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.

**Dermatologic and Hypersensitivity Reactions**

**Maculopapular Rash and Pruritus**

Maculopapular rash and pruritus are common early side effects. 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.**

- 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 new 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 serious problem with clofazimine.
- Hypothyroidism.
- Acneiform lesions may flare with the use of INH, ethionamide, and clofazimine. This will usually resolve after several months, often with improvement in the patient's acne. Standard topical antibiotic 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 rifampin (RIF) or pyrazinamide (PZA). It is usually mild and resolves in time 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, plus possible hot flashes, palpitation, or headache 2 to 3 hours after consuming tyramine-containing foods (cheese, salami, red wine) or certain fish (tuna). **Advise patients not to ingest foods that precipitate the reaction while they are receiving INH.**

### Phototoxicity

Warn patients about the potential for phototoxicity if they are taking PZA, clofazimine, or fluoroquinolones. Caution patients to limit sun exposure and to use sunscreens. This is especially important with clofazimine because sun exposure markedly increases the hyperpigmentation that occurs with this medication. Phototoxicity may occur for prolonged periods even after the causative drug is stopped.

Pseudojaundice (brownish discoloration of the skin) has been reported due to rifabutin. The sclera is clear and the bilirubin and other liver functions are normal.

### 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 may 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, and cycloserine have all been identified as causing these lesions.

### Hives, Urticaria

Hives and urticaria may be caused by nearly any drug in the regimen. They more commonly are due to INH, RIF, PZA, ethionamide, fluoroquinolones, and EMB.
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 one at a time.** 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, a desensitization attempt might be made. 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.

**TABLE 1.**

**Suggested Drug Rechallenge Doses Following Non-anaphylactic Allergic Reaction***

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose – Day 1</th>
<th>Dose – Day 2</th>
<th>Dose – Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>50 mg</td>
<td>300 mg</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>75 mg</td>
<td>300 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>PZA</td>
<td>250 mg</td>
<td>1 gram</td>
<td>full dose</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>125 mg</td>
<td>375 mg</td>
<td>500–750 mg</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>125 mg</td>
<td>250 mg</td>
<td>500–750 mg</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>100 mg</td>
<td>500 mg</td>
<td>full dose</td>
</tr>
<tr>
<td>PAS</td>
<td>1 gram</td>
<td>4 gram</td>
<td>6–8 grams</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>125 mg</td>
<td>500 mg</td>
<td>full dose</td>
</tr>
</tbody>
</table>

*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:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose – Day 1</th>
<th>Dose – Day 2</th>
<th>Dose – Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>125 mg</td>
<td>500 mg</td>
<td>full dose</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>125 mg</td>
<td>500 mg</td>
<td>full dose</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>50 mg</td>
<td>200–250 mg</td>
<td>full dose</td>
</tr>
</tbody>
</table>

* Philadelphia TB Program 1998

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.

**If the initial reaction was severe, use 1/10th of the Day 1 dose listed in Table 1 and then increase carefully if tolerated. Give the drugs in a setting where a healthcare provider can respond to any reaction.”
Implement these protocols only in a hospital or in a clinical area with the ability to monitor and respond to possible anaphylaxis, and when the drug is determined essential to success of therapy. Because isoniazid and rifampin are such important drugs, desensitization is most commonly attempted with these 2 medications.

Steroid therapy may be 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 and/or mucous membranes as occurs with Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).**

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### TABLE 2: Oral Desensitization for Isoniazid, Rifampin, and Ethambutol

<table>
<thead>
<tr>
<th>Time from start (hour:minute)</th>
<th>Dose of INH* (mg)</th>
<th>Dose of RIF** (mg)</th>
<th>Dose of EMB** (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:00</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
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<tr>
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<td>8:30</td>
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<td>17:30</td>
<td>150 bid x 3 days</td>
<td>300 bid x 3 days</td>
<td>400 tid x 3 days</td>
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</tbody>
</table>

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* Holland 1990
** Matz 1994
**Hematologic Abnormalities**

Table 3 summarizes potential hematologic abnormalities associated with TB medications.

**TABLE 3.**

Hematologic Abnormalities Associated with Anti-Tuberculosis Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Amikacin</th>
<th>Amox/clav</th>
<th>Capreomycin</th>
<th>Clofazimine</th>
<th>Cycloserine</th>
<th>Ethambutol</th>
<th>Ethionamide</th>
<th>Imipenem</th>
<th>INH</th>
<th>Kanamycin</th>
<th>Levofloxacin</th>
<th>Linezolid</th>
<th>Moxifloxacin</th>
<th>PAS</th>
<th>Pyrazinamide</th>
<th>Rifabutin</th>
<th>Rifampin</th>
<th>Streptomycin</th>
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<tbody>
<tr>
<td>Aplastic anemia</td>
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Other etiologies of hematologic abnormalities should be concurrently sought.
Severe Drug Reactions

Anaphylaxis is rare but can occur. Anaphylaxis 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 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. **Do not include drugs identified as causing anaphylaxis in the treatment regimen; do not try to desensitize to these agents.**

Severe drug reactions may occur with any medication. Reactions associated with systemic toxicity—high fever, widely distributed urticaria, and bulla, along with mucous membrane involvement—are characteristic of SJS. When there is extensive sloughing of skin, TEN 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 of the diagnosis. INH, RIF, EMB, streptomycin, ofloxacin, and cycloserine have been reported as causative agents. **If a drug is identified as responsible for one of these reactions, it should never be used again.**

Hypersensitivity Syndrome

The drug-induced hypersensitivity syndrome has been described with several of the anti-tuberculosis medications. A dramatic drug rash is present along with significant systemic symptoms. **This syndrome is an idiosyncratic reaction characterized by the development of fever, rash, and internal organ involvement which develops within the first 1–2 months of therapy.** Fever, often the first manifestation, may be as high as 40 degrees centigrade. A variety of types of rashes have been noted, but a morbilliform rash is most common. This can become indurated after several days, with development of bullae and purpura. Facial swelling may occur, and some patients have mucosal lesions, but these are not as prominent as with SJS or TEN. Lymphadenopathy is a prominent finding and is present in up to 75% of patients. Biopsy usually shows benign lymphoid hyperplasia. Hepatitis is seen in more than half and is severe when the offending agent is not withdrawn. The overall mortality of this syndrome is 10%, but when hepatitis is present, mortality can be as high as 40%, with acute liver failure the most common cause of death. Eosinophilia is a prominent feature, and some patients have an atypical lymphocytosis.

Although first described with phenytoin use, hypersensitivity syndrome has been attributed to ethambutol, isoniazid, and rifampin.

A variety of other drugs has also been implicated, including sulfonamides, dapsone, minocycline, many of the antiepileptic agents, and allopurinol. Skin biopsy and liver biopsy may help to establish the diagnosis. The reaction occurs later than SJS or TEN, and these reactions are not characterized by significant organ involvement.
Steroid therapy is life-saving, and tapering may need to be slow and guided by recurrence of clinical and laboratory abnormalities. The presumed offending agent is usually withdrawn, and rechallenge can be associated with rapid recurrence of severe hepatitis. When the offending agent is unknown, careful reintroduction of medications thought not likely to be involved should be considered only when alternative therapy is not possible. High-dose steroids may be required if the responsible drug is re-introduced. Most experts would not recommend rechallenge once a drug is identified as the causative agent.

Rifampin Hypersensitivity Reactions

A variety of reactions have been reported with RIF therapy. One of these is a flu-like syndrome which 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 rifampin if they are changed back to daily therapy.

For most of the 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
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, sensory loss can occur. Ankle reflexes may be lost and weakness of dorsiflexion of the toes may be present. Symptoms may progress centrifugally 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, ethionamide, cycloserine, and linezolid. Fluoroquinolones and ethambutol have rarely been associated with the development of neuropathy.

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 to 150 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, ethionamide, cycloserine, or linezolid, but especially those taking ethionamide and/or cycloserine. Some experts prescribe 50 mg of pyridoxine for every 250 mg of cycloserine used. If symptoms develop or progress, doses of 150 to 200 mg may be tried. Caution should be exercised with individuals with end-stage renal disease, as pyridoxine may develop toxic levels in these cases and cause neurologic symptoms.

There are rare reports of neuropathy attributed to pyridoxine in doses of 200 mg or greater. Neuropathy associated with linezolid usually tends to occur after 4 months of therapy and is probably dose-related. Use of the 600 mg once-daily linezolid dosing may prolong the ability to use the drug compared to other infections that require a 600 mg twice-daily dose. Patients may have further progression of symptoms even when linezolid is discontinued. Limited information about the toxicity of long-term linezolid is available and patients should be watched carefully.

Additional interventions include:

- Correct vitamin and nutritional deficiencies.
- Address additional medical problems.
- Evaluate and correct electrolytes.
- Identify and change other medications that may cause peripheral neuropathy, if possible.
- Consider whether the dose of ethionamide or cycloserine can be reduced without compromising the regimen. Doses of aminoglycosides or fluoroquinolones should be reduced only if adequate serum concentrations will still be present. Monitor serum drug concentrations if doses are lowered.
- Physical therapy may be helpful but is often not available.
- NSAIDs or acetaminophen may be helpful.
• 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. Linezolid 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, and a complete blood count (CBC) and liver function should be routinely monitored in patients on this medication.

• Patients who fail to respond to a tricyclic may respond to gabapentin (Neurontin). 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 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. Decrease dosage with renal insufficiency.

• 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 should not lead to the discontinuation of a medication unless unusual circumstances are present.

• Give medication at a time of day to minimize the effects. Consult the patient as to timing of drugs.

• Analgesics or NSAIDs may help headache.

• Limiting caffeine intake in the evenings may improve sleep disturbances.

• Exercise may also be effective.

Depression

Depression can be relatively mild and managed with supportive attention from family and healthcare providers. Some level of situational depression is to be expected for most patients who deal with the difficulties of drug-resistant TB therapy.

• Assess and address underlying psycho/social issues.

• Assess patients for coexisting substance abuse and refer to counseling if appropriate.

• When depression is more significant, give a trial of antidepressant therapy. Consider psychiatric consultation. Tricyclic antidepressants and SSRIs should not be given to patients on linezolid.

• Question the patient regarding suicidal ideation any time depression is judged to be more than mild.

• Reduce the dose of cycloserine and ethionamide to 500 mg daily to see if depression is lessened.

Support from caregivers and family members and acceptance of the patient’s mood changes and irritability will make these side effects more tolerable.
If depression progresses or is not improved by a trial of antidepressant therapy, discontinue cycloserine and, possibly, ethionamide as well.

Cycloserine 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 cycloserine and ethionamide.

INH has been associated with depression, which has been reported as severe in several case reports. Withdrawal of the drug is associated with rapid recovery.

**Psychosis**

- If severe psychosis is present, hospitalize patient and put under 24-hour surveillance.
- Consider psychiatric consultation.
- Hold all medications that possibly contribute until the patient stabilizes.

**The most likely drugs to cause psychosis are cycloserine and fluoroquinolones; INH can occasionally be implicated.**

- Pyridoxine (150 mg) should be given if not already part of the treatment.
- Start antipsychotic therapy (haloperidol [Haldol] PO, IV, or IM 0.5 to 5 mg) at the earliest sign of psychosis.
- When symptoms resolve, the least likely medications that contributed to the symptoms should be reintroduced first, one at a time, with careful observation. If no alternative drug is available, cycloserine may be tried at low dose. Do not increase the dose to previous quantities without first checking a serum drug concentration. If any recurrence of psychotic behavior occurs, promptly and permanently discontinue cycloserine.
- When the patient has stabilized, all medications have been successfully restarted, and all symptoms have resolved, the antipsychotic drugs can be tapered 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 cycloserine 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 cycloserine 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 cycloserine
- Request psychiatric consultation
- Initiate antidepressant therapy
- Lower the dose of ethionamide to 500 mg daily until the patient is stable
- Check the serum drug concentration of the fluoroquinolone and lower the dose if the serum concentration is high
- Keep the patient in the hospital until the risk of suicide has passed
- If no improvement occurs after holding cycloserine, hold INH and/or ethionamide
Seizures

- Hospitalize patient.
- **Intravenous pyridoxine will stop seizures due to pyridoxine deficiency.**
- Hold cycloserine, fluoroquinolones, and INH and initiate anticonvulsant therapy (phenytoin, valproic acid). Monitor anti-epileptic drug levels as drug interactions and synergistic toxicity are possible.
- Increase pyridoxine to 150 to 200 mg daily.
- When seizures have resolved, restart medications one at a time. Cycloserine 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.
- Evaluate for other etiologies of seizures.
- Check serum electrolytes, calcium, and magnesium.
- A history of prior seizures is not an absolute contraindication to the use of cycloserine, fluoroquinolones, and INH. Do not include cycloserine 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).

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

Although linezolid alone is not potent enough to cause it, serotonin syndrome may occur when linezolid is given along with other medications that increase the serotonin level. This may be especially important in patients with MDR-TB because many require antidepressant medication or other psychotropic drugs. 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.

The 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 linezolid and an SSRI or tricyclic antidepressant. The half-lives of these drugs are prolonged, and if linezolid therapy is planned, these agents should be withdrawn at least two weeks prior to its use. The patient should be observed carefully; there are reports of serotonin syndrome occurring even two weeks after withdrawal of these agents.

Once serotonin syndrome is identified, linezolid 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 stopping linezolid, 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 benzodiazepines, lorazepam and cyproheptadine. Some patients need aggressive correction of their cardiorespiratory and thermal abnormalities.

Ototoxicity

All of the aminoglycosides and capreomycin are toxic to the eighth cranial nerve and can cause both vestibular and auditory toxicity. Transient giddiness and numbness, especially around the mouth, occur with streptomycin treatment. Medication can be continued. If the effects are particularly troublesome, consider a reduction in dose to alleviate the symptoms, if the treatment regimen is not compromised.

Vestibular Toxicity

- Observe the patient closely for tinnitus and unsteadiness.
- At least monthly, assess vestibular toxicity.
- **Fullness in the ears and intermittent ringing in the ears are early symptoms of vestibular toxicity. When these are reported, it is sometimes possible to change the dosing to 2 or 3 times a week and continue the injectable agent for another month or more.**
- 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 cycloserine, fluoroquinolones, ethionamide, INH, or linezolid. Prior to stopping the injectable agent, evaluate whether these and/or other medications are causing the symptoms. Stopping the injectable should be done after carefully excluding other causes of the symptoms. Other drugs or all drugs can be held for several days to see if the symptoms improve. Symptoms of vestibular toxicity generally do not improve with holding medication.
• 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 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 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 loss occurs in nearly all patients treated for drug-resistant TB. High-frequency loss usually occurs first. 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, when the cultures are negative.
• Avoid loop diuretics because they increase eighth nerve toxicity.
• Streptomycin has less auditory toxicity, but has more vestibular toxicity.
• Resistance to streptomycin 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 an expert in the management of drug-resistant TB and also with the patient.

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 feel that doses of 15 mg/kg given for less than 2 months are rarely associated with toxic changes to the optic nerve. Doses of EMB used to treat drug-resistant TB are frequently high (25 mg/kg), at least until culture conversion occurs, and EMB is continued for a period of up to 24 or more months. Ethionamide, linezolid, rifabutin, INH, and clofazimine are rare causes of ocular toxicity.

Clofazimine toxicity produces a bull’s-eye pigmentary maculopathy and generalized retinal degeneration.

Linezolid produces a toxic optic neuropathy that is sometimes reversible.

Visual loss due to rifabutin is part of a pan-uveitis that is reversible.
When using any of these drugs:

- Conduct baseline visual assessment with acuity testing (Snellen chart) and testing of color discrimination (Ishihara tests) 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.

**Avoid or adjust the EMB dose and dosing interval, and monitor concentrations when the creatinine clearance is less than 30 ml/minute.**

- Correct nutritional deficiencies; consider a multivitamin for individuals with malnutrition along with TB therapy (wait until they are tolerating TB therapy before starting the multivitamin; remember to dose 2 hours before or after fluoroquinolone drugs).

**Retrobulbar Neuritis**

- 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 linezolid, ethionamide, and clofazimine 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. However, some series report fairly abrupt vision loss that is permanent. **Whenever a question about visual toxicity exists, immediately discontinue the offending medication.** Rifabutin 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.

**Uveitis**

Rifabutin, especially in higher doses (or given along with medications that decrease clearance, i.e., protease inhibitors), can cause pan-uveitis. Patients typically present with erythematous, painful eyes, and blurring of vision.

- Hold rifabutin until symptoms have resolved and then reinstitute at a lower dose. A lower dose is needed if other drugs cause decreased clearance of the rifabutin, i.e., protease inhibitors
- Consult an ophthalmologist
- Consider other etiologies, especially in HIV-infected individuals; exclude bacterial and viral infection
- Use topical steroid drops if ocular infection is ruled out

Some patients may even improve with continued rifabutin therapy. If recurring uveitis is a problem, stop rifabutin.
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.
- For adults over 59 years of age, decrease the dose of the injectable drugs to 10 mg/kg (max dose 750 mg) and monitor drug concentrations.
- If baseline creatinine clearance is less than 70 ml/min, begin injectable therapy with a 3-times-a-week dosing regimen; if creatinine clearance is less than 50 ml/min, start twice weekly.
- Monitor serum drug concentrations and adjust the medication dose accordingly. See Chapter 4, “Medication Fact Sheets,” and Appendix 12, “Therapeutic Drug Monitoring,” 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 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, cycloserine, all of the aminoglycosides, and capreomycin.
- **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 35 and 50 ml/min, 2-times-a-week aminoglycoside dosing at 12 mg/kg should be tried.**
- Monitor peak and trough drug concentrations. It is especially important that trough concentrations be less than the critical value before another dose of the drug is given.
- Follow renal function carefully.

Electrolyte Loss

All of the aminoglycosides and capreomycin can cause electrolyte disturbances due to renal tubular wasting of potassium, magnesium, and calcium salts. These effects are most pronounced with capreomycin. 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.

- 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 the potassium is low, also check the calcium and magnesium.
• Hypocalcemia is most commonly caused by hypoalbuminemia. If the calcium is low, check albumin and free calcium.
• Hypomagnesemia, if present, must be treated in order to correct hypocalcemia.

For severe electrolyte abnormalities, hospitalize and monitor the patient.
• Perform an electrocardiogram.
• Hold medications contributing to prolongation of the QT interval (fluoroquinolones).
• Hold medications (digoxin, tricyclic antidepressants) that may precipitate arrhythmias.
• Consider change of capreomycin to amikacin.

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, rifabutin, INH, and ethionamide. Electrolyte disturbances associated with the aminoglycosides and capreomycin may also cause muscle pain and cramping. Hypothyroidism may also contribute.

• Do not discontinue medications.
• NSAIDs are usually helpful.
• If acute swelling, erythema, and warmth are present, evaluate for the presence of inflammatory diseases:
  • Aspirate joint for diagnosis if fluid is present
  • Evaluate for infection, gout, or autoimmune disease
  • Institute treatment (often indomethacin) if the diagnosis is gout
  • Consult with a rheumatologist
• Evaluate for hypothyroidism or hyperthyroidism.
• Draw serum electrolytes, calcium, and magnesium. Correct deficiencies.

Tendonitis and Tendon Rupture

Tendon rupture has been reported with fluoroquinolone use and is more likely when new physical activities are undertaken and is more common in older patients and diabetics.

When significant inflammation of tendons or tendon sheaths occurs:
• Fluoroquinolones should generally be stopped.
• Administer nonsteroidal anti-inflammatory agents.
• Rest the joint.
• 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.
  • **Evaluate the fluoroquinolone dose and reduce if possible.** Serum drug concentrations may help to direct therapy with the fluoroquinolone.
  • **Rest the involved joint and avoid any strenuous activity.**

When tendon inflammation is mild:

• Administer nonsteroidal anti-inflammatory agents and rest the joint.
• Evaluate the fluoroquinolone dose and reduce if possible. Serum drug concentrations may help to direct fluoroquinolone therapy.
• If symptoms progress, stop the fluoroquinolone therapy unless doing so is likely to cause treatment failure.

### Miscellaneous Adverse Reactions

#### Hypothyroidism

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

• Assess baseline thyroid function prior to start of these medications and correct if needed. Assess thyroid function every 3 months unless clinical assessment indicates the need to evaluate sooner. Conduct monthly clinical assessments for hypothyroidism. Clinical assessments may be a better indicator of thyroid function than laboratory values.
• When thyroid stimulating hormone (TSH) begins to increase, evaluate for clinical evidence of hypothyroidism. Begin to monitor more frequently.
• When TSH rises to 1.5 to 2 times above 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 thyroid hormone replacement until the patient’s TSH is within the normal range.**
  • Increase thyroid hormone slowly in patients with significant cardiovascular disease
  • When TB treatment is complete, stop thyroid hormone replacement; the thyroid gland will now be able to respond to endocrine stimulation with release of thyroid hormone.
Metallic Taste

Metallic taste is reported as an adverse reaction in patients taking ethionamide and clarithromycin. 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 ethionamide 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 ethionamide. 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.

Superficial Fungal Infection

Vaginal or penile candidiasis may occur. This is most common with fluoroquinolone 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. Exclude other diseases if response to treatment is not prompt.
Summary

- Adverse reactions and toxicity accompany essentially all treatment courses 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 cannot be permanently discontinued; patients and staff need to understand that the treatment regimen would be compromised without the inclusion of many medications.

- 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)

References


