REVIEW ARTICLE

Liver Injury Associated with Antituberculosis Medications

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ABSTRACT

Tuberculosis remains a major global health concern, with a sharp increase in new cases in 2022, exceeding the prevalence before the coronavirus disease 2019 (COVID-19) pandemic. Conventional antituberculosis therapy, comprising a combination of first-line medications, is essential for controlling tuberculosis. However, more than 7% of patients undergoing treatment may develop drug-induced liver injury (DILI), mainly from isoniazid and rifampicin. This literature review aimed to evaluate DILI in tuberculosis, focusing on its causes, diagnosis, and management. Several factors, including age, sex, genetic predisposition, and pre-existing liver conditions, affect the occurrence of antituberculosis DILI. Advanced age and being female are significant risk factors for severe liver injury. Diagnosing DILI requires careful differentiation from other hepatic disorders, as its clinical presentation may include symptoms such as jaundice, abdominal pain, and elevated liver enzyme levels. Early detection relies heavily on liver function tests and clinical assessments. Managing DILI involves promptly discontinuing the offending drug, closely monitoring the patient, and gradually reintroducing medications, prioritizing less hepatotoxic options, such as rifampicin. Hepatoprotective agents and alternative drug regimens, particularly those excluding pyrazinamide, may be used to mitigate the risk of liver injury. The rise in tuberculosis cases in 2022 underscores the ongoing global burden of this disease and the critical need for effective treatment strategies. Tailored therapeutic approaches, comprehensive liver function monitoring, and early identification of DILI are vital for minimizing hepatotoxicity while ensuring successful tuberculosis management. Although hepatoprotective drugs and alternative regimens show promise, further research is necessary to optimize their application across diverse patient populations.

Keywords: Tuberculosis; drug-induced liver injury (DILI); antituberculosis; hepatotoxicity

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Highlights:
1. This article presents a thorough evaluation of antituberculosis drug-induced liver injury, particularly concerning its causes, diagnosis, and management, highlighting the importance of a meticulous differentiation from other liver disorders through a comprehensive assessment of clinical indicators.
2. The literature review included studies utilizing advanced diagnostic tools for precise causality determination as well as innovative approaches, such as the selective omission of pyrazinamide or the integration of non-standard treatment protocols, which offer promising avenues to mitigate hepatotoxicity risk.
3. This literature review suggests that hepatoprotective agents, such as N-acetylcysteine, may have advantages due to their notable efficacy in preserving liver function, offering a proactive strategy for patient safety.

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INTRODUCTION

In 2022, 7.5 million new tuberculosis cases were reported globally, marking the highest single-year incidence since the World Health Organization began tracking the disease in the mid-1990s. This figure represents a 16% increase from 2021, a 28% rise from 2020, and a prevalence rate surpassing the 7.1 million cases documented in 2019 prior to the coronavirus disease 2019 (COVID-19) pandemic (Li et al., 2022). Approximately 1.13 million fatalities occurred among individuals who tested negative for

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human immunodeficiency virus (HIV), alongside an estimated 167,000 deaths among HIV-positive individuals (World Health Organization, 2023).

According to the World Health Organization, antituberculosis drugs, which combine bactericidal and bacteriostatic agents, are critical for the prevention and treatment of tuberculosis. This standard therapy comprises five first-line drugs that effectively combat tuberculosis infection, including streptomycin, pyrazinamide, ethambutol, isoniazid, and rifampicin. However, one of the most serious side effects of antituberculosis drug use is drug-induced liver injury (DILI). This type of liver injury may necessitate the discontinuation of treatment, potentially resulting in therapeutic failure, relapse, and the development of drug resistance. It is estimated that approximately 7% of patients undergoing tuberculosis therapy experience DILI, rendering it one of the primary challenges in tuberculosis management (Soedarsono & Riadi, 2020; Zhao et al., 2020).

Antituberculosis drugs have been recognized to be highly effective in treating tuberculosis. However, it is essential to carefully monitor their adverse effects to ensure treatment success and prevent further complications. This study sought to comprehensively review the effects of antituberculosis DILI, specifically by addressing its causes, diagnosis, and management.

MECHANISM OF DRUG-INDUCED LIVER INJURY

The liver plays a central role in metabolizing and eliminating foreign chemicals, continuously exposing it to various xenobiotics and potentially harmful substances. Historically, idiosyncratic liver injury was attributed to immunological or metabolic abnormalities, classified as either allergic or non-allergic toxicity. Recent studies have associated certain human leukocyte antigen (HLA) genotypes with an increased risk of DILI, highlighting the crucial involvement of the immune system in the pathophysiology of idiosyncratic DILI. This has led to a preference for a more unified theory (Fu et al., 2020).

According to the acknowledged theory, an offending chemical undergoes hepatic metabolism, generating reactive metabolites that form covalent bonds with proteins or peptides. This process can initiate an immune response by presenting the adduct as an antigen and activating cytotoxic cluster of differentiation 8^+ ($CD8^+$) T cells or cluster of differentiation 4^+ ($CD4^+$) T helper cells. An antigen-presenting cell (APC) absorbs the adduct and presents it to $CD4^+$ T helper 0 (Th0) cells via an HLA class II receptor, triggering $CD4^+$ cell activation. The $CD4^+$ Th0 cells allegedly initiate an adaptive immune response, as shown in Figure 1 (Björnsson & Björnsson, 2022).

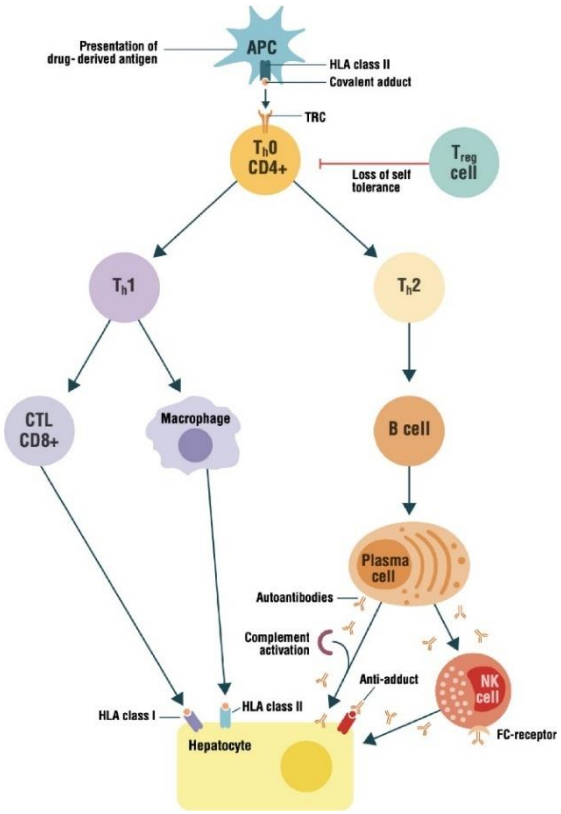

Figure 1. Putative activation of the adaptive immune response in idiosyncratic drug-induced liver injury (Björnsson & Björnsson, 2022)
Notes: APC=antigen-presenting cell; TCR=T-cell receptor; Th0=T helper 0 cell; $CD4^+$=cluster of differentiation 4^+; Treg=T regulatory cell; Th1=T helper 1 cell; Th2=T helper 2 cell; CTL=cytotoxic T lymphocyte; $CD8^+$=cluster of differentiation 8^+; HLA=human leukocyte antigen; NK=natural killer cell.

Antituberculosis medications can result in DILI, a complex condition influenced by multiple risk factors. Individuals between the ages of 35 and 55 years are particularly vulnerable to DILI, with older patients showing an even higher predisposition. In previous studies, individuals aged 55 years and older exhibited an odds ratio of 3.67, indicating a multiple-fold increase for the risk of developing hepatotoxicity (Cavaco et al., 2022; Li et al., 2022).

Host and demographic factors significantly affect the risk of DILI. Severe liver injuries, particularly DILI classified as grades 4 and 5, have consistently been associated with female patients. Additional host-related risk factors include malnutrition, coexisting illnesses, and specific genetic variations (Cavaco et al., 2022).

Concurrent medical conditions also significantly contribute to the risk of DILI. Alcohol consumption, positive results of hepatitis B surface antigen (HBsAg) testing, and pre-existing illnesses are among

the notable risk enhancers of DILI. Previous studies have indicated that HBsAg-positive patients have a 1.516-fold increased risk of developing DILI (Zheng et al., 2020; Jiang et al., 2021).

Treatment characteristics further influence the likelihood of DILI. Multidrug antituberculosis regimens pose a higher risk of hepatotoxicity, particularly during the initial phase of treatment. Consequently, liver function should be closely monitored, especially during the first month of therapy (Naqvi et al., 2015).

DIAGNOSIS OF DRUG-INDUCED LIVER INJURY

Drug-induced liver injury (DILI) is a major cause of liver damage, presenting with a range of symptoms and indicators that may resemble other hepatic disorders. This disorder may manifest as anything from severe liver failure to asymptomatic elevations in liver enzymes. The signs and symptoms vary depending on the type of liver injury, i.e., hepatocellular, cholestatic, or mixed. Table 1 presents the three types of liver injury as specified in the study conducted by Garcia-Cortes et al. (2020). This categorization was modified based on the framework developed in a prior study carried out by Hoofnagle & Björnsson (2019).

One of the most noticeable symptoms of DILI is jaundice, characterized by the yellowing of the skin and sclera due to elevated bilirubin levels, which is commonly observed among patients with this disorder (Wong et al., 2023; Brown et al., 2024; Francis & Navarro, 2024). Patients experiencing DILI often report abdominal pain, particularly in the right upper quadrant, indicating that the liver has been affected. Pruritus, or itching, is another common symptom, especially in cases of cholestatic liver injury. This symptom frequently coexists with jaundice (Brown et al., 2024; Francis & Navarro, 2024). Gastrointestinal symptoms, such as nausea and anorexia, reflect the critical role of the liver in metabolism and detoxification (Rodrigo et al., 2019; Rios et al., 2023). Additionally, fatigue, a nonspecific but common symptom, is frequently reported by patients with liver injury, including those suffering from DILI (Rodrigo et al., 2019).

Laboratory tests often reveal elevated levels of

Table 1. Types of drug-induced liver injury (Garcia-Cortes et al., 2020)

Characteristics	Direct (intrinsic)	Idiosyncratic	Indirect
Dose-related	Yes	No	No
Latency	Short (few days)	Variable (days to months), may occur after treatment discontinuation	Typically delayed (weeks to months
Rate of occurrence	High	Low	Intermediate
Predictable	Yes	No	Occasionally
Clinico-pathological phenotypes	Acute (centrozonal necrosis), acute fatty liver, vascular injury (sinudoidal obstruction, NRH)	Acute hepatocellular, cholestatic or mixed injury, chronic hepatitis, bland cholestasis	Acute (immune mediated hepatitis), fatty liver, chronic hepatitis
Implicated drugs	Acetaminophen (paracetamol), nicotinic acid, aspirin, cocaine, cancer chemotherapy, amiodarone, metho-trexate (intravenous), plants containing pyrrolizidine alkaloids	Isoniazid, amoxicillin-clavulanate, macrolide antibiotics, fluoroqui-nolones, statins	IV bolus corticosteroids, antineoplastic agents (immune check points inhibitors, protein kinase inhibitors), monoclonal antobodies (anti-TNF, anti-CD20 rituximab), daclixumab, anti-PCSK9 (hipercholesterolemia)
Mechanism	Intrinsic hepatotoxicity	Metabolic (mito-chondrial) damage or immune-mediated damage	Drug effect (regulating immune response or reducing cholesterol levels) provokes undesirable effects on the liver (i.e. immune-mediated hepatitis, fatty liver)

Notes: NRH=nodular regenerative hyperplasia; TNF=tumor necrosis factor; CD20=cluster of differentiation 20; PCSK9=proprotein convertase subtilisin/kexin type 9.

liver enzymes, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP). The pattern of enzyme elevation helps classify the type of liver injury as either hepatocellular, cholestatic, or mixed. Elevated total and direct bilirubin levels, typically observed in clinically diagnosed jaundice, correlate with the severity of the condition. While liver biopsy is not always necessary, histological findings such as inflammation, necrosis, and cholestasis can provide valuable confirmation of a DILI diagnosis (McKinney et al., 2023; Brown et al., 2024).

Table 2. Grading of clinical severity in drug-induced liver injury (Rizzi et al., 2023)

Grades	Severity	Laboratory biomarkers	Clinical manifestations
0	None	None	None
1	Mild	Raised ALT and/or ALP, TBIL < 2.5 mg/dL, and INR < 1.5	Fatigue, nausea, asthenia, jaundice, rash, pruritus, right upper quadrant abdominal pain
2	Moderate	Raised ALT and/or ALP, and TBIL ≥ 2.5 mg/dL or INR ≥ 1.5 without hyperbilirubinemia	Symptoms similar to grade 1 but more severe
3	Severe	Raised ALT and/or ALP and TBIL ≥ 2.5 mg/dL with or without INR ≥ 1.5	Necessity for hospitalization
4	Acute	Raised ALT and/or ALP and TBIL ≥ 2.5 mg/dL, with one or more of the following manifestations: 1) prolonged jaundice more than three months, 2) signs of hepatic decompensation (INR ≥ 1.5, ascites, and encephalopathy), or 3) other organ failure thought to be related to DILI	Encephalopathy, ascites, and organ dysfunction related to DILI
5	Lethal	Death or liver transplantation	Death or the need for liver transplantation

Notes: ALT=alanine aminotransferase; ALP=alkaline phosphatase; TBIL=Total bilirubin; INR=international normalized ratio; DILI=drug-induced liver injury.

Diagnosing DILI can be challenging due to its variable presentation and the need to exclude other potential causes of liver damage, such as metabolic disorders, autoimmune liver diseases, and viral hepatitis (Rodrigo et al., 2019; Garcia-Cortes et al., 2020). Tools such as the Roussel Uclaf Causality Assessment Method (RUCAM) are often employed to assess the risk of DILI, although further refinement is required for improved diagnostic accuracy (Garcia-Cortes et al., 2020). Accurate diagnosis relies on clinical suspicion and thorough evaluation, as DILI symptoms frequently overlap with existing liver conditions in patients. Additionally, a detailed medical history is critical, particularly regarding the use of prescription drugs, non-prescription medications, and supplements, as patients may not always disclose this information (Taj et al., 2023).

The severity of DILI is classified into five clinical grades, ranging from grade 1 to grade 5. The absence of liver damage is marked by grade 0, whereas grade 5 denotes death or liver transplantation resulting from the liver injury. Table 2 outlines the severity grading of DILI according to the classification described by Rizzi et al. (2023).

MANAGEMENT OF DRUG-INDUCED LIVER INJURY

Managing DILI caused by antituberculosis medications requires a multimodal approach that includes early detection, risk factor management, and therapeutic interventions. Due to the hepatotoxic potential of antituberculosis drugs, especially isoniazid, close monitoring and proactive management are essential to prevent liver damage. Moreover, these practices can ensure effective treatment for patients with tuberculosis (Soedarsono & Riadi, 2020; Lewis et al., 2024).

As previously mentioned, the risk of hepatotoxicity is highest during the initial phase of tuberculosis treatment. Therefore, routine liver function tests are critical to prevent adverse effects (Soedarsono & Riadi, 2020). Patients exhibiting any symptoms of DILI, such as fever, nausea, or jaundice, should undergo prompt evaluation. Subsequently, adjustments to the treatment plan may be implemented if deemed necessary (Acosta et al., 2022).

Risk factors, such as alcohol consumption, malnutrition, and concurrent diseases, should be identified and managed to reduce the likelihood of DILI. These factors have been linked to a higher risk of liver injury in patients receiving antituberculosis therapy. Concurrent hepatotoxic medications, such as paracetamol, should also be avoided to minimize additional liver strain (Akkahadsee et al., 2024).

In confirmed cases of DILI, it is often necessary to temporarily discontinue the administration of the offending medication. Guidelines have been used to determine the indications for ceasing or continuing tuberculosis treatment. The American Thoracic Society recommend the gradual reintroduction of antituberculosis following the resolution of symptoms

(Acosta et al., 2022).

Tuberculosis treatment should be paused in patients presenting with DILI symptoms, including jaundice, nausea, and vomiting, or when AST or serum glutamic oxaloacetic transaminase (SGOT) and ALT or serum glutamic pyruvic transaminase (SGPT) levels are elevated to at least three times the normal value. Treatment is also suspended in patients without clinical symptoms if bilirubin levels exceed 2 mg/dL or if AST/ALT levels rise to more than five times the normal value. However, treatment may continue under careful monitoring in cases where AST/ALT levels are elevated to at least three times the normal range without clinical signs of DILI (Soedarsono & Riadi, 2020).

Tuberculosis therapy should remain on hold until clinical symptoms, such as nausea and abdominal pain, subside and liver function returns to normal. If liver function tests are unavailable, tuberculosis medications can be resumed two weeks after symptoms resolve. Rifampicin, which has a lower risk of hepatotoxicity compared to isoniazid (INH) or pyrazinamide, is recommended for reintroduction. Isoniazid may be added three to seven days later. Patients with a history of jaundice may continue receiving isoniazid and rifampicin, but pyrazinamide should be avoided (Soedarsono & Riadi, 2020).

The potential role of hepatoprotective drugs in treating DILI has been investigated in prior research (Saito et al., 2016; Moosa et al., 2021). However, N-acetylcysteine indicates no significant effects in accelerating the normalization of liver enzymes. Nevertheless, the medication exhibits an association with shorter hospital stays, suggesting its role in supportive care.

Multiple regimens have been successfully used to manage DILI. The combinations of drugs consist of isoniazid, rifampicin, and ethambutol (HRE), ethambutol and levofloxacin (E-LEVO), and streptomycin and levofloxacin (SE-LEVO). These regimens allow for continuous tuberculosis therapy while avoiding the most hepatotoxic drugs, such as pyrazinamide (Tandon et al., 2023).

Essential phospholipids and glycyrrhizin (phosphogliv) have been shown to reduce the incidence of transaminase elevation and clinically significant DILI in patients with chronic tuberculosis and hepatitis (Ivanova et al., 2019). However, a large cohort study revealed that the prophylactic use of hepatoprotective drugs, such as silymarin and glycyrrhetinic acid, does not significantly lower the incidence of DILI (Marjani et al., 2019). This suggests that their efficacy may depend on specific patient characteristics and conditions (Chen et al., 2022).

While the previously outlined strategies are effective in managing DILI, it is essential to balance the minimization of liver damage with the assurance of successful tuberculosis treatment. Supplements and alternative therapies should be used cautiously, as further research remains necessary to confirm their safety and effectiveness across diverse populations (Benić et al., 2022).

DISCUSSION

The sharp rise of tuberculosis cases in 2022, amid the coronavirus disease 2019 (COVID-19) pandemic, exceeded the pre-pandemic prevalence rate. This drastic rise in prevalence highlights the persistent global burden of tuberculosis. In addition, it reinforces the need for effective tuberculosis treatment regimens while also emphasizing the importance of monitoring for adverse effects, such as DILI.

Several recommendations can be made to improve the management of DILI in tuberculosis treatment. Early detection through routine liver function tests, particularly during the initial phase of treatment, is crucial to identify DILI before it progresses to more severe stages. Clinicians should remain vigilant in recognizing high-risk populations, including those with comorbidities (e.g., hepatitis B or alcohol use) and individuals with genetic predispositions (e.g., slow acetylator status). These factors significantly increase the risk of liver toxicity. The diverse clinical presentations of DILI complicate diagnosis, as symptoms often overlap with other liver disorders. The Roussel Uclaf Causality Assessment Method (RUCAM) may be used as a tool that can aid in diagnosing DILI. However, its application requires further refinement to improve accuracy (Taj et al., 2023).

Given the complexity of DILI, a stepwise reintroduction of antituberculosis medications—starting with rifampicin, which is less hepatotoxic—is recommended once liver function normalizes. Alternative regimens, including isoniazid, rifampicin, and ethambutol (HRE) and ethambutol and levofloxacin (E-LEVO), which exclude highly hepatotoxic drugs such as pyrazinamide, should be considered for patients with a history of liver injury. Supportive therapies, consisting of N-acetylcysteine and certain herbal supplements, may help alleviate symptoms and support liver recovery, although more research is necessary to confirm their efficacy (Tao et al., 2019; Shi et al., 2020).

Personalized treatment strategies that account for individual risk factors, such as age, sex, and underlying health conditions, should guide clinical decisions to balance effective tuberculosis treatment with the prevention of liver injury. The immunological mechanism of DILI, characterized by reactive metabolites attaching to hepatocyte proteins and triggering immune responses (i.e., $CD4^+$ and $CD8^+$ T cells), provides valuable insights into its pathogenesis. These findings may inform future therapeutic approaches and preventive strategies, ensuring that tuberculosis patients receive the safest and most effective care (Moosa et al., 2021).

This literature review has thoroughly discussed the epidemiology, mechanisms, diagnosis, and management of liver injury associated with anti-tuberculosis medications, providing a well-rounded perspective. The discussion on hepatoprotective agents and alternative regimens offers practical guidance for clinicians managing tuberculosis patients with liver injury. However, this review might be limited by the lack of quantitative data on the outcomes of DILI management.

CONCLUSION

While antituberculosis treatment remains essential for disease management, the risk of drug-induced liver injury (DILI) poses considerable challenges to both treatment efficacy and patient safety. With the increasing global incidence of tuberculosis and the complexities of DILI management, a comprehensive approach that includes early detection, consistent monitoring, and tailored management strategies is critical. Host-related and demographic risk factors, such as age, sex, and pre-existing liver conditions, must be carefully considered, and treatment plans should be adjusted accordingly. Accurate diagnosis, timely intervention, and the administration of alternative non-hepatotoxic drugs are vital for minimizing liver damage while ensuring continuous therapeutic success. Despite the potential of alternative treatment regimens, additional research is required to enhance their administration in patients from diverse populations.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION

SM contributed to the conception and design, critical revision of the article for important intellectual content, final approval of the article, and funding. LS contributed to the analysis and interpretation of the data, drafting of the article, administrative, technical, or logistic support, and collection and assembly of data.

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