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Antituberculosis drug-induced liver injury: current concepts in pathogenesis, diagnosis, and management

Oštećenje jetre izazvano antituberkuloticima: aktuelni koncepti u patogenezi, dijagnozi i lečenju

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Abstract

Antituberculosis drug-induced liver injury (ATB-DILI) is one of the most significant adverse effects of first-line tuberculosis therapy and a leading cause of treatment discontinuation. Hepatotoxicity associated with isoniazid, rifampicin, and pyrazinamide may substantially impair treatment adherence, prolong treatment duration, and, in severe cases, lead to acute liver failure. This paper provides an overview of contemporary trends in the epidemiology, pathogenesis, diagnosis, and management of ATB-DILI, with particular emphasis on clinically relevant aspects and ongoing controversies. The underlying mechanisms of ATB-DILI origin involve complex interactions between drug metabolism, genetic susceptibility, oxidative stress, mitochondrial dysfunction, and immune-mediated injury, with emerging evidence suggesting a potential role of ferroptosis. Diagnosis relies on biochemical and clinical criteria, the exclusion of alternative causes, and causality assessment tools, such as the Roussel Uclaf Causality Assessment Method – RUCAM scale. Early recognition and timely discontinuation of hepatotoxic agents are of paramount importance, while optimal strategies for treatment reintroduction and the role of hepatoprotective agents are still not fully defined. A better understanding of risk factors and mechanisms, alongside the development of predictive biomarkers and pharmacogenetic approaches, may enable more individualized and safer tuberculosis treatment.

Keywords:
antitubercular agents; chemical and drug-induced liver injury; diagnosis; drug-related side effects and adverse reactions; tuberculosis.

Apstrakt

Oštećenje jetre izazvano antituberkuloticima (*antituberculosis drug-induced liver injury* – ATB-DILI) jedan je od najznačajnijih neželjenih efekata terapije prve linije tuberkuloze i jedan od glavnih uzroka prekida lečenja. Hepatotoksičnost povezana sa izoniazidom, rifampicinom i pirazinamidom može značajno narušiti adherenciju, produžiti trajanje terapije i, u težim slučajevima, dovesti do akutne insuficijencije jetre. Ovaj rad pruža pregled savremenih trendova u epidemiologiji, patogenezi, dijagnostici i lečenju ATB-DILI, sa posebnim naglaskom na klinički bitne aspekte i aktuelne dileme. Osnovni mehanizmi nastanka ATB-DILI uključuju složene interakcije između metabolizma lekova, genetske predispozicije, oksidativnog stresa, mitohondrijalne disfunkcije i imunski posredovanog oštećenja, sa novim dokazima koji ukazuju na potencijalnu ulogu feroptoze. Dijagnoza se zasniva na biohemijskim i kliničkim kriterijumima, isključenju drugih uzroka i alatima za procenu uzročnosti, kao što je Roussel Uclaf Causality Assessment Method – RUCAM skala. Rano prepoznavanje i pravovremeni prekid terapije hepatotoksičnim lekovima od ključnog su značaja, dok optimalne strategije ponovnog uvođenja terapije i uloga hepatoprotektivnih agenasa još uvek nisu definisane u potpunosti. Bolje razumevanje faktora rizika i mehanizama, uz razvoj prediktivnih biomarkera i farmakogenetskih pristupa, može omogućiti personalizovanije i bezbednije lečenje tuberkuloze.

Ključne reči:
antituberkulotici; jetra, oštećenje, hemijsko i lekovima izazvano; dijagnoza; lekovi, neželjeni efekti i neželjene reakcije; tuberkuloza.

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Introduction

Although tuberculosis (TB) is sometimes considered a forgotten disease, it remains a major global public health problem. According to the recent estimates [1], over 10 million people develop TB annually, and the disease continues to be a leading cause of death from a single infectious agent. Major factors contributing to inadequate disease control include human immunodeficiency virus (HIV) infection, poverty, malnutrition, diabetes mellitus, smoking, alcohol misuse, as well as treatment interruptions related to adverse effects of the therapy [2].

Although the World Health Organization (WHO) has recently recommended a shortened 4-month rifapentine-based regimen for the treatment of drug-susceptible TB in selected patient populations [3], the standard 6-month regimen remains the cornerstone of therapy in most settings. This regimen includes a combination of isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB) during the initial 2 months of treatment, followed by INH and RMP for an additional 4 months during the continuation phase. Despite high treatment success rates [1], the effectiveness of therapy may be compromised by adverse drug reactions, which can contribute to treatment failure, increased morbidity and mortality, and the development of drug resistance [4, 5].

Among these, hepatotoxicity, referred to as antituberculosis (ATB) drug-induced liver injury (LI) – DILI (ATB-DILI), is one of the most common and clinically significant complications. Hepatotoxicity associated with first-line agents, mainly INH, RMP, and PZA, may lead to treatment interruption, reduced adherence, prolonged therapy, and, in severe cases, liver failure (LF) [6]. Although substantial progress has been made in understanding the mechanisms, risk factors (RF), and clinical management of ATB-DILI, important uncertainties remain, particularly regarding early prediction, optimal monitoring strategies, and safe reintroduction of therapy. This paper provides an overview of current concepts in the pathogenesis, diagnosis, and management of ATB-DILI, with emphasis on clinically relevant aspects and ongoing controversies.

Definition of antituberculosis drug-induced liver injury

According to the clinical practice guidelines of the European Association for the Study of the Liver, DILI, regardless of the causative agent, is defined by one of the following laboratory criteria: elevation of alanine aminotransferase (ALT) ≥ 5 times the upper limit of normal (× ULN), elevation of alkaline phosphatase (ALP) ≥ 2 × ULN, or combined increase in ALT ≥ 3 × ULN and total bilirubin (TBIL) ≥ 2 × ULN in the absence of alternative causes of LI [7]. These biochemical criteria are widely used in clinical research and practice to standardize the diagnosis of DILI.

A wide range of medications may induce DILI. While acetaminophen is the leading cause of intrinsic hepatotoxicity, ATB drugs rank among the most frequent causes of idiosyncratic DILI on a global scale [8, 9]. In addition to these drugs, numerous other medications are commonly associated with DILI, including antibiotics (e.g., amoxicillin-clavulanate), antiepileptic drugs (e.g., valproate), amiodarone, nonsteroidal anti-inflammatory drugs, statins, and herbal and dietary supplements [10].

ATB-DILI represents one of the most clinically significant complications of TB treatment because it may lead to treatment interruption, modification of therapeutic regimens, prolongation of therapy duration, and, in severe cases, increased morbidity and mortality due to acute LF [6, 11]. Clinical manifestations range from asymptomatic elevations of liver enzymes, which occur in approximately 50–75% of patients, to symptomatic hepatitis characterized by nausea, vomiting, jaundice, and coagulopathy, and in rare cases, progression to acute LF [12]. Because hepatotoxicity most frequently occurs during the intensive phase of therapy, careful clinical and biochemical monitoring is recommended during the early stages of treatment, particularly in patients with known RF for LI, in order to allow early detection of hepatotoxicity and prevent progression to severe liver damage [13].

Among first-line ATB drugs, INH, RMP, and PZA are most commonly associated with hepatotoxicity, particularly when used in combination. In contrast, EMB and streptomycin have minimal hepatotoxic potential [14]. When administered as monotherapy (such as in the treatment of latent TB infection), INH is the most frequent cause of hepatotoxic reactions, whereas PZA is generally considered the most hepatotoxic drug in a dose-dependent manner. RMP rarely causes severe hepatocellular injury (HCI) on its own but may enhance hepatotoxicity through interactions with other ATB drugs [15]. With the increasing prevalence of drug-resistant TB, hepatotoxicity associated with second-line ATB drugs has also gained clinical importance. Among these agents, bedaquiline and pretomanid have been associated with a higher risk of LI, while delamanid and respiratory fluoroquinolones appear to have a more favorable hepatic safety profile [5, 16, 17].

Classification of antituberculosis drug-induced liver injury

DILI can be classified according to pathogenesis and predictability into intrinsic and idiosyncratic forms [10]. Intrinsic (direct) DILI represents a predictable and dose-dependent type of hepatotoxicity that occurs in most individuals once the concentration of the offending drug or its toxic metabolite in hepatocytes exceeds a certain threshold. This type of LI usually has a short latency period, ranging from several hours to a few days, and can be reproduced in experimental models. The underlying mechanism typically involves direct toxicity of reactive metabolites leading to oxidative stress (OS), mitochondrial dysfunction, and hepatocyte necrosis [18]. The prototypical example of intrinsic DILI is acetaminophen-induced hepatotoxicity, which represents the most common cause of acute drug-related LF in many developed countries [7]. In contrast, idiosyncratic DILI is unpredictable and generally

not strictly dose-dependent. It occurs in a relatively small proportion of exposed individuals and usually develops after a longer latency period, typically several days to weeks after drug exposure. Idiosyncratic hepatotoxicity is often associated with genetic susceptibility, interindividual differences in drug metabolism, or immune-mediated mechanisms. In such cases, reactive drug metabolites may bind to hepatocellular proteins, forming hapten-protein complexes that trigger immune responses directed against liver tissue [19]. In the context of ATB therapy (ATBT), most cases of LI are considered idiosyncratic because they occur in only a minority of treated patients and are frequently associated with genetic polymorphisms affecting drug metabolism. Nevertheless, some ATB drugs may also exhibit elements of intrinsic hepatotoxicity due to the formation of reactive metabolites capable of directly damaging hepatocytes, as observed with INH and PZA [12].

Another important classification of ATB-DILI is based on the biochemical pattern of LI, determined according to the dominant elevation of liver enzymes. The biochemical pattern of ATB-DILI is commonly classified using the R-ratio, calculated as serum (ALT/ULN) / serum (ALP/ULN). Based on this value, LI can be categorized as hepatocellular ($R \geq 5$), cholestatic ($R \leq 2$), or mixed ($2 < R < 5$) [19].

Epidemiology

The reported incidence of ATB-DILI varies considerably depending on the diagnostic criteria used and the geographic region studied, which may influence both the prevalence of TB and genetic susceptibility to hepatotoxicity. Overall, ATB-DILI has been reported in approximately 2–28% of patients receiving ATBT [5, 14]. A recent large meta-analysis including over 100,000 patients reported a pooled incidence of approximately 11.5%, with an increasing temporal trend worldwide [20]. The incidence of ATB-DILI demonstrates significant geographic variability, being lower in low TB-burden regions such as Western countries [21, 22] and higher in endemic areas, particularly within the African [6, 23] and the Asia–Pacific regions [24–26]. Although most patients with ATB-DILI experience complete clinical and biochemical recovery following withdrawal or modification of therapy, severe LI may develop in a subset of cases requiring hospitalization. In such situations, progression to acute LF may occur and may necessitate liver transplantation, with reported mortality rates ranging from 10% to 35% in severe cases [11].

The prognosis of ATB-DILI largely depends on the pattern of LI. HCI is generally associated with the highest risk of severe outcomes, whereas mixed patterns tend to have a more favorable prognosis [7].

Numerous studies have identified several RF associated with the development of ATB-DILI. These include older age, female sex, alcohol consumption, HIV infection, chronic viral hepatitis (hepatitis B or hepatitis C virus), pre-existing chronic liver disease, malnutrition and hypoproteinemia, anemia, as well as genetic polymorphisms in enzymes involved in the metabolism of ATB drugs, particularly variants affecting N-acetyltransferase (NAT) - 2 activity [26–29].

Mechanisms of hepatotoxicity

The hepatotoxic effects of ATB drugs arise from complex interactions between drug metabolism, genetic susceptibility, OS, and immune-mediated mechanisms. Among first-line ATB agents, INH, RMP, and PZA, in other words, their integrated mechanisms play the most important role in the development of ATB-DILI [5, 15, 18, 30, 31] (Figure 1).

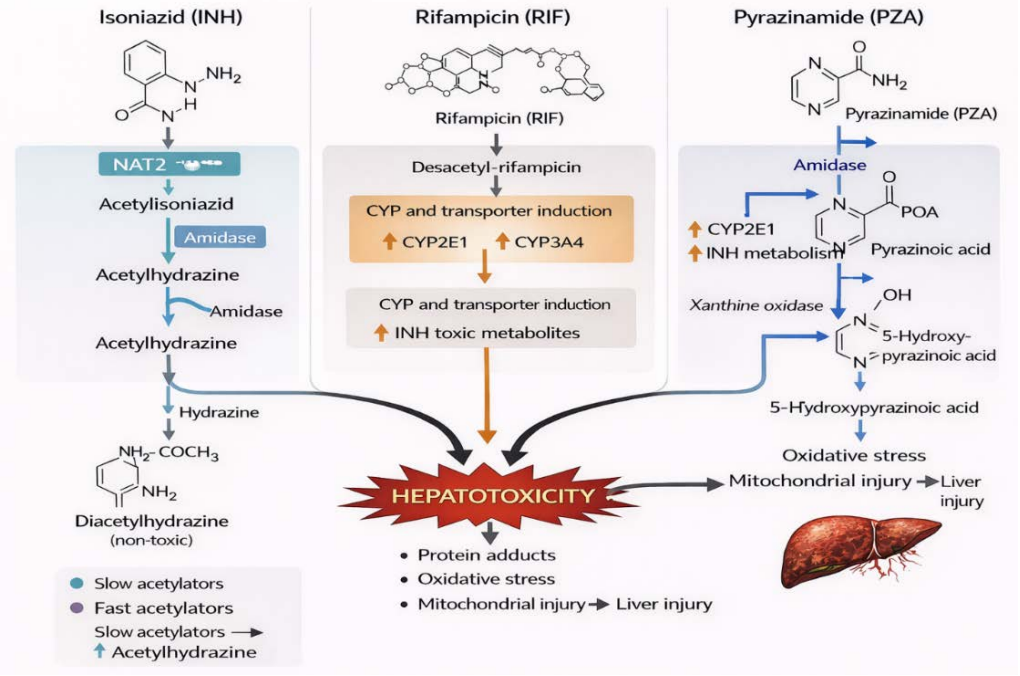

Fig. 1 – Integrated mechanism of antituberculosis drug-induced liver injury (ATB-DILI) development. CYP – cytochrome P450.

***Note*: Illustration generated by the author based on the cited papers [5, 15, 18, 30, 31].**

Isoniazid

INH undergoes extensive hepatic metabolism, primarily through acetylation catalyzed by the enzyme NAT2. In this process, INH is converted into acetylisoniazid, which is subsequently hydrolyzed to isonicotinic acid and acetylhydrazine. Acetylhydrazine represents a key intermediate metabolite that can follow two metabolic pathways. In the detoxification pathway, acetylhydrazine is further acetylated by NAT2 to form diacetylhydrazine, a relatively non-toxic metabolite. Alternatively, acetylhydrazine may be oxidized by cytochrome P450 (CYP) enzymes, particularly CYP2E1, yielding reactive, hepatotoxic intermediates that can induce OS, mitochondrial dysfunction, and hepatocyte necrosis. Additionally, a portion of INH can be directly hydrolyzed to hydrazine, another hepatotoxic metabolite that may also be oxidized by CYP2E1. Reactive metabolites generated during these processes may be detoxified through conjugation with glutathione, primarily mediated by glutathione-S-transferase [5].

Genetic polymorphisms affecting NAT2 activity play a crucial role in determining susceptibility to INH-induced hepatotoxicity [32]. Individuals are commonly classified as rapid, intermediate, or slow acetylators. In slow acetylators, reduced metabolic capacity leads to higher circulating levels of INH and its toxic metabolites, thereby increasing the risk of adverse effects, including hepatotoxicity and peripheral neuropathy [33, 34]. Several studies and meta-analyses have demonstrated a significantly increased risk of INH-induced LI among individuals with slow NAT2 acetylator status [4]. In addition to NAT2, other genetic factors may contribute to susceptibility to ATB-DILI. The *GSTM1* homozygous null genotype, associated with reduced detoxification capacity, and the *CYP2E1* c1/c1 genotype, linked to increased formation of hepatotoxic metabolites, have both been associated with an increased risk of LI [5, 25]. Furthermore, emerging pharmacogenetic studies highlight substantial interindividual and interethnic variability in the distribution of these genetic variants, which may partly explain differences in ATB-DILI incidence across populations [35]. Slow acetylator genotypes, more common in European, South American Indigenous, and Middle Eastern populations, are associated with increased hepatotoxicity risk [24, 35].

Rifampicin

RMP rarely causes severe HCI when administered alone; however, it can significantly increase the risk of hepatotoxicity during combination ATBT. RMP is a potent inducer of hepatic drug-metabolizing enzymes through activation of the pregnane X receptor, which upregulates the expression of multiple CYP enzymes and transport proteins involved in bile acid metabolism. This induction accelerates the metabolism of co-administered drugs, particularly INH, thereby promoting the formation of hepatotoxic metabolites [18].

In addition, RMP may interfere with hepatobiliary transport mechanisms, potentially leading to cholestatic or mixed patterns of LI [36]. Genetic variability in hepatic transporters and metabolic enzymes may further influence intrahepatic concentrations of RMP and modulate individual susceptibility to hepatotoxicity [5].

Pyrazinamide

PZA is considered one of the most hepatotoxic first-line ATB drugs, and its hepatotoxicity appears to be dose-dependent. In the liver, PZA is metabolized by microsomal amidase to pyrazinoic acid, which is subsequently oxidized by xanthine oxidase to form 5-hydroxypyrazinoic acid. These metabolites may induce mitochondrial dysfunction, OS, and direct HCI, leading predominantly to a hepatocellular pattern of liver damage. Because of its hepatotoxic potential, PZA is generally administered only during the initial intensive phase of TB treatment [30].

Emerging mechanisms

Despite significant advances in understanding ATB-DILI, the precise mechanisms of hepatotoxicity remain incompletely elucidated. Recent experimental studies have suggested a potential role of ferroptosis, a form of programmed cell death characterized by iron-dependent lipid peroxidation [31]. This process appears to be regulated by the HIF-1α/SLC7A11/GPx4 signaling pathway. Suppression of the cystine transporter SLC7A11 results in depletion of intracellular glutathione, impairing the activity of glutathione peroxidase 4, a key enzyme responsible for neutralizing reactive lipid species. As a consequence, lipid peroxidation accumulates and promotes hepatocyte injury. Elevated intracellular iron levels may further amplify OS and enhance the susceptibility of hepatocytes to ATB drug toxicity [36].

Overall, pharmacogenetic research in ATB-DILI is evolving from single-gene associations toward a more integrated, multi-gene framework that includes metabolic enzymes, detoxification pathways, and transport systems. In addition to genetic polymorphisms affecting drug metabolism, variants in hepatic transporters, including *ABCB11*, which encodes the bile salt export pump, have also been implicated in susceptibility to ATB-DILI, suggesting that impaired bile acid transport may contribute to cholestatic or mixed patterns of LI [37]. Although most evidence still derives from studies on INH metabolism, emerging data indicate that genetic variability may also influence hepatotoxicity associated with other ATB drugs [32, 38]. However, compared to INH, these findings remain less consistent and are often population-specific, highlighting the need for further validation in large, prospective studies. While integrating multiple genetic markers may improve risk stratification and support the concept of individualized TB therapy, routine pharmacogenetic testing has not yet been widely implemented due to limited availability, cost, and lack of standardization [39].

Diagnostic criteria for antituberculosis drug-induced liver injury

The diagnosis of ATB-DILI is based on a combination of biochemical evidence of LI, clinical assessment, and evaluation of the causal relationship between LI and exposure to ATB drugs [7, 40–42] (Figure 2). Because no single diagnostic test exists, ATB-DILI remains a diagnosis of exclusion.

Biochemical criteria for drug-induced liver injury

Initial laboratory evaluation of suspected ATB-DILI should include measurement of ALT, aspartate aminotransferase (AST), ALP, gamma-glutamyltransferase (GGT), total and direct bilirubin, and coagulation parameters such as prothrombin time or international normalized ratio (INR) [7, 40]. As previously described, according to established clinical guidelines, DILI is defined by specific biochemical thresholds involving elevations in ALT, ALP, and TBIL [7]. Other proposed biochemical criteria for DILI [3, 7, 40, 41, 43] are shown in Table 1.

It is important to distinguish mild asymptomatic elevations of liver enzymes from clinically significant hepatotoxicity, as transient abnormalities in liver function tests may occur during ATBT without fulfilling diagnostic criteria for DILI [44]. Persistent elevation of TBIL and ALP beyond 2 months after the onset of DILI is considered indicative of chronic DILI [7].

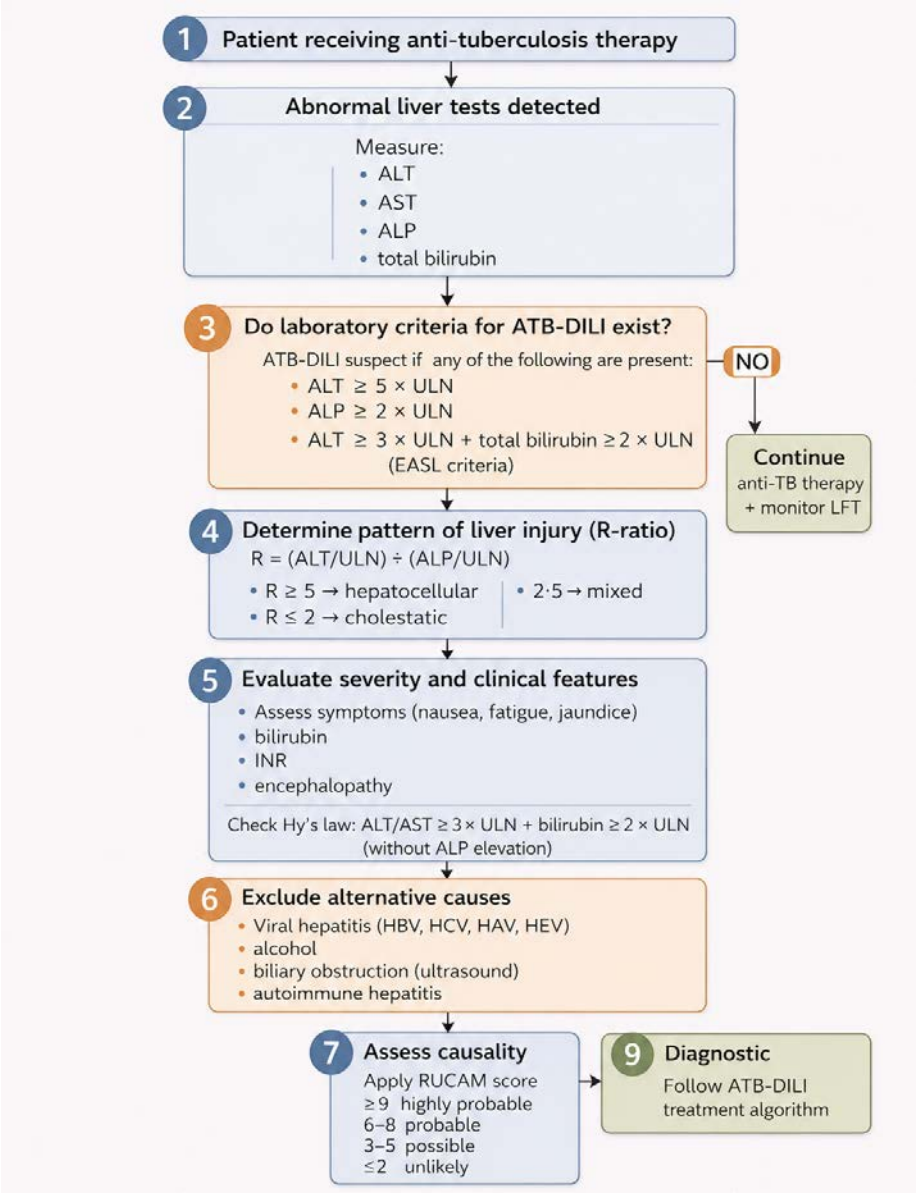

Fig. 2 – Proposed diagnostic algorithm for suspected anti-tuberculosis drug-induced liver injury (ATB-DILI). ALT – alanine aminotransferase; AST – aspartate aminotransferase; ALP – alkaline phosphatase; ULN – upper limits of normal; EASL – European Association for the Study of the Liver; TB – tuberculosis; LFT – liver function tests; INR – international normalized ratio; HBV – hepatitis B virus; HCV – hepatitis C virus; HAV – hepatitis A virus; HEV – hepatitis E virus; RUCAM – Roussel-Uclaf Causality Assessment Method.
***Note*: Illustration generated by the author based on the cited papers [7, 40, 41, 42].**

Table 1

Diagnostic criteria and treatment interruption thresholds for drug-induced liver injury (DILI) in patients receiving antituberculosis therapy

Guideline/Source	Diagnostic criteria for ATB-DILI	Criteria for interruption of anti-TB therapy	Key notes
European Association for the Study of the Liver [7]	ALT ≥ 5 × ULN; or ALP ≥ 2 × ULN; or ALT ≥ 3 × ULN + TBIL ≥ 2 × ULN	not specifically defined for TB therapy	widely accepted diagnostic criteria for DILI used in clinical research and hepatology practice
American Association for the Study of Liver Diseases [41]	same biochemical criteria as EASL	not specifically defined for TB therapy	emphasizes causality assessment, Hy's law, and exclusion of alternative causes
Chinese Medical Association Tuberculosis Branch [40]	ALT ≥ 3 × ULN and/or TBIL ≥ 2 × ULN; or simultaneous elevation of AST, ALP, and TBIL with ≥ 2 × ULN for at least one parameter	not TB-specific	recommends broader biochemical testing including GGT and coagulation parameters
ATS/CDC/IDSA [43]	not primarily focused on defining DILI	ALT ≥ 5 × ULN without symptoms or ALT ≥ 3 × ULN with symptoms	mild DILI – ALT < 5 × ULN moderate DILI – ALT 5–10 × ULN severe DILI – ALT ≥ 10 × ULN
WHO [3]	not specifically defining DILI	ALT ≥ 5 × ULN (asymptomatic) or ≥ 3 × ULN (symptomatic)	global TB management guidance largely consistent with ATS recommendations

ATB-DILI – antituberculosis drug-induced liver injury; TB – tuberculosis; ALT – alanine aminotransferase; ULN – upper limits of normal; ALP – alkaline phosphatase; TBIL – total bilirubin; EASL – European Association for the Study of the Liver; GGT – gamma-glutamyl transferase; ATS – American Thoracic Society; CDC – Center for Disease Control and Prevention; IDSA – Infectious Diseases Society of America; WHO – World Health Organization.

After confirming biochemical LI, the pattern of injury should be determined using the R-ratio. As previously mentioned, based on this value, three patterns of ATB-DILI are recognized: HCI (R ≥ 5), cholestatic injury (R ≤ 2), or mixed injury (2 < R < 5) [19]. The hepatocellular pattern is characterized by a predominant elevation of ALT with relatively normal or mildly elevated ALP levels and reflects primary hepatocyte injury. The cholestatic pattern is characterized by a predominant increase in ALP, often accompanied by elevated bilirubin levels, indicating impairment of hepatobiliary transport and bile canalicular injury. The mixed pattern represents an intermediate form in which both transaminases and ALP are significantly elevated [5]. In the context of ATB-DILI, HCI is most commonly associated with INH and PZA, whereas RMP more frequently produces cholestatic or mixed patterns of LI [19].

Particular clinical importance is attributed to the concept known as Hy's law, which describes the presence of HCI (ALT or AST ≥ 3 × ULN) accompanied by elevation of TBIL ≥ 2 × ULN in the absence of significant cholestasis. This pattern represents a strong predictor of severe DILI and is associated with an increased risk of acute LF and mortality [41].

Diagnostic criteria and treatment interruption thresholds for DILI in patients receiving ATBT [3, 7, 40, 41, 43] are shown in Table 1.

Clinical assessment

In addition to biochemical criteria, clinical evaluation plays an important role in the assessment of suspected ATB-DILI. Symptoms of hepatotoxicity may include fatigue, anorexia, nausea, vomiting, right upper quadrant abdominal pain, dark urine, and jaundice. However, a substantial proportion of patients may remain completely asymptomatic, which underscores the importance of routine monitoring of liver biochemical parameters during ATBT [14]. In severe cases, ATB-DILI may progress to acute LF characterized by coagulopathy and varying degrees of hepatic encephalopathy [15].

Assessment of severity

The severity of ATB-DILI may be classified according to biochemical abnormalities and clinical manifestations [44], ranging from mild liver enzyme elevation to acute LF characterized by coagulopathy and hepatic encephalopathy, as shown in Table 2. Severe forms of ATB-DILI may require hospitalization and, in rare cases, liver transplantation.

Severity classification of ATB-DILI that has been modified from Yu et al. [44] is shown in Table 2.

Causality assessment

Once DILI has been confirmed either biochemically or in combination with clinical findings, the next step is to evaluate causality, specifically, determining whether the observed LI is likely related to ATBT. The most widely used tool for this purpose is the Roussel-Uclaf Causality Assessment Method (RUCAM) [42]. RUCAM evaluates several parameters, including the temporal relationship between drug

Table 2

Severity classification of ATB-DILI (adapted from Yu et al. [44])

Liver injury, severity	Grade	Laboratory criteria	Clinical manifestations
None	0	no elevation of ALT or ALP; normal TBIL and INR	none
Mild	1	elevated ALT and/or ALP with TBIL < 2.5 mg/dL and INR < 1.5	usually mild or nonspecific symptoms such as fatigue, nausea, malaise, pruritus, or right upper quadrant discomfort
Moderate	2	elevated ALT and/or ALP with TBIL ≥ 2.5 mg/dL or INR ≥ 1.5 (without hepatic failure)	more pronounced symptoms of liver injury; jaundice may occur
Severe	3	elevated ALT and/or ALP with TBIL ≥ 2.5 mg/dL and/or INR ≥ 1.5 requiring hospitalization	clinically significant liver injury requiring hospital admission
Acute liver failure	4	marked elevation of liver enzymes with TBIL ≥ 2.5 mg/dL and evidence of hepatic failure (e.g., INR ≥ 1.5 with hepatic encephalopathy, ascites, or other signs of hepatic decompensation)	acute liver failure with encephalopathy, coagulopathy, or multi-organ involvement
Fatal outcome	5	liver failure leading to death or need for liver transplantation	death or liver transplantation

ATB-DILI – antituberculosis drug-induced liver injury; ALT – alanine aminotransferase; ALP – alkaline phosphatase; TBIL – total bilirubin; INR – international normalized ratio.

exposure and onset of LI, the course of liver enzyme changes after drug withdrawal (dechallenge), the presence of RF such as alcohol consumption or older age, exclusion of alternative causes of LI, and the known hepatotoxic potential of the suspected drug. Based on the total score, causality is categorized as follows: highly probable (≥ 9 points), probable (6–8 points), possible (3–5 points), unlikely (1–2 points), and excluded (≤ 0 points) [7]. Despite its widespread use, RUCAM has several important limitations. Its application may be challenging in the setting of polypharmacy, as it requires separate assessment for each drug and may be affected by incomplete clinical data and interobserver variability [42]. Furthermore, the hepatotoxic risk of newer biologics and herbal products may be underestimated due to inadequate labeling and limited safety data in the RUCAM database [45].

Exclusion of alternative causes

Because DILI is fundamentally a diagnosis of exclusion, other causes of LI must be systematically ruled out in order to confirm ATB-DILI. These include viral infections such as hepatitis B and C, HIV infection (in immunocompromised Epstein-Barr virus, cytomegalovirus, and herpes simplex virus), autoimmune liver diseases, alcohol-related liver disease, biliary obstruction, and exposure to other hepatotoxic medications (acetaminophen, statins) or herbal supplements [43]. Abdominal ultrasound is commonly performed in patients with suspected ATB-DILI to exclude structural liver disease or biliary obstruction [6]. However, imaging findings are typically nonspecific. Liver biopsy is generally not required for the diagnosis of ATB-DILI, but may be considered in selected cases when diagnostic uncertainty persists or when alternative etiologies such as autoimmune hepatitis are suspected [15].

Rechallenge

Re-exposure to the suspected drug (rechallenge) represents the strongest evidence for causality in ATB-DILI. A positive rechallenge is typically defined as a recurrent elevation of aminotransferases, usually ALT > 3 × ULN, following reintroduction of the suspected drug. Rechallenge should be undertaken with caution because recurrent LI may occur more rapidly and may be more severe than the initial episode [7]. However, in clinical practice, rechallenge is often avoided due to safety concerns, particularly in cases of severe initial hepatotoxicity or when drug labeling contraindicates re-exposure, as is the case with PZA [46].

Management of antituberculosis drug-induced liver injury

Management of ATB-DILI primarily involves prompt recognition of hepatotoxicity, temporary discontinuation of hepatotoxic drugs, and careful reintroduction of therapy once liver function improves. At the same time, clinicians must balance the risk of worsening LI with the need to maintain effective treatment of TB.

Discontinuation of antituberculosis drugs

During the initial phase of TB treatment, approximately 20% of patients may develop asymptomatic elevations of aminotransferases. In asymptomatic individuals with ALT levels < 5 × ULN, discontinuation of ATBT is generally not

required, although close clinical and biochemical monitoring is recommended [43]. However, treatment interruption is indicated in the following situations [3, 7, 40, 41, 43], as shown in Table 1: ALT ≥ 3 × ULN in the presence of symptoms suggestive of hepatotoxicity, or ALT ≥ 5 × ULN in asymptomatic patients, or significant elevation of bilirubin and/or ALP. In such cases, all potentially hepatotoxic ATB drugs should be discontinued. Following drug withdrawal, the majority of patients show gradual improvement in liver function, and most recover completely [25, 47]. Nevertheless, a small proportion of patients may develop chronic DILI or progress to acute LF [28].

Reintroduction of antituberculosis therapy

Once liver function improves, ATBT can usually be safely reintroduced in approximately 80–90% of patients [48]. Reintroduction is typically considered when serum transaminase levels decrease to < 2 × ULN, bilirubin levels normalize, and clinical symptoms resolve [49]. Drugs are generally reintroduced sequentially, one at a time, with close monitoring of liver enzymes in order to identify the offending agent if hepatotoxicity recurs [25]. A commonly used approach is to reintroduce drugs over a period of approximately 7–10 days, starting with the least hepatotoxic agents [19]. While both strategies–full-dose initiation and gradual dose escalation from minimum to maximum dose–have been described, current evidence does not support a significant difference in safety between these approaches [50].

Several strategies for reintroduction of ATBT after ATB-DILI have been described, reflecting differences across international guidelines and the lack of a universally accepted approach. However, recommendations from the WHO [3] and the National Institute for Health and Care Excellence (NICE) [49] are broadly aligned, favoring a cautious, stepwise reintroduction strategy. This approach typically involves initiating treatment with less hepatotoxic agents, such as EMB, followed by sequential addition of RMP and INH with close biochemical monitoring, while PZA is often omitted, particularly after severe LI. In those cases, treatment duration is subsequently extended to at least 8–9 months [43, 46]. In contrast, other guidelines propose alternative strategies, including full-dose initiation or gradual dose escalation of individual drugs; however, available evidence does not demonstrate clear superiority of any single approach [50]. Therefore, in clinical practice, reintroduction is generally individualized, guided by the severity of LI, the importance of specific drugs for TB treatment, and careful monitoring of liver function. If hepatotoxicity recurs following reintroduction, the suspected drug should be permanently discontinued. The proposed algorithm for reintroduction of ATB drugs, proposed by NICE [49], is shown in Figure 3.

Alternative antituberculosis regimens

In patients requiring continued ATB treatment despite hepatotoxicity, alternative regimens may be considered. In such situations, hepatotoxic agents such as INH, RMP, and PZA may be temporarily replaced with lower hepatotoxic potential drugs, including EMB and streptomycin, often combined with respiratory fluoroquinolones such as levofloxacin or moxifloxacin [49]. These regimens are typically used as temporary treatment strategies until standard therapy can be safely resumed.

Adjunctive hepatoprotective therapy

The role of hepatoprotective agents in ATB-DILI remains controversial. Despite widespread clinical use, hepatoprotective agents remain controversial due to heterogeneity of studies, small sample sizes, and lack of high-quality randomized trials.

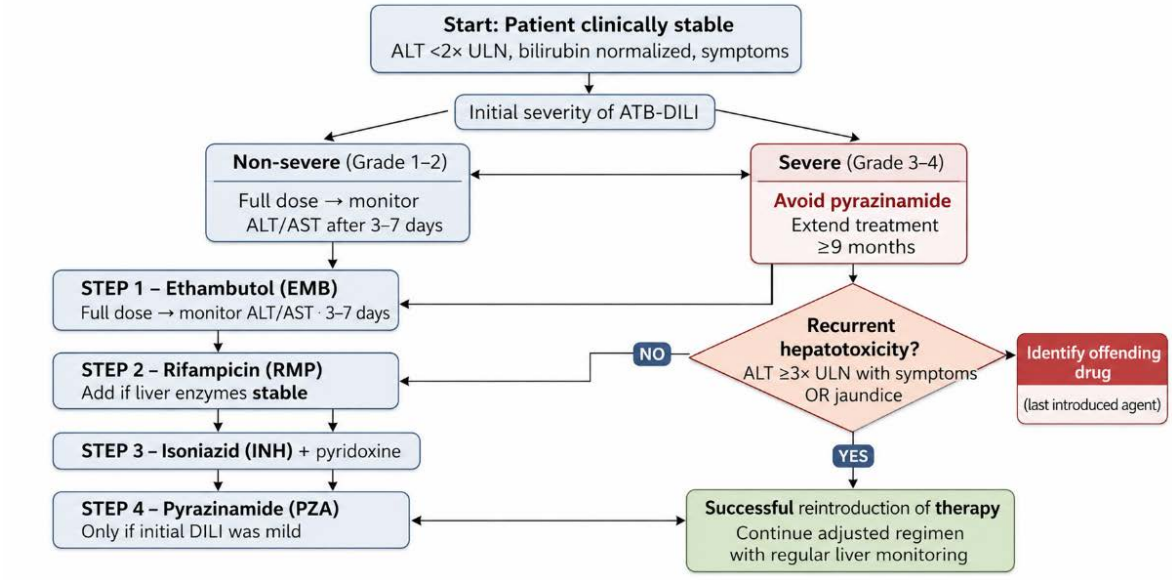

Fig. 3 – Algorithm for reintroduction of antituberculosis therapy after ATB-DILI. ALT – alanine aminotransferase; ULN – upper limits of normal; ATB-DILI – antituberculosis drug-induced liver injury; AST – aspartate aminotransferase.
***Note*: Illustration generated by the author based on the cited paper [49].**

N-acetylcysteine (NAC), which is well established in the treatment of acetaminophen-induced LI, has been investigated as a potential adjunctive therapy in non-acetaminophen DILI [51]. NAC acts as a precursor of glutathione and may exert antioxidant and anti-inflammatory effects. Some studies suggest that NAC may shorten recovery time and improve transplant-free survival in severe cases of DILI [52]; however, evidence remains limited, and its routine use in ATB-DILI has not yet been firmly established. Glucocorticoids are generally not recommended for routine treatment of ATB-DILI but may be considered in selected cases of immune-mediated DILI or when features of drug-induced autoimmune hepatitis are suspected [44].

Several hepatoprotective agents are frequently used in clinical practice as supportive therapy in patients with ATB-DILI, although robust evidence supporting their routine use remains limited [53]. These include compounds with antioxidant, anti-inflammatory, or membrane-stabilizing properties, such as silymarin, polyene phosphatidylcholine, glycyrrhizin derivatives, and S-adenosyl-L-methionine [40]. Some data suggest that these agents may contribute to faster normalization of liver enzymes and improvement of hepatic function [54]; however, current international guidelines do not recommend their routine use due to insufficient high-quality clinical evidence [40, 53].

Management of severe liver injury

In severe cases, ATB-DILI may progress to acute LF characterized by coagulopathy and hepatic encephalopathy. Such patients require intensive supportive care and evaluation for liver transplantation. Extracorporeal liver support techniques, including large-volume plasma exchange or albumin dialysis, may be used as temporary bridging therapies in selected cases [40]. Although liver transplantation can be life-saving in severe ATB-DILI, reported survival rates remain limited, largely due to the severity of the underlying LI at the time of transplantation [15].

Prevention

Prevention of ATB-DILI primarily involves identification and modification of known RF. One of the most important preventive strategies is avoidance of concomitant use of other hepatotoxic medications, including certain herbal and traditional medicinal products, with careful evaluation of the benefit–risk ratio of all prescribed drugs. In patients with chronic viral hepatitis, timely initiation of antiviral therapy should be considered when clinically indicated. Pharmacogenetic approaches have also been proposed as a strategy for preventing ATB-DILI. In particular, genotyping of the *NAT2* gene may allow dose adjustment of INH according to an individual's acetylator status, potentially reducing the risk of hepatotoxicity [40, 55, 56]. However, although promising, routine pharmacogenetic testing is expensive and has not yet been widely implemented in clinical practice [53].

The prophylactic use of hepatoprotective agents may be considered in patients at high risk for LI, although routine preventive use is generally not recommended due to limited evidence. Because the pathogenesis of ATB-DILI involves the formation of reactive metabolites and OS, antioxidant and anti-inflammatory agents such as NAC have been investigated as potential preventive strategies [15], but further clinical studies are required to confirm their effectiveness. Recent meta-analysis has also explored the potential protective effects of certain herbal preparations, including combinations containing *Curcuma longa* (turmeric) and *Tinospora cordifolia*, as well as polyherbal formulations [57]. Although some studies reported a reduction in the incidence of ATB-DILI [57], these findings are based on a limited number of heterogeneous trials, and additional well-designed studies are needed before such interventions can be recommended as part of standard clinical practice.

Conclusion

Antituberculosis drug-induced liver injury remains one of the most clinically significant complications of tuberculosis therapy. Although first-line antituberculosis drugs are highly effective, their hepatotoxic potential may lead to treatment interruption, prolonged therapy, and increased morbidity. Early recognition through regular monitoring of liver function tests, especially during the initial phase of treatment, is essential for preventing severe hepatic injury. Prompt discontinuation of hepatotoxic drugs and careful reintroduction of therapy after recovery remain the cornerstone of management.

Despite significant advances in understanding the mechanisms and clinical management of antituberculosis drug-induced liver injury, several important gaps remain. There is a lack of validated predictive biomarkers that could enable early identification of high-risk patients. In addition, pharmacogenetic approaches, although promising, are not yet routinely implemented in clinical practice due to limited availability and cost-effectiveness concerns. Future research should focus on the development of reliable risk prediction models integrating clinical, biochemical, and genetic factors, as well as on the standardization of treatment interruption and reintroduction protocols. Furthermore, emerging mechanisms such as ferroptosis may represent potential therapeutic targets, but their clinical relevance remains to be clarified.

Conflict of interest

The authors declare no conflict of interest.

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