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REVIEW

Common Adverse Reactions and Management Strategies of First-Line Anti-Tuberculosis Drugs

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Abstract: This review synthesizes evidence from recent clinical and mechanistic studies published between 2015 and 2024 to provide updated insights into the prevention and management of adverse drug reactions (ADRs) associated with first-line anti-tuberculosis drugs (ATDs)—namely isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB)—which are essential for tuberculosis (TB) treatment but frequently cause significant ADRs that threaten therapeutic success. We examine four major toxicities: hepatotoxicity (primarily from INH and RIF, mediated by oxidative stress, mitochondrial dysfunction, and cytochrome P450 induction); peripheral neuropathy (driven by INH-induced pyridoxine depletion and EMB-related copper chelation leading to optic and axonal damage); central nervous system (CNS) toxicity (notably INH-induced seizures due to GABAergic disruption); and myelosuppression (mainly RIF- or PZA-related, involving oxidative injury to hematopoietic stem cells and impaired DNA synthesis). Key risk factors include advanced age, malnutrition, pre-existing organ dysfunction, and pharmacogenetic variations (eg, NAT2 acetylator status). Management strategies emphasize protocol-driven monitoring—including baseline and serial liver function tests (LFTs), complete blood counts (CBC), neurologic exams, and monthly visual assessments for EMB—and graded interventions based on severity thresholds (eg, temporary discontinuation if ALT >3× upper limit of normal (ULN) with symptoms or >5× ULN asymptomatic), alongside targeted therapies such as pyridoxine for neuropathy and N-acetylcysteine for hepatotoxicity. Proactive measures, including pretreatment risk stratification, patient education, and multidisciplinary coordination, are critical to optimizing adherence and outcomes. Effective management of first-line anti-TB drug toxicity requires mechanism-informed monitoring, individualized interventions, and proactive patient education to maintain treatment adherence and improve global TB outcomes.

Keywords: anti-tuberculosis drugs, adverse reactions, hepatotoxicity, neurotoxicity

Introduction

Tuberculosis (TB) remains one of the world's deadliest infectious diseases, with millions of new cases reported annually and hundreds of thousands of deaths worldwide. The treatment of TB primarily relies on the administration of first-line anti-tuberculosis drugs (ATDs), which include isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB).[1] These medications are essential for curing TB and preventing its spread, but they can also induce a range of adverse reactions that affect patient tolerance and adherence to treatment regimens.

Adverse reactions to first-line ATDs can range from mild and transient symptoms to severe and potentially life-threatening conditions.[2] Globally, the incidence of ATD-induced hepatotoxicity ranges from 5% to 28%, with higher rates reported in Asian and African settings.[3] Neuropathy affects up to 10% of patients on isoniazid without pyridoxine supplementation, particularly in those with malnutrition or HIV co-infection. These toxicities not only compromise treatment adherence but also pose significant challenges in the management of multidrug-resistant TB, where regimen interruptions can lead to resistance amplification and poor outcomes.[4]

Adverse reactions to first-line ATDs can range from mild and transient symptoms to severe and potentially life-threatening conditions. Common adverse reactions include hepatotoxicity, peripheral neuropathy, central nervous system toxicity, and myelosuppression. Globally, the incidence of ATD-induced hepatotoxicity ranges from 5% to 28%, varying

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by region, age, and comorbidities.[5] Neuropathy rates with isoniazid monotherapy can reach up to 10% in high-risk populations, particularly in low-resource settings. The management of these adverse reactions is crucial for ensuring successful treatment outcomes while minimizing risks to patients.

This review examines the common adverse reactions associated with first-line ATDs, with a focus on hepatotoxicity, peripheral neuropathy, CNS toxicity, and myelosuppression, and outlines evidence-based strategies for their monitoring and management to guide for healthcare professionals treating of tuberculosis patients.

Understanding and effectively managing the adverse reactions to first-line ATDs is essential for optimizing patient care and improving treatment outcomes. By identifying risk factors, implementing appropriate monitoring strategies, and employing effective management techniques, healthcare providers can enhance patient adherence to treatment and reduce the likelihood of treatment interruptions or failures.

Hepatotoxicity

Hepatotoxicity is one of the most common adverse reactions associated with first-line ATDs, particularly with isoniazid, rifampicin, and pyrazinamide.[6] The liver is the primary organ responsible for metabolizing these drugs, making it vulnerable to drug-induced injury. Hepatotoxicity can range from mild, asymptomatic elevations in liver transaminases to severe forms such as hepatitis, liver failure, and even death in rare cases.

The clinical manifestations of hepatotoxicity can vary widely among patients. Some individuals may experience no symptoms at all, while others may present with nausea, vomiting, abdominal pain, fatigue, jaundice, or dark urine. Laboratory findings typically reveal elevated serum transaminases (aspartate aminotransferase and alanine aminotransferase), increased total bilirubin, and prolonged prothrombin time. In severe cases, patients may develop ascites, hepatic encephalopathy, or signs of hepatic decompensation.

Several risk factors can predispose individuals to drug-induced hepatotoxicity from ATDs. Age is a significant factor, with older adults being at higher risk. Studies have shown that approximately 40% of ADRs in the elderly involve liver function abnormalities.[7] Underlying liver disease, including hepatitis B or C infection, alcohol abuse, and non-alcoholic fatty liver disease, also increases vulnerability to hepatotoxicity. Genetic factors, such as polymorphisms in enzymes involved in drug metabolism, can affect individual susceptibility. Additionally, concomitant use of other hepatotoxic medications or certain herbal supplements can potentiate liver damage.

The mechanisms by which first-line ATDs induce hepatotoxicity involve multiple pathways. Rifampicin impairs bone marrow function via microenvironment disruption, with oxidative stress as a shared pathway.[8] Isoniazid can cause direct mitochondrial damage through the generation of reactive oxygen species and depletion of glutathione.[9] Pyrazinamide, particularly at high doses, can induce oxidative stress and inhibit mitochondrial function. These mechanisms ultimately lead to hepatocellular injury, inflammation, and, in severe cases, necrosis.

The management of ATD-induced hepatotoxicity requires a multifaceted approach. Temporary discontinuation of hepatotoxic drugs is recommended if ALT >3× the upper limit of normal (ULN) with symptoms (eg, jaundice, nausea, fatigue) or ALT >5× ULN even in the absence of symptoms.

In cases of confirmed isoniazid-induced hepatotoxicity, alternative agents such as ethionamide may be considered only after drug susceptibility testing confirms susceptibility and under expert supervision. Rifampicin-induced hepatotoxicity may necessitate switching to a rifabutin-based regimen, which is associated with less hepatotoxicity. In severe cases, discontinuation of the offending agent and institution of supportive care is required.[10]

Supportive measures for managing hepatotoxicity include the administration of antioxidants such as N-acetylcysteine, which can help mitigate oxidative stress. Antioxidants and other hepatoprotective agents may be used as adjunctive therapy, although their efficacy in preventing or treating ATD-induced hepatotoxicity requires further investigation. It is important to note that these agents should not be used as a rationale for continuing the administration of hepatotoxic ATDs without appropriate monitoring or consideration of alternative therapies.

Risk assessment and prevention are equally important components of managing hepatotoxicity. Patients at higher risk for hepatotoxicity should be identified and closely monitored. This includes older adults, individuals with pre-existing liver disease, and those with genetic predispositions. In some cases, dose adjustments may be necessary based on hepatic function, particularly for drugs known to be metabolized by the liver. Additionally, patient education about the signs and

symptoms of hepatotoxicity—such as jaundice, fatigue, nausea, and abdominal pain—and the importance of regular follow-up and liver function testing is crucial for early detection and timely intervention.

Collectively, hepatotoxicity represents a significant challenge in the management of tuberculosis treatment. By understanding the risk factors, implementing appropriate monitoring strategies, and employing effective management techniques, healthcare providers can minimize the risk of severe liver injury and optimize patient outcomes. Regular liver function monitoring, prompt recognition of hepatotoxicity, and timely intervention are essential components of effective tuberculosis care.

Peripheral Neuropathy

Peripheral neuropathy is a significant adverse reaction associated with first-line anti-tuberculosis drugs, particularly isoniazid and ethambutol. This condition involves damage to the peripheral nerves, leading to characteristic neurological symptoms that can significantly impact patient quality of life and treatment adherence.

Isoniazid-induced peripheral neuropathy is one of the most commonly reported neurological adverse reactions. The symptoms typically begin with a stocking-glove distribution, affecting the lower limbs first and potentially progressing to the upper limbs. Patients often describe numbness, tingling, burning sensations, and pain that may be worse at night. In severe cases, muscle weakness and wasting can occur, leading to significant functional impairment. The risk of developing isoniazid-induced neuropathy is dose-dependent, with higher cumulative doses associated with a greater likelihood of developing symptoms.[11] However, it is important to note that even at standard doses, neuropathy can occur, particularly in certain patient populations.

The pathophysiology of isoniazid-induced peripheral neuropathy involves several mechanisms. Isoniazid is known to interfere with vitamin B6 metabolism, either by directly competing with pyridoxal phosphate or by promoting its degradation. This leads to decreased levels of active vitamin B6, which is essential for neurotransmitter synthesis and myelin formation.[12] The resulting deficiency can cause axonal degeneration and demyelination in peripheral nerves. Isoniazid-induced neuropathy is primarily driven by vitamin B6 depletion. Oxidative stress contributes as a secondary mechanism. The cumulative effect of these mechanisms is a progressive neuropathy that can be disabling if not properly managed.

Ethambutol, another first-line anti-tuberculosis drug, is primarily associated with dose- and duration-dependent optic neuropathy, rather than peripheral neuropathy. The neurotoxic effects of ethambutol typically manifest as bilateral, painless visual disturbances, including blurred vision, decreased visual acuity, central scotoma, and impaired color vision —particularly red-green color discrimination.[13] These symptoms can progress to severe and often irreversible visual loss if not recognized and managed promptly. The mechanism of ethambutol-induced neuropathy appears to involve its interaction with mitochondrial function in sensory neurons. Ethambutol can chelate metals, particularly copper, leading to impaired mitochondrial function and reduced ATP synthesis.[14] This energy depletion can affect the transport of mitochondria from the cell body to the distal side of nerve axons, leading to axonal damage and neuronal dysfunction. The risk of ethambutol-induced neuropathy is influenced by daily dosage and renal function, with higher doses and renal impairment increasing the risk significantly.

Genetic susceptibility plays a critical role in isoniazid neurotoxicity. Individuals with the NAT2 slow acetylator phenotype exhibit reduced clearance of isoniazid, leading to higher drug exposure and increased risk of pyridoxine depletion and peripheral neuropathy. Pharmacogenetic testing for NAT2 status may help identify high-risk patients who would benefit from prophylactic pyridoxine or dose adjustment.

Management strategies for peripheral neuropathy induced by first-line ATDs should be initiated promptly upon recognition of symptoms. The primary approach involves supplementation with vitamin B6, particularly in cases of isoniazid-induced neuropathy. Pyridoxine (vitamin B6) at doses of 50–100 mg daily can help mitigate the neuropathy by counteracting the effects of isoniazid on vitamin B6 metabolism.[15] In some cases, higher doses up to 300 mg daily may be required for symptom resolution. However, it is important to note that excessive vitamin B6 can cause its own set of adverse effects, including sensory neuropathy, so dosing should be carefully monitored.

In addition to vitamin supplementation, dose reduction or temporary discontinuation of the offending agent may be necessary in cases of severe neuropathy. For isoniazid-induced neuropathy, reducing the dose or switching to an

alternative agent such as ethionamide or Amikacin may be considered.[16] For ethambutol-induced neuropathy, dose reduction based on renal function is often effective, with particular caution advised for elderly patients and those with renal impairment. The decision to continue, reduce, or discontinue the offending agent should be based on the severity of the neuropathy, the patient's clinical status, and the availability of alternative treatment options.

Supportive care measures can also be beneficial in managing symptoms of peripheral neuropathy. Antidepressant medications such as amitriptyline or duloxetine can be effective for neuropathic pain, particularly when pain is the predominant symptom.[17] Other medications such as gabapentin or pregabalin may also be useful for pain management. Physical therapy, including nerve gliding exercises and sensory retraining, can help maintain function and prevent disability. Patient education about the nature of the condition, expected course, and importance of adherence to treatment and monitoring is also crucial.

Preventive strategies are equally important in the management of peripheral neuropathy. Given the dose-related nature of isoniazid-induced neuropathy, initial dose adjustments should be based on body weight, age, and renal function to minimize the risk of toxicity. Furthermore, therapeutic drug monitoring (TDM) of serum isoniazid levels can provide critical insights into individual pharmacokinetic variability, particularly in slow or fast acetylators, allowing for more precise dose titration.[18] Maintaining drug concentrations within the therapeutic window helps maximize efficacy while reducing the likelihood of neurotoxicity. Regular monitoring for symptoms and signs of neuropathy during treatment—such as numbness, tingling, or burning sensations in the extremities—is essential for early detection and intervention. In high-risk patients, such as those with pre-existing neuropathy, diabetes, malnutrition, or alcohol use disorder, close clinical surveillance, pyridoxine (vitamin B6) supplementation, and consideration of alternative treatment regimens may be warranted.

Taken together, peripheral neuropathy represents a significant challenge in the management of tuberculosis treatment, particularly with isoniazid and ethambutol. Prompt recognition, appropriate management strategies including vitamin supplementation, dose adjustments, and supportive care, can help mitigate the impact of this adverse reaction. Regular monitoring and preventive measures are essential components of effective tuberculosis care to ensure optimal patient outcomes and treatment adherence. Mechanistic features of neurotoxicity are summarized in Table 1, and clinical management strategies are outlined in Table 2.

Central Nervous System Toxicity

Central nervous system (CNS) toxicity is a significant concern with first-line anti-tuberculosis drugs, particularly isoniazid, and can range from mild symptoms to severe neurological complications. This adverse reaction can significantly impact patient quality of life and treatment adherence, making proper recognition and management essential.

Isoniazid is most commonly associated with CNS toxicity. Seizures occur in approximately 1–2% of patients receiving high-dose isoniazid, particularly in those with underlying risk factors such as malnutrition, renal impairment, or slow acetylator status. Other anti-tuberculosis drugs can also contribute to neurological adverse effects, though less

Table 1 Mechanisms and Key Characteristics of INH- and EMB-Induced Neurotoxicity

Feature	INH	EMB
Mechanism of neurotoxicity	(1) Pyridoxal phosphate inhibition → impaired GABA/serotonin;[19] (2) Oxidative stress/mitochondrial dysfunction[20]	(1) Copper chelation → mitochondrial dysfunction;[21] (2) Impaired oxidative phosphorylation → ATP depletion[22]
Clinical manifestations	Symmetric distal sensory neuropathy[23]	Bilateral painless visual loss; red–green color vision loss[24]
Key risk factors	High cumulative dose; NAT2 slow acetylator; malnutrition/HIV/diabetes/advanced age[25]	Daily dose >15–20 mg/kg; renal impairment; prolonged duration; advanced age[26]
Key references	[19,22,24,27]	[20,21,23,25]

Abbreviations: INH, isoniazid; EMB, ethambutol.

Table 2 Clinical Management Strategies for INH- and EMB-Induced Neurotoxicity

Strategy	INH	EMB
Monitoring	(1) Baseline/periodic neurologic exams; (2) Assess for sensory symptoms[28]	(1) Monthly visual acuity and color vision testing; (2) Fundoscopy if symptomatic[29]
Prevention	Prophylactic pyridoxine: 25–50 mg/day in high-risk patients[30]	Dose adjustment if GFR <30 mL/min (eg, 10 mg/kg/day)[31]
Treatment interventions	(1) Pyridoxine 50–300 mg/day;[32] (2) Dose reduction or switch to ethionamide;[33] (3) Gabapentin or pregabalin for neuropathic pain[34]	(1) Immediate discontinuation if visual symptoms;[35] (2) Copper supplementation (controversial; limited evidence);[36] (3) No reversal agent; early detection critical
Key references	[28,30,32–34]	[29,31,35,36]

Abbreviations: INH, isoniazid; EMB, ethambutol.

frequently. The manifestations of isoniazid-induced CNS toxicity can vary widely, from mild symptoms such as headache and insomnia to more severe manifestations including seizures, encephalopathy, and even coma in extreme cases.[37] The risk of developing CNS toxicity is dose-related, with higher doses increasing the likelihood of adverse effects. Additionally, certain patient populations, such as those with pre-existing neurological conditions or those with impaired drug metabolism, may be at higher risk.

The pathophysiology of isoniazid-induced CNS toxicity primarily involves GABAergic system disruption due to vitamin B6 depletion, which lowers the seizure threshold.[38] In severe cases, accumulation of the drug or its metabolites in the brain may contribute to encephalopathy or coma. In some cases, isoniazid-induced CNS toxicity may be related to accumulation of the drug or its metabolites in the brain, particularly in patients with impaired drug elimination.

Management of isoniazid-induced CNS toxicity begins with prompt recognition of symptoms and appropriate dose reduction or discontinuation of the offending agent.[39] In cases of mild symptoms such as headache or insomnia, reducing the isoniazid dose and ensuring adequate vitamin B6 levels may be sufficient. Vitamin B6 supplementation at doses of 50–100 mg daily can help mitigate the CNS effects by counteracting the effects of isoniazid on vitamin B6 metabolism. Close monitoring of symptoms and adjustment of therapy based on response is essential.

In cases of isoniazid overdose, which can cause rapid-onset seizures and coma, immediate high-dose pyridoxine (vitamin B6) is lifesaving. The recommended dose is 1 gram of pyridoxine per gram of INH ingested, administered intravenously as soon as possible.[40] In acute settings where the ingested dose is unknown, an empiric dose of 5 g (or 70 mg/kg in children, up to 5 g) may be given.

In cases of more severe CNS toxicity, such as seizures or encephalopathy, immediate intervention is required. Discontinuation of isoniazid and institution of anticonvulsant therapy may be necessary. For seizures, benzodiazepines can be used for acute management, followed by phenytoin or another anticonvulsant for seizure prophylaxis.[41] Supportive measures, including maintenance of airway, breathing, and circulation, and correction of any underlying metabolic abnormalities, are also important components of management. In severe cases, hospitalization may be required for close monitoring and intensive care.

Once the acute symptoms have been managed and the patient has stabilized, consideration should be given to alternative anti-tuberculosis regimens. Depending on the severity of the CNS toxicity and the patient's clinical status, options may include dose reduction of isoniazid with close monitoring, substitution of isoniazid with another agent such as ethionamide or Amikacin, or modification of the overall treatment regimen.[42] The decision should be based on the individual patient's circumstances, the availability of alternative agents, and the potential for continued effectiveness against tuberculosis infection.

Preventive strategies are equally important in the management of isoniazid-induced CNS toxicity. Given the dose-related nature of this adverse reaction, appropriate dosing based on body weight, age, and renal function is crucial. Regular monitoring for symptoms of CNS toxicity during treatment can allow for early intervention. In high-risk

patients, such as those with pre-existing neurological conditions or those with impaired drug metabolism, close monitoring and consideration of alternative treatment regimens may be warranted.

Other first-line anti-tuberculosis drugs can also contribute to CNS toxicity, although to a lesser extent than isoniazid. Rifampicin can cause dizziness, vertigo, and less commonly, seizures. Ethambutol can cause dizziness and, in severe cases, a Wernicke's encephalopathy–like syndrome, possibly due to thiamine deficiency or mitochondrial dysfunction in thalamic nuclei.[43] Pyrazinamide can cause dizziness, vertigo, and ataxia.[44] Management of CNS toxicity from these agents generally involves dose reduction, discontinuation of the offending agent, and supportive care, with consideration of alternative treatment regimens as appropriate.

To summarize, CNS toxicity represents a significant challenge in the management of tuberculosis treatment, particularly with isoniazid. Prompt recognition, appropriate management strategies including dose adjustments, vitamin supplementation, and supportive care, can help mitigate the impact of this adverse reaction. Regular monitoring and preventive measures are essential components of effective tuberculosis care to ensure optimal patient outcomes and treatment adherence. A schematic overview of the key pathological mechanisms underlying major adverse reactions is provided in Figure 1.

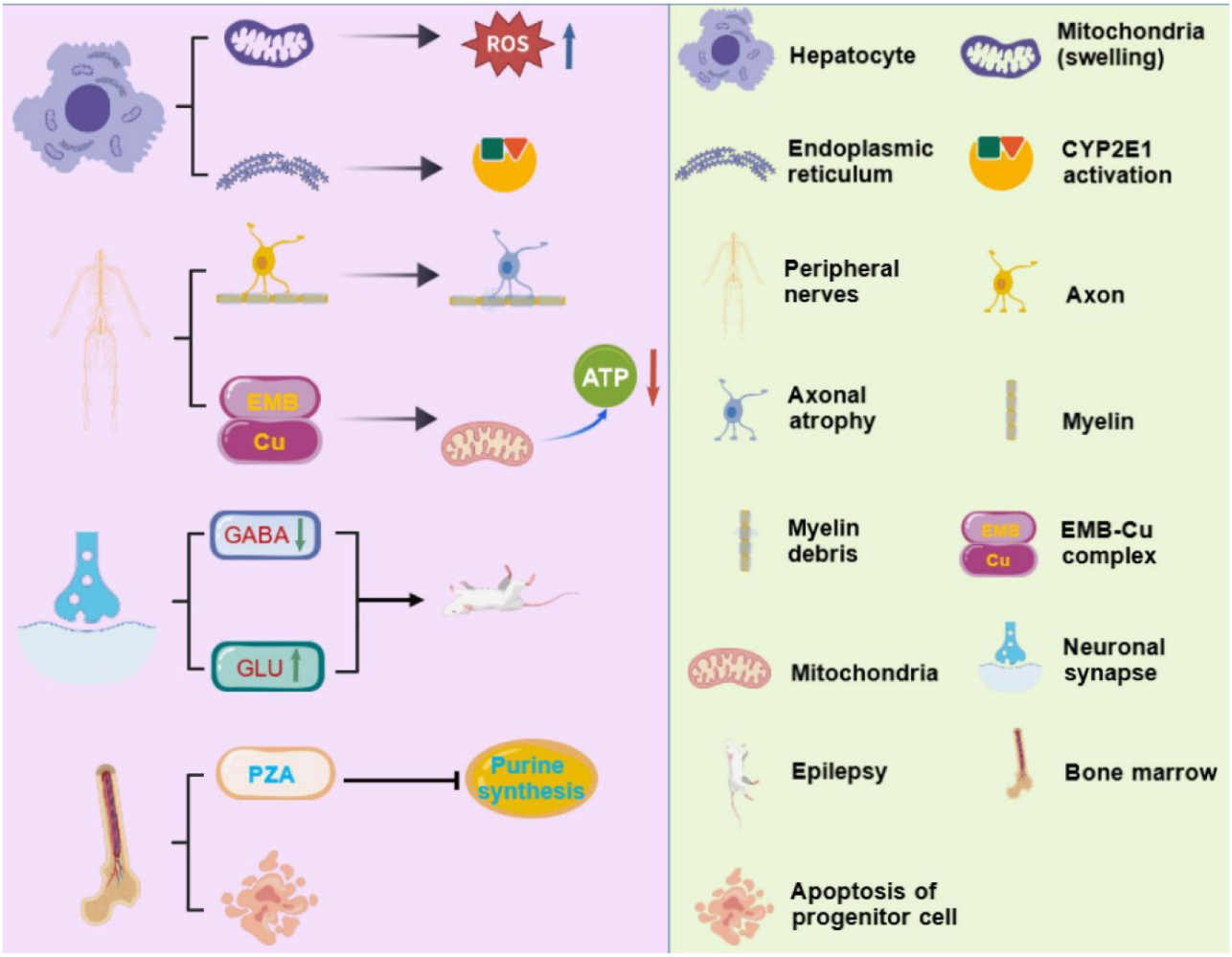

Figure 1 Mechanisms and targets of major adverse drug reactions induced by first-line anti-tuberculosis drugs. The left panel illustrates the core molecular mechanisms triggered by INH, RIF, PZA, and EMB, including ROS generation, CYP450 induction, mitochondrial dysfunction, vitamin B6 depletion, and copper chelation. The right panel depicts the corresponding tissue- and organ-level effects: hepatocyte injury (hepatotoxicity), axonal degeneration in peripheral nerves (neuropathy), neuronal hyperexcitability in the CNS (CNS toxicity), and apoptosis of hematopoietic progenitor cells (myelosuppression). Arrows indicate causal relationships between molecular events and clinical manifestations.

Abbreviations: INH, isoniazid; RIF, rifampicin; PZA, pyrazinamide; EMB, ethambutol; ROS, reactive oxygen species; CYP450, cytochrome P450; CNS, central nervous system.

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Myelosuppression

Myelosuppression, characterized by the suppression of bone marrow function leading to decreased production of blood cells, is a significant adverse reaction associated with first-line anti-tuberculosis drugs. Among these drugs, rifampicin and pyrazinamide have been most commonly implicated in causing myelosuppression, particularly in the form of neutropenia and, less commonly, thrombocytopenia and anemia.

Rifampicin-induced neutropenia is one of the most commonly reported forms of myelosuppression. The condition typically presents with a gradual decline in neutrophil counts, often without specific symptoms unless a superimposed infection occurs.[45] In severe cases, patients may develop fever, signs of infection, and, in extreme cases, sepsis or neutropenic enterocolitis. The risk of developing rifampicin-induced neutropenia appears to be dose-related, with higher doses associated with a greater likelihood of developing significant neutropenia. Additionally, certain patient populations, such as those with pre-existing hematological disorders or those receiving concomitant myelosuppressive agents, may be at higher risk.

The pathophysiology of anti-tuberculosis drug-induced myelosuppression involves several mechanisms. Rifampicin impairs bone marrow function via microenvironment disruption, with oxidative stress as a shared pathway. Additionally, rifampicin can directly affect the bone marrow microenvironment, impairing the proliferation and differentiation of hematopoietic progenitor cells.[46] Pyrazinamide can inhibit DNA synthesis in bone marrow cells, leading to reduced production of blood cells.[47] These mechanisms ultimately result in decreased production of neutrophils, platelets, and red blood cells, depending on the specific drug and individual susceptibility.

Management of myelosuppression induced by first-line ATDs should be initiated promptly upon recognition of significant blood count abnormalities. The primary approach involves close monitoring of complete blood counts, with particular attention to neutrophil counts for patients receiving rifampicin and other agents known to cause neutropenia. In cases of mild neutropenia (neutrophils $>1.0 \times 10^9$/L), continuation of therapy with close monitoring may be appropriate. However, in cases of severe neutropenia (neutrophils $<0.5 \times 10^9$/L), dose reduction or temporary discontinuation of the offending agent is typically required to prevent the risk of severe infections.

In some cases, growth factor support may be considered for management of severe neutropenia. Granulocyte colony-stimulating factor (G-CSF) can be used to stimulate neutrophil production in patients with severe neutropenia due to rifampicin. The decision to use G-CSF should be based on the severity of neutropenia, the patient's clinical status, and the availability of alternative treatment options.[48]

For pyrazinamide-induced myelosuppression, dose reduction based on renal function is often effective, with particular caution advised for elderly patients and those with renal impairment. The decision to continue, reduce, or discontinue the offending agent should be based on the severity of the myelosuppression, the patient's clinical status, and the availability of alternative treatment options.

Supportive care measures are also important in the management of myelosuppression. Close monitoring for signs of infection, prompt treatment of any identified infections, and general supportive care to maintain adequate nutrition and hydration are essential components of management. In cases of severe anemia, blood transfusion may be required to maintain adequate oxygen delivery to tissues. Similarly, in cases of severe thrombocytopenia, platelet transfusion may be necessary to prevent or manage bleeding complications.

Preventive strategies are equally important in the management of myelosuppression. Given the dose-related nature of this adverse reaction, appropriate dosing based on body weight, age, and renal function is crucial. Regular monitoring of complete blood counts during treatment can allow for early detection and intervention. In high-risk patients, such as those with pre-existing hematological disorders or those receiving concomitant myelosuppressive agents, close monitoring and consideration of alternative treatment regimens may be warranted.

In cases where myelosuppression is severe or persistent despite dose reduction, consideration should be given to alternative anti-tuberculosis regimens. Depending on the severity of the myelosuppression and the patient's clinical status, options may include dose reduction with close monitoring, substitution of the offending agent with another anti-tuberculosis drug, or modification of the overall treatment regimen. The decision should be based on the individual patient's circumstances, the availability of alternative agents, and the potential for continued effectiveness against

Table 3 Hematologic Adverse Reactions Associated with First-Line Anti-Tuberculosis Drugs

Drug	Hematologic Reaction	Reported Frequency	Key Management Strategies
Rifampicin	Neutropenia	~5–10% (higher with high-dose therapy)	Monitor CBC weekly; discontinue if neutrophils <0.5 × 10^9/L; consider G-CSF in febrile neutropenia[49]
Pyrazinamide	Thrombocytopenia	Rare (<1%)	Monitor platelet counts; discontinue if platelets <50 × 10^9/L; consider platelet transfusion if bleeding[50,51]
Isoniazid	Anemia	Uncommon (1–2%)	Monitor hemoglobin; evaluate for other causes; transfuse if Hb <7 g/dL[52]

Abbreviations: CBC, complete blood counts; G-CSF, granulocyte colony-stimulating factor.

tuberculosis infection. Table 3 summarizes the key hematologic adverse reactions observed with first-line anti-tuberculosis drugs, along with their estimated frequencies, monitoring recommendations, and management thresholds.

Overall, myelosuppression represents a significant challenge in the management of tuberculosis treatment, particularly with rifampicin and pyrazinamide. Prompt recognition, appropriate management strategies including dose adjustments, supportive care, and consideration of alternative treatment regimens, can help mitigate the impact of this adverse reaction. Regular monitoring and preventive measures are essential components of effective tuberculosis care to ensure optimal patient outcomes and treatment adherence.

This schematic diagram summarizes the key pathological mechanisms of four major adverse drug reactions caused by first-line anti-tuberculosis medications: (1) Hepatotoxicity (INH/RIF/PZA) mediated through mitochondrial damage, oxidative stress via ROS generation, and CYP450 enzyme induction; (2) Peripheral neuropathy (INH/EMB) involving vitamin B6 deficiency-induced axonal degeneration and EMB's copper-chelating effects on neuronal mitochondria; (3) CNS toxicity (INH) resulting from GABAergic system disruption and impaired vitamin B6 metabolism; and (4) Myelosuppression (RIF/PZA) caused by oxidative damage to hematopoietic stem cells and inhibition of DNA synthesis, with critical molecular pathways highlighted for each reaction type. This figure was created using templates and elements from Figdraw (www.Figdraw.com).

Management Strategies for Adverse Reactions

Monitoring

The management of adverse reactions to first-line anti-tuberculosis drugs begins with systematic and protocol-driven monitoring. A baseline assessment of liver function, renal function, and complete blood count should be performed before initiating therapy, followed by regular monitoring throughout the treatment course. The frequency of testing should be tailored to the specific drug and individual risk profile. Liver function tests are typically performed weekly or bi-weekly during the intensive phase and less frequently thereafter. Regular monitoring of liver function tests is essential throughout the treatment period. Baseline liver function tests should be performed before initiating ATD therapy.[53] For patients receiving ethambutol, monthly visual acuity and color vision assessments are recommended. Complete blood counts should be monitored periodically, especially in those on rifampicin or pyrazinamide. Therapeutic drug monitoring (TDM) of serum concentrations—particularly for isoniazid, rifampicin, and ethambutol—can further guide safe and effective dosing by ensuring drug levels remain within the therapeutic window.[54]

Dose Adjustment and Regimen Modification

When mild to moderate adverse reactions occur, dose reduction of the offending agent may allow therapy to continue without interruption. For instance, in cases of mild hepatotoxicity or isoniazid-induced neuropathy, reducing the dose while closely monitoring clinical and laboratory parameters can be effective.[55] Similarly, ethambutol dosing should be adjusted based on renal function to prevent optic neuropathy, and pyrazinamide doses may require modification in patients with impaired clearance. However, dose reduction alone risks subtherapeutic exposure, which may compromise efficacy and foster drug resistance. Therefore, therapeutic

drug monitoring (TDM) of serum concentrations is strongly recommended to guide dose individualization.[56,57] Recent evidence supports that TDM-guided regimens significantly improve treatment outcomes in high-risk patients, including those with malnutrition, HIV, or suspected non-adherence.[58] In severe or persistent cases, temporary discontinuation or substitution with alternative agents—such as ethionamide for isoniazid or rifabutin for rifampicin—may be necessary, always considering drug susceptibility and clinical context.[55]

Supportive and Targeted Therapies

Supportive care plays a critical role in mitigating symptoms and preventing complications. For hepatotoxicity, antioxidants such as N-acetylcysteine may help counteract oxidative stress, although their use should not justify continuing hepatotoxic regimens without risk reassessment. Vitamin B6 supplementation is standard for preventing and treating isoniazid-induced neuropathy and should be administered prophylactically in high-risk patients.[15] In cases of central nervous system toxicity, anticonvulsants such as benzodiazepines or phenytoin may be required for seizure control.[41] For myelosuppression, granulocyte colony-stimulating factor can be considered in severe neutropenia, particularly when infection is present.[48] General measures—including adequate nutrition, hydration, and rest—also support recovery and overall treatment tolerance.

Patient Education and Adherence Support

Patient education is fundamental to early detection and effective management of adverse reactions. Patients should be informed about the common signs and symptoms of drug toxicity—such as jaundice, numbness, blurred vision, or unexplained fatigue—and instructed to report them promptly. Emphasizing the importance of regular follow-up and laboratory monitoring can enhance vigilance. Additionally, addressing psychosocial barriers to adherence, including stigma, complex dosing schedules, or fear of side effects, is crucial. Counseling and multidisciplinary support can improve treatment continuity and outcomes, particularly in vulnerable populations.[54]

Risk Stratification and Interdisciplinary Coordination

Individualized management requires proactive risk assessment. Older adults, patients with pre-existing liver or kidney disease, those with malnutrition, and individuals with pharmacogenetic variants—such as NAT2 slow acetylator status—are at heightened risk for specific toxicities.[27,59] Identifying these patients early enables intensified monitoring or preventive strategies, such as visual screening. A thorough medication review should also be conducted to identify potential drug–drug or drug–herb interactions that may exacerbate toxicity. Close collaboration among infectious disease specialists, pharmacists, hepatologists, neurologists, and primary care providers ensures comprehensive and coordinated care. Documentation of all adverse events, interventions, and outcomes further supports clinical decision-making and contributes to pharmacovigilance efforts.

Conclusion

The management of adverse reactions associated with first-line anti-tuberculosis drugs (ATDs) remains a critical challenge in tuberculosis (TB) treatment, requiring a balanced approach to ensure both therapeutic efficacy and patient safety. Hepatotoxicity, neurotoxicity, CNS disturbances, and myelosuppression are among the most significant adverse effects, driven by complex mechanisms such as oxidative stress, mitochondrial dysfunction, and pharmacogenetic variability. Effective mitigation hinges on proactive risk stratification, vigilant monitoring, and evidence-based interventions, including dose adjustments, targeted supportive therapies (eg, vitamin B6 for neuropathy, hepatoprotectants for liver injury), and timely regimen modifications when necessary. Furthermore, patient education, multidisciplinary collaboration, and adherence to pharmacovigilance protocols are essential to minimize treatment interruptions and improve outcomes, particularly in high-risk populations and drug-resistant TB cases. Future research should focus on personalized medicine strategies, including pharmacogenomic profiling and safer alternative regimens, to further optimize TB therapy while reducing the burden of adverse drug reactions. By integrating these approaches, clinicians can enhance treatment tolerability and success, ultimately contributing to global TB control efforts.

To enhance clinical utility, we recommend the following evidence-based practices:

1. Perform baseline liver function tests, complete blood count, and renal assessment before initiating ATDs;
2. Administer prophylactic pyridoxine (25–50 mg/day) to all patients receiving isoniazid, especially those with risk factors (eg, diabetes, malnutrition, HIV);
3. Conduct monthly visual acuity and red-green color vision testing in patients on ethambutol;
4. Consider therapeutic drug monitoring in high-risk or complex cases to balance efficacy and toxicity;
5. Discontinue offending drugs promptly when severe ADRs occur (eg, ALT >5× ULN, vision loss, neutrophils $<0.5\times10^9$/L).

Implementing these measures can significantly reduce treatment interruptions and improve TB cure rates.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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