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MINIREVIEWS

Understanding antituberculosis drug-induced hepatotoxicity: Risk factors and effective management strategies in the pediatric population

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Abstract

Antituberculosis drug-induced hepatotoxicity (ATDIH) is a significant concern while managing pediatric tuberculosis. There is limited data on pediatric ATDIH, and much of the management practices are extrapolated from adult experiences. This article provides a comprehensive overview of the incidence, risk factors, clinical presentation, and management strategies for ATDIH in children. Pyrazinamide, isoniazid, and rifampicin are the most hepatotoxic first-line antituberculosis therapy (ATT). Though pyrazinamide has the highest potential for ATDIH, isoniazid is most frequently implicated. Hepatotoxicity typically manifests within the first 2–8 weeks of treatment, particularly during the intensive phase. Risk factors include younger age, female gender, malnutrition, hypoalbuminemia, and baseline liver dysfunction. Extra-pulmonary TB, particularly tuberculous meningitis, and concomitant hepatotoxic medications such as antiretro viral therapy or antiepileptic drugs further increase susceptibility. Genetic predisposition, including N-acetyltransferase 2 and cytochrome P4502E1 polymorphisms and specific HLA alleles also contribute to the increased risk. Clinically, ATDIH ranges from asymptomatic transaminase elevation to severe acute liver failure (ALF), necessitating prompt recognition and intervention. Diagnosis relies on the temporal association of liver injury with ATT initiation, supported by liver function tests, improvement upon ATT cessation, and recurrence upon reintroduction. Management involves discontinuing hepatotoxic drugs, initiating non-hepatotoxic regimens, and sequential reintroduction of ATT under close monitoring. For children with ALF, care in a tertiary center with liver transplantation expertise is essential. While pediatric ATDIH generally has favorable outcomes with timely intervention, delays can result in significant morbidity and mortality. Improved understanding of risk factors, vigilant monitoring

protocols, and standardized pediatric management strategies are critical for optimizing outcomes in pediatric ATDIH.

Key Words: Antituberculosis therapy; Drug; Liver; Injury; Isonaizid; Rifampicin; Pyrazinamide

Core Tip: Antituberculosis therapy (ATT) causes hepatotoxicity as a major side effect. The withdrawal of ATT and modification of ATT remains the cornerstone for immediate management of ATT induced hepatotoxicity.

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INTRODUCTION

Tuberculosis is a common disease in children. An estimated 10.6 million people contracted tuberculosis in the world in 2022 including 1.3 million (12%) children[1]. Antituberculosis therapy (ATT) is essential for treating tuberculosis. Antituberculosis drug-induced hepatotoxicity (ATDIH) is one of the most common and serious adverse events during the treatment of tuberculosis[2]. Among the first-line ATT, pyrazinamide is considered to have the highest hepatotoxic potential, followed by isoniazid and rifampicin; however, isoniazid is the most frequently implicated drug in clinical cases of ATDIH. Other hepatotoxic drugs in multidrug-resistant tuberculosis regimens include ethionamide, p-aminosalicylic acid, and bedaquiline[3]. Hepatotoxicity can lead to treatment interruption and thus increased risk of treatment failure, progression of disease, and development of resistance. Lack of appropriate management can lead to significant morbidity and mortality. Understanding the risk factors and effective management strategies for ATDIH is crucial for optimizing outcomes in children with tuberculosis. Literature on pediatric ATDIH is limited, prompting us to write this review to summarize the pediatric aspects of this topic and provide valuable insights for clinicians.

DEFINITIONS AND TERMINOLOGY

Terms like tuberculosis-tuberculosis drug-induced liver injury (DILI), antituberculosis liver injury, antituberculosis drug-induced hepatitis and ATDIH are often used interchangeably in pediatric studies, creating potential confusion. Establishing consistent terminology and definitions for ATDIH is essential for more accurate data analysis in pediatric patients. Defining ATDIH can be challenging because different studies use varying definitions based on the Asian Pacific Association for the Study of Liver, American Thoracic Society (ATS), British Thoracic Society (BTS) guidelines, and National tuberculosis Elimination Programme (NTEP)[4-7]. In pediatric studies, the definitions used are outlined in Table 1. By and large, an acceptable definition of ATDIH is: Aspartate/alanine aminotransferase (AST/ALT) $^{3}5$ fold upper limit of normal (ULN) with or without symptoms or AST/ALT $^{3}3$ fold ULN with symptoms and/or total bilirubin > 2 fold ULN. DILI is categorized into three types based on serum biochemical profiles: Hepatocellular, cholestatic, and mixed injury. The classification depends on the R-value, calculated by dividing the serum ALT/ULN ratio by serum alkaline phosphatase/ULN. An R-value of ≥ 5 indicates hepatocellular injury, ≤ 2 signifies cholestatic injury, and an R-value between 2 and 5 indicates mixed injury[8]. However, none of the pediatric studies categorize ATDIH based on the type of liver injury.

EPIDEMIOLOGY AND BURDEN

ATDIH is a major and significant adverse effect, representing over 7.0% of all observed adverse reactions. The incidence of ATDIH in children varies greatly, ranging from 0-27% depending on the population and criteria used[9-16]. The World Health Organization revised ATT dosages in 2010, however, the incidence of hepatotoxicity was not significantly different among the two groups. Additionally, no hepatotoxicity was observed during prophylactic therapy[12].

Table 1 Summary of pediatric studies on antitubercular therapy-induced hepatotoxicity in children

Ref.	Terminologies	Definition	Prevalence	Monitoring	Management
Mehra *et al*[9]	TB-DILI	Any 1: ALT/AST > 3 × ULN with symptoms; ALT/AST > 5 × ULN without symptoms; bilirubin > 1.5 mg/dL	12.3%	LFT baseline, 2/4/6 weeks, then every 2 months	Stop ATT, monitor LFTs every 3–5 days; Reintroduce full doses sequentially (Rifampicin, then Isoniazid, then Pyrazinamide)
Gafar *et al*[10]	ATLI	Any 1: ALT/AST > 3 × ULN with symptoms (> 5 × ULN without symptoms); bilirubin > 2 mg/dL with jaundice	26.8%	LFT at baseline, and 2 weeks. Then 4, 6, 8 weeks if 2 weeks LFT was abnormal	LFT weekly, Reintroduction of all 3 drug simultaneously
Yunivita *et al*[11]	ADIH	ALT/AST > 3 × ULN or > 1.5 × ULN if baseline is abnormal	27.9%	Not mentioned	Not mentioned
Indumathi *et al*[12]	ATDH	ALT > 3 or 5 × ULN with or without symptoms	2.7%	Clinical follow-up every 2 weeks (in IP); every 1 month (in CP)	Stop ATT; Rifampicin, INH and pyrazinamide were restarted in sequential manner
Aishatu *et al*[13]	Hepatotoxicity	ALT or AST > 3 × ULN	0%	LFT at baseline, at 2 and 5 months	ATT stopped; gradual reintroduction: Rifampicin first, then isoniazid
Nataprawira *et al*[14]	ADIH	Jaundice and/or total bilirubin > 1.5 mg/dL; and/or ALT > 3-5 × ULN above normal levels	3.5%	Not mentioned	Not mentioned
Hotchandani *et al*[15]	ATDIH	Jaundice and/or total bilirubin > 1.5 mg/dL; ALT 3-5 × ULN above normal level	13.92%	LFT baseline, 2/4/6 weeks, then every 2 months	ATT stopped; LFT twice per week; low-dose Rifampicin (7 days), then low-dose Isoniazid (7 days); increase doses of both over 10-14 days. PZA after 2 weeks
Mansukhani *et al*[16]	Hepatic Dysfunction	SGPT > 3 × ULN	15.2%	SGPT at baseline and after 15 days, then every 2 months	Not mentioned

TB-DILI: Tuberculosis drug-induced liver injury; ATLI: Antituberculosis liver injury, ADIH: Antituberculosis drug-induced hepatitis; ATDH: Antituberculosis drug hepatotoxicity; ATDIH: Antituberculosis drug-induced hepatotoxicity; ×: Times of; ATT: Antitubercular therapy; CLD: Chronic liver disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LFT: Liver function test; ULN: Upper limit of normal; IP: Intensive Phase; CP: Continuation Phase; INH: Isoniazid.

PATHOPHYSIOLOGY

Hepatic adaptation

Hepatic adaptation describes the transient asymptomatic elevation of serum transaminases during the early phase of ATT and resolves spontaneously with ongoing drug therapy at the same dosage without clinical symptoms or intervention. According to the study by Devarbhavi *et al*[17], this process involves the physiological adaptation of the liver to damage induced by ATT, facilitating tolerance and potentially attenuating the severity of ATDIH.

This adaptation may include the upregulation of hepatic enzymes, compensatory pathways, and the development of tolerance. Hepatic adaptation involves the induction of cytochrome P450 enzymes, which enhances the liver's metabolic activity and leads to mild, asymptomatic elevation of transaminases. This enzyme upregulation is a natural physiological response and does not necessarily indicate hepatotoxicity. Additionally, the liver undergoes transient hepatocyte stress due to initial drug exposure, but cellular adaptation and regeneration processes effectively prevent progression to significant liver injury[5].

In their study, Mehra *et al*[9] observed a 13.5% prevalence of hepatic adaptation, while other studies did not report this phenomenon. It is essential to distinguish hepatic adaptation from true ATDIH to avoid unnecessary treatment interruptions that can compromise tuberculosis management. Misinterpreting hepatic adaptation as ATDIH can lead to premature discontinuation of ATT, which poses significant risks such as treatment failure, relapse of tuberculosis, development of drug resistance, and increased morbidity and mortality, particularly in the pediatric population. Recognizing hepatic adaptation allows clinicians to make informed decisions, ensuring uninterrupted tuberculosis treatment, better disease control, and reduced risk of ATDIH-related complications. Proper monitoring and understanding of this phenomenon are critical for balancing safety and therapeutic efficacy in tuberculosis management.

Mechanism of ATDIH

Isoniazid, rifampicin, and pyrazinamide are potent hepatotoxic drugs. Isoniazid is the most frequently implicated drug in ATDIH due to its widespread and prolonged use in the continuation phase, despite pyrazinamide having a higher intrinsic hepatotoxic potential[15]. DILI due to isoniazid is an immune-related idiosyncratic reaction resulting in hepatocellular necrosis and steatosis. The enzymes involved in the metabolic pathway, N-acetyltransferase 2 (NAT2) and cytochrome P4502E1 (CYP2E1), play a crucial role in determining the risk of hepatotoxicity. Isoniazid is predominantly

metabolized by NAT2 into diacetylhydrazine, which is a non-toxic compound. Individuals who are fast acetylators metabolize isoniazid quickly and clear acetylhydrazine more rapidly, whereas slow acetylators accumulate increased amounts of acetylhydrazine, increasing the risk of isoniazid-induced hepatotoxicity by four-fold[18,19]. Human hepatic NAT2 is polymorphic, with *in vitro* acetylation activity progressively decreasing from NAT24 > NAT27 > NAT26 > NAT25 alleles[20]. Hydrolysis (CYP2E1) is a minor pathway in the isoniazid metabolism. The minor pathway dominates in the presence of enzyme inducers like rifampicin and in slow acetylators. This results in the accumulation of toxic by-products (acetyldiazine), reactive acetyl onium ions, and acetyl radicals. These compounds covalently bind to cellular macromolecules and cause DILI. Also, glutathione has free radical scavenging activity. Roy *et al*[20], showed that null mutations at glutathione S-transferase loci would have twice the incidence of ATDIH.

Rifampicin undergoes hepatic metabolism *via* deacetylation and hydrolysis to diacetyl rifampicin and 3-formylrifampicin, respectively. The metabolites are excreted in bile. The mechanism of hepatotoxicity is mainly dose-dependent. It leads to unconjugated hyperbilirubinemia by competing with bilirubin uptake at the sinusoidal membrane and conjugated hyperbilirubinemia by inhibiting the major bile salt export pump[21]. It potentiates the hepatotoxicity of other ATT drugs by its enzyme-inducing action. The incidence of ATDIH is around 1.6% and 2.5% in patients with isoniazid without rifampicin and combined isoniazid - rifampicin respectively[22].

Pyrazinamide, a nicotinic acid derivative, is converted to pyrazinoic acid through deamidation. It is then further oxidized by xanthine oxidase into 5-hydroxy pyrazinoic acid. Pyrazinamide can cause dose-dependent and idiosyncratic hypersensitivity hepatotoxicity, potentially triggering eosinophilia and liver damage or granulomatous hepatitis[14]. Hepatotoxicity is seen in 15% of those consuming higher doses of pyrazinamide[23].

CLINICAL PRESENTATION

Children with ATDIH may have varied presentations ranging from asymptomatic elevation of transaminases to acute liver failure (ALF). Those who are symptomatic may experience nausea, vomiting, abdominal pain, loss of appetite, jaundice, unexplained fatigue, and newly detected hepatomegaly[9]. Signs of severe illness include pronounced jaundice, coagulopathy, hypoalbuminemia, and hypoglycemia.

RISK FACTORS

Several risk factors in the pediatric population have been associated with ATDIH, which may be patient- related, drug-related or disease - related. In a study by Yunivita *et al*[11], younger age and female gender were associated with a higher risk of hepatotoxicity. Nutritional status plays a significant role in increasing the risk of ATDIH. Patients with hypoalbuminemia, low body mass index, and malnutrition are more susceptible to hepatotoxicity due to depletion of glutathione stores, leading to oxidative damage and impairment of hepatic drug metabolism[10]. Mehra *et al*[9], reported that an elevated baseline ALT level is an independent risk factor for ATDIH, as seen in patients with underlying liver disease and chronic viral hepatitis. This indicates that pre-existing liver dysfunction predisposes patients to more significant liver damage following ATT administration. Disease-related factors, such as the form and severity of tuberculosis, also influence the likelihood of hepatotoxicity. Gafar *et al*[10], reported that the risk of ATDIH is higher with extra-pulmonary tuberculosis, especially tuberculosis meningitis compared to pulmonary tuberculosis due to the severity of the underlying disease or the use of concomitant hepatotoxic anti-epileptic drugs.

In other studies, genetic factors, including polymorphisms in drug-metabolizing enzymes such as NAT2 and CYP2E1, can also affect susceptibility to hepatotoxicity. Additionally, the presence of *HLA-DQB10201* and the absence of *HLA-DQA1*0102 are linked to an increased risk[17]. The use of concomitant medications such as antiretrovirals or anticonvulsants may enhance the risk of hepatotoxicity by increasing the metabolic burden on the liver[24,25]. Additionally, drug-related factors, such as the combination of isoniazid and rifampicin, are associated with a significantly higher hepatotoxic potential compared to the use of individual drugs alone. This synergistic toxicity arises from their combined effects on hepatic enzyme induction and oxidative stress[5]. In summary, pediatric ATDIH is a multifactorial condition influenced by patient-specific vulnerabilities (*e.g.*, age, gender, and nutrition), pre-existing liver disease, disease severity, genetic predisposition, and drug interactions. A comprehensive evaluation of these risk factors is essential to identify high-risk patients early and optimize treatment strategies to minimize hepatotoxicity.

TIME FRAME TO DEVELOP ATDIH

ATDIH primarily occurs during the intensive phase of therapy in the first 8 weeks, with a median duration of onset around 2 weeks. In children, Mehra *et al*[9] reported that 60% developed hepatotoxicity within the first 7 days, 20% within 8–14 days, and the remainder by 21 days[9]. Gafar *et al*[10], observed ATDIH in 26.8% of children, with cases emerging between 14–42 days, while Yunivita *et al*[11] noted that 58% of hepatotoxicity cases presented during the intensive phase. Comparatively, adult data shows that 53% of cases of ATDIH occur within 2 weeks and 87% by 2 months of starting treatment, with a median onset of 12.5 days[26]. Both children and adults are at higher risk of ATDIH in the intensive phase, though onset may be earlier in pediatric populations, necessitating close monitoring.

DIAGNOSIS OF ATDIH

The initiation of ATT and the onset of hepatotoxic effects typically exhibit a temporal relationship, with symptoms manifesting within a few weeks to several months. An improvement in liver function test (LFT) upon discontinuing ATT and worsening of LFT on reintroducing ATT implies a causal association. Excluding other potential sources of liver injury, such as acute viral hepatitis, biliary tract disease, adverse effects from concomitant medications, and herbal supplements, supports the diagnosis of ATDIH[27].

Role of liver biopsy

Liver biopsy is not routinely recommended for diagnosing ATDIH, as the diagnosis is primarily clinical. However, liver biopsy is warranted in selected cases where the diagnosis remains uncertain, or the liver injury persists despite drug cessation. This is particularly important to rule out other etiologies, such as autoimmune hepatitis, Wilson disease, or metabolic liver disorders[4]. The pathological findings in ATDIH can vary depending on the causative drug and the severity of liver injury. In general, lobular hepatitis, submassive to massive necrosis, and hydropic degeneration of hepatocytes are observed in severe cases. Hepatocellular necrosis is the predominant pattern seen with isoniazid-induced hepatotoxicity. In rifampicin-associated hepatotoxicity, histological features include focal hepatocellular necrosis, apoptosis predominantly in zone 3, and cholestasis. These findings underscore the variability in liver injury patterns and emphasize that biopsy serves a limited role primarily for differential diagnosis[28].

MANAGEMENT STRATEGIES

The withdrawal of ATT remains the cornerstone for the immediate management of ATDIH. Modified ATT including at least three non-hepatotoxic drugs (levofloxacin, ethambutol, and streptomycin) can be started based on the severity of symptoms. The period of modified ATT should not be taken into account for deciding the final duration of therapy[29]. Supportive care, including hydration, nutritional support, and treatment of symptoms, is essential for patient recovery. Close monitoring of LFT and clinical parameters is necessary to track the resolution of hepatotoxicity and assess treatment response[8]. Management guidelines for ATDIH are available from the ATS[5], BTS[6], WHO[30], Asia Pacific Association for the Study of the Liver[4] and NTEP of India[7]; so practices are adapted from these sources. Reintroduction strategies can be sequential with incremental, sequential with full dosages, or simultaneous with full dosages. The sequential regimen helps in identifying the offending drug and modifying the ATT regimen if needed. Several pediatric studies have adopted a sequential approach to the reintroduction of ATT[9,12,13,15]. Table 2 summarizes these guidelines with slight variations in the reintroduction of ATT and LFT monitoring.

Sharma *et al*[31] studied the safety of three different ATT reintroduction regimens in adults and found no differences in the three groups. A systematic review by Soni *et al*[32], concluded that a sequential and incremental regimen may have lower risk of ATDIH compared to a concomitant regimen. However, their results were not statistically significant.

Contraindications to therapy reintroduction include fulminant hepatitis and underlying decompensated liver disease. Recurrence during reintroduction is rare in children. If symptoms recur or transaminase levels rise, the most recently added drug should be discontinued. Table 1 summarizes the various management and monitoring approaches in children with ATDIH. Given the lack of a standardized pediatric guideline, we propose an algorithm for managing ATDIH, as shown in Figure 1. The stepwise approach ensures close monitoring and gradual reintroduction of ATT drugs to mitigate the risk of further hepatotoxicity.

ATT INDUCED ALF

ALF secondary to ATDIH in children is a rare but life-threatening condition that requires urgent intervention. Diagnosis is based on established ALF criteria, including the absence of pre-existing chronic liver disease (CLD), biochemical evidence of acute liver injury, and hepatic coagulopathy defined as international normalized ratio (INR) ≥ 1.5 unresponsive to Vitamin K in the presence of clinical hepatic encephalopathy, or INR ≥ 2 irrespective of encephalopathy [33]. Children with ATT-induced ALF should be managed in tertiary care centers equipped with expertise in pediatric hepatology and liver transplantation. Management involves immediate discontinuation of hepatotoxic drugs and initiation of alternative non-hepatotoxic regimens. Supportive care focuses on liver function monitoring, glucose maintenance, and managing hepatic encephalopathy. While intravenous N-acetylcysteine has shown benefits in adults by reducing IL-17, a cytokine linked to hepatic encephalopathy and poor outcomes, however pediatric data is inconclusive regarding its routine use in non-acetaminophen ALF[12,34]. Liver transplantation remains the definitive treatment for irreversible liver failure[33]. Early recognition of ALF progression and timely referral for liver transplantation are critical to improve survival outcomes in pediatric ATDIH.

ATT IN CLD

Managing ATDIH in patients with CLD presents significant challenges. These patients may have a higher risk of developing DILI, and the prevalence of tuberculosis in CLD patients is 15 times higher than in the general population due

Table 2 Management guidelines by various societies

	American Thoracic Society (2006: updated 2016) 14	British Thoracic Society (1998) 15	WHO (2010) 30	APASL (2021) 12	NTEP (2022) 16
Stopping hepatotoxic drugs in ATDIH	Yes	Yes	Yes	Yes	Yes
When to reintroduce ATT	ALT return to < 2 × ULN	ALT return to <2 × ULN	LFT return to normal and clinical Symptoms resolve	AST/ALT < 2× ULN Bilirubin < 1.5 × ULN	ALT return to < 2 × ULN
What drug and which regimen (sequentially or simultaneously)	RIF ± EMB full dose, after 3–7 days, INH full dose followed by PZA	INH → RIF→PZA (Dose titration every 2–3 days)	RIF→ introduce; INH after 3–7 days); PZA to avoid	RIF →INH→PZA (start low dose of each drug and titrate dose upwards every 3 days); Continue EMB full dose PZA (Restart only if mild DILI without jaundice)	RIF ± EMB full dose, after 3–7 days, INH full dose, followed by full dose PZA full dose
LFT monitoring during reintroduction	Check ALT 3–7 days after INH rechallenge	Daily Monitoring of LFT	LFT Monitoring (No recommendation on frequency)	Monitor LFT and INR every 3–7 days, earlier if symptoms arise	Check ALT 3–7 days after INH rechallenge

WHO: World Health Organization; APASL: Asia Pacific Association for the Study of the Liver; NTEP: National Tuberculosis Elimination Program, India; ATT: Antitubercular therapy; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LFT: liver function test; ULN: Upper limit of normal; RIF: Rifampicin; INH: Isoniazid; EMB: ethambutol; PZA: Pyrazinamide; INR: International normalized ratio; DILI: Drug induced liver injury; →: Followed by; ×: Times of.

to immune dysfunction[35]. ATDIH in cirrhotic patients is defined by an increase in transaminases or bilirubin exceeding two times the baseline value, after ruling out other potential causes[36]. Therefore, in contrast to patients without liver disease, baseline liver function tests are recommended in all patients with CLD before starting ATT. The impact of ATDIH in individuals with limited hepatic reserve can be severe and potentially fatal. Monitoring ATDIH in patients with underlying liver disease can be complicated due to fluctuations in liver function tests. The administration of ATT in CLD patients is guided by the Child-Turcotte-Pugh score, and regular weekly monitoring of liver function tests is recommended[37]. If a patient exhibits symptoms of ATDIH, management protocols include discontinuing ATT and providing symptomatic care. During the reintroduction of ATT, a stepwise approach starting with incremental doses of rifampicin followed by isoniazid is preferred, whereas pyrazinamide should not be reintroduced in these patients[35].

PROGNOSIS

The prognosis for children with ATDIH is generally favorable with timely intervention and monitoring. Gafar *et al*[10] reported resolution of symptoms and liver function within 1–2 weeks. However, outcomes can vary, as seen in a study by Nataprawira *et al*[14], where 68% completed treatment, but 8% died, and 24% were lost to follow-up. In another study by Mehra *et al*[9], 80% of patients recovered, while one case resulted in ALF and death. These findings emphasize the importance of early diagnosis, adherence to treatment, and vigilant monitoring to improve outcomes and reduce mortality. Overall, with prompt recognition, close monitoring, and appropriate intervention, most ATDIH cases show favorable outcomes. However, delays in management or attrition on follow-up can lead to severe complications, treatment failure, and mortality. There is a need for vigilant monitoring protocols and improved strategies for patient retention in tuberculosis management programs.

COMPARISON OF PEDIATRIC AND ADULT ATDIH

While the clinical presentation of ATDIH is similar mainly in both pediatric and adult populations, certain distinctions are notable in children. Hepatomegaly has been observed more frequently in pediatric studies, which could serve as an important clinical clue. Symptom interpretation can be challenging in very young children, particularly those under 5 years, due to limited communication abilities. As a result, clinicians often rely heavily on clinical signs and biochemical evidence for diagnosis. In terms of risk factors, adults exhibit additional contributors to hepatotoxicity, including advancing age, alcohol use, underlying comorbidities (*e.g.*, diabetes, hypertension), and the use of concomitant medications. These factors are less prevalent in children. Ongoing granulomatous hepatitis may be a confounder in both groups while interpreting ATDIH.

Management strategies for ATDIH are generally consistent between adults and children, focusing on drug withdrawal, liver function monitoring, and stepwise reintroduction of ATT. Notably, the NTEP 2022 provides the sole specific pediatric framework for managing ATDIH in children[7]. Unlike adults, pediatric patients necessitate more intensive and frequent monitoring due to their developing liver functions, higher vulnerability, and dependency on caregivers. This

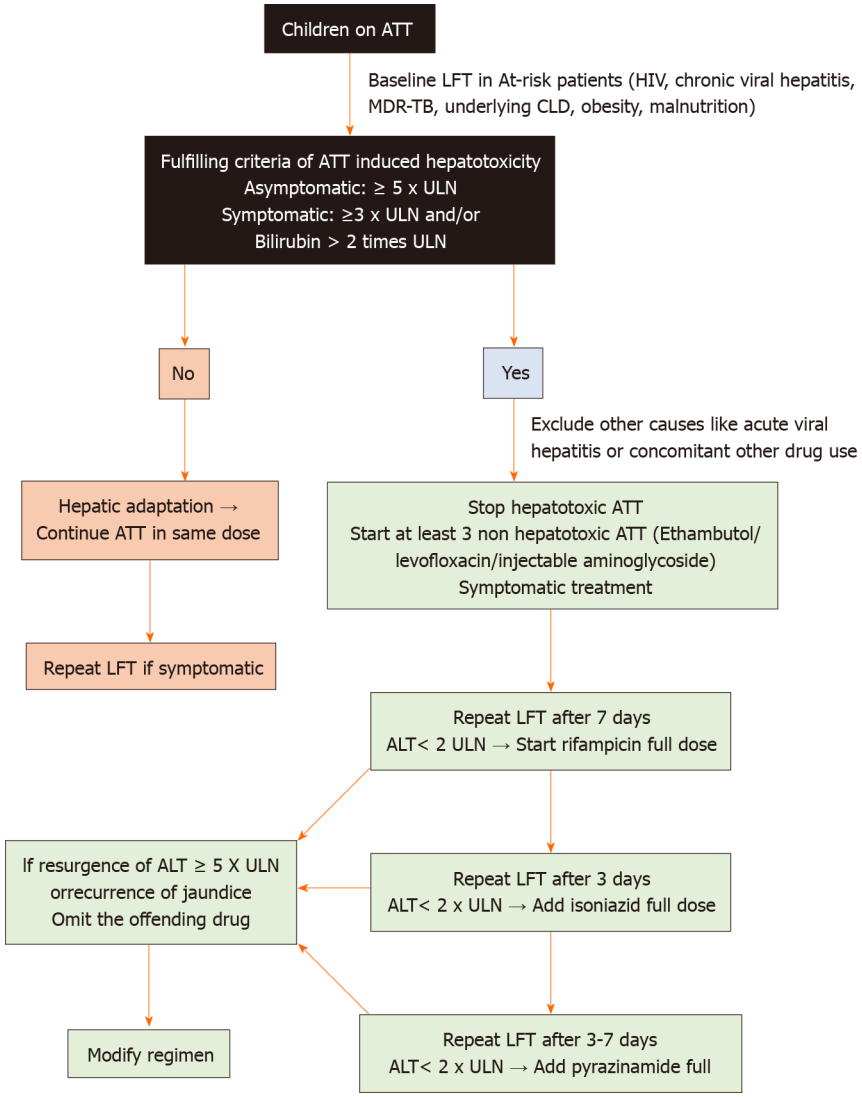

Figure 1 Algorithm for management of antitubercular therapy-induced hepatotoxicity in children. MDR: Multidrug resistance; ATT: Antitubercular therapy; HIV: Human immunodeficiency virus; CLD: Chronic liver disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LFT: Liver function test; ULN: Upper limit of normal.

underscores the importance of close observation and individualized care in pediatric ATDIH to optimize outcomes and minimize complications.

CONCLUSION

In summary, ATDIH is a significant concern in pediatric tuberculosis patients, necessitating close monitoring. Identifying risk factors helps in screening high-risk groups such as underlying malnutrition, underlying liver disease, severe extrapulmonary tuberculosis, concomitant antiretroviral therapy or anti-epileptic drugs, drug-resistant tuberculosis, and performing baseline liver function tests in these patients may prevent severe complications like ALF. Parents should be instructed in detail about symptoms of ATDIH such as vomiting, high coloured urine, visible jaundice and irritability in young infants. Usually patients develop ATDIH within the first three weeks of starting the intensive phase of ATT. Early detection of hepatotoxicity and immediate discontinuation of the offending drugs are key for a favorable outcome. The phenomenon of hepatic adaptation should be kept in mind while interpreting LFT in asymptomatic patients. Sequential reintroduction of the full dosage regimen may be considered for ATT, but more studies are needed before making a final conclusion. A simplified, universal management protocol is needed to refine treatment strategies and improve care for this population of pediatric tuberculosis patients.

FOOTNOTES

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