ANTI-TUBERCULOSIS INDUCED HEPATITIS IN PEDIATRIC POPULATION

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ABSTRACT:

Background: Tuberculosis (TB) remains a major cause of pediatric morbidity in low- and middle-income countries. First-line anti tuberculosis therapy (ATT) includes drugs known for hepatotoxic potential. Anti-tuberculosis drug-induced hepatitis (ATLI) is a clinically significant adverse effect that can lead to treatment interruption, poor adherence, and increased morbidity.

Objective: To determine the frequency of anti-tuberculosis induced hepatitis among children receiving first-line ATT.

Methods: A cross-sectional study was conducted in the Department of Pediatrics, Sandaman Provincial Hospital, Quetta, over 6 months. A total of 186 children aged 1–15 years on ATT for at least 4 weeks were enrolled. Children with viral hepatitis, biliary obstruction, hepatotoxic drug use, or liver lesions were excluded. Clinical evaluation and liver function tests (bilirubin, ALT, AST, and ALP) were performed. ATLI was diagnosed based on clinical features (jaundice or abdominal pain) plus predefined biochemical criteria. Data were analyzed using SPSS v26 with $p \leq 0.05$ considered significant.

Results:

The frequency of ATLI was 15.6% (29 out of 186 children). The mean age of affected patients was 9.2 ± 3.4 years; 55.2% were males. The most common presenting symptom was abdominal pain (58.6%), followed by yellowish discoloration of skin (37.9%). Most cases developed hepatotoxicity between 4–8 weeks of treatment. Mean ALT, AST, and bilirubin among ATLI cases were significantly higher compared to non-ATLI children ($p < 0.001$). Duration of ATT greater than 6 weeks ($p = 0.02$), low body weight ($p = 0.03$), and rural residence ($p = 0.04$) were significantly associated with hepatotoxicity.

Conclusion: Anti-tuberculosis induced hepatitis is a significant complication in pediatric patients receiving first-line ATT, with an observed frequency of 15.6%. Early biochemical monitoring especially during the first 8 weeks can prevent treatment interruption and reduce morbidity. Strengthening screening and early recognition protocols is crucial for improving pediatric TB outcomes.

Keywords: Tuberculosis, pediatrics, hepatotoxicity, anti-tuberculosis therapy, drug-induced hepatitis.

Introduction

Tuberculosis (TB) remains one of the most significant infectious diseases globally, with children representing a substantial proportion of its burden. According to the World Health Organization (WHO), an estimated 10.4 million people developed TB in 2016, including approximately one million children (World Health Organization, 2017). TB accounts for about 1.3 million deaths annually, disproportionately affecting low- and middle-income countries, especially those in Africa and South Asia (World Health Organization, 2017).

Anti-tuberculosis therapy (ATT) is essential for TB control; however, it is associated with several adverse drug reactions. Among these, anti-tuberculosis drug-induced hepatotoxicity (ATLI) is of greatest concern due to its potential severity (Yee et al., 2018; Tostmann et al., 2008). The most hepatotoxic first-line agents include isoniazid, rifampicin, and pyrazinamide, all of which undergo hepatic metabolism and can lead to drug-induced liver injury (Ramappa & Aithal, 2013). Pyrazinamide is particularly known for its strong hepatotoxic potential, while rifampicin increases the effect of isoniazid through enzyme induction (Tostmann et al., 2008).

Pakistan is among the top high-burden TB countries. With an estimated 510,000 new cases annually, including 46,000 among children fewer than 14 years, TB remains a critical public health challenge (Ansari et al., 2014). Treatment success depends greatly on adherence to ATT, yet adverse drug reactions such as hepatotoxicity threaten treatment continuity and increase the risk of resistance (Wares et al., 2018; Devarbhavi et al., 2013).

Pediatric patients may have different susceptibility to hepatotoxicity due to developmental physiology, nutritional status, and genetic factors. Several studies have reported pediatric hepatotoxicity rates ranging from 15% to 27% (Gafar et al., 2019; Mansukhani & Shah, 2012; Sultan et al., 2018). The onset often occurs during the intensive phase of treatment, typically within the first 4–8 weeks (Gafar et al., 2019). Clinical presentation ranges from abdominal pain to frank jaundice, although some cases may be asymptomatic, making biochemical screening essential (Choudhary et al., 2013; Durand & Bernuau, 2002).

Given the high TB prevalence in Pakistan and the potential severity of ATLI, understanding its burden and characteristics in children is vital. Evidence from Balochistan remains scarce, and local data are necessary to guide clinical monitoring and improve treatment outcomes. This study aims to determine the frequency and clinical profile of ATLI in pediatric patients receiving first-line ATT at a tertiary care center in Quetta.

Literature Review

TB continues to pose a global health challenge, especially among children in low-resource regions. Childhood TB accounts for an estimated 10% of the global TB burden, a figure likely underestimated due to diagnostic difficulties (World Health Organization, 2017; Saukkonen et al., 2006). Pediatric TB management is further complicated by the potential for adverse drug reactions, including hepatotoxicity.

ATT-induced hepatotoxicity is among the most common and serious complications associated with TB therapy. The incidence varies widely across studies, with reports ranging from 3% to

27% in pediatric populations (Gafar et al., 2019; Mansukhani & Shah, 2012; Yadav et al., 2018). Contributing factors include differences in drug metabolism, nutritional deficiencies, comorbid infections, and genetic predisposition (Taneja et al., 2017; Ramappa & Aithal, 2013).

Isoniazid, rifampicin, and pyrazinamide are the most hepatotoxic agents (Tostmann et al., 2008). Isoniazid toxicity is linked to slow acetylation phenotypes, while pyrazinamide is considered the most directly hepatotoxic. Rifampicin can potentiate hepatotoxicity when combined with isoniazid. Pediatric studies have confirmed that most cases of ATLI occur during the first two months of therapy, corresponding with concurrent exposure to these agents (Gafar et al., 2019; Saunders et al., 2002).

The clinical presentation of ATLI varies. Common symptoms include abdominal pain, nausea, vomiting, jaundice, and malaise, although some children present only with biochemical derangements (Choudhary et al., 2013; Durand & Bernuau, 2002). Laboratory findings typically include elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase (ALP). Patterns of hepatocellular, cholestatic, or mixed injury may be observed (Lee, 2003). Regional studies in South Asia demonstrate comparable ATLI frequencies. In Pakistan, Ansari et al. (2014) noted an increased risk in patients with hepatitis B or C co-infection. Another local study by Sultan et al. (2018) found a 14% incidence in children receiving ATT. Studies from India and Nepal similarly report hepatotoxicity as an important treatment-limiting complication (Tiwari & Dutta, 2018; Wares et al., 2018).

Risk factors for ATLI in children include malnutrition, low body weight, anemia, prolonged use of ATT, and rural residence (Choudhary et al., 2013; Malik et al., 2017). Nutritional status is a key determinant since children with protein-energy malnutrition may have impaired hepatic detoxification pathways (Parkin & Preece, 2002). Limited access to healthcare in rural areas may delay detection, thereby increasing severity.

The consequences of ATLI are significant. Hepatotoxicity often necessitates treatment interruption, which increases the risk of treatment failure, relapse, and drug resistance (Devarbhavi et al., 2013; Saukkonen et al., 2006). In resource-limited settings, lack of routine biochemical monitoring exacerbates these risks.

Given this background, local data on ATLI in Pakistani children particularly in underserved provinces such as Balochistan are essential. Understanding the frequency, clinical characteristics, and risk factors can help guide evidence-based monitoring, early detection, and safer TB treatment strategies.

METHODOLOGY

Study Design

This study employed a cross-sectional design to determine the frequency of anti-tuberculosis induced hepatitis among children receiving anti tuberculosis therapy (ATT). A cross-sectional approach was selected due to its suitability for estimating disease burden and identifying associations between clinical and biochemical variables at a single point in time.

Study Setting

The study was conducted in the Department of Pediatrics, Sandaman Provincial Hospital, Quetta, which is a major tertiary care and referral center in Balochistan. The hospital receives a large number of pediatric tuberculosis cases from both urban and rural areas, making it an appropriate site for this investigation.

Study Duration

The study was carried out over a period of six months, commencing after approval from the Institutional Ethical Review Committee and the College of Physicians and Surgeons Pakistan (CPSP).

Sample Size

A sample size of 186 children was calculated using the WHO sample size calculator. The following parameters were used:

- Expected frequency of anti-tuberculosis induced hepatitis: 14% (based on Sultan et al., 2018)
- Margin of error: 5%
- Confidence level: 95%

This sample size provided adequate statistical power to detect the expected frequency and perform subgroup analyses.

Sampling Technique

A consecutive non-probability sampling technique was used. All eligible children presenting consecutively to the outpatient department for TB follow-up visits during the study period were invited to participate.

Inclusion Criteria

Children were eligible for inclusion if they met the following criteria:

- Age between 1 and 15 years
- Both genders
- Diagnosed with pulmonary or extra pulmonary tuberculosis
- Receiving first-line ATT for at least 4 weeks prior to enrollment

Exclusion Criteria

Children were excluded if they had evidence or history of the following:

- Hepatitis A infection (anti-HAV IgM positive)
- Hepatitis B infection (HBsAg positive)
- Hepatitis C infection (anti-HCV IgM positive)
- Biliary obstruction, confirmed through abdominal ultrasonography
- Congestive hepatomegaly due to cardiac disease
- Previous hepatotoxic drug use (e.g., anticonvulsants, antiretroviral)
- Liver abscesses or focal liver lesions, confirmed by ultrasonography

These exclusions ensured that any detected liver injury could be attributed to ATT with minimal confounding.

Operational Definitions

Anti-Tuberculosis Induced Hepatitis (ATLI)

ATLI was defined as the presence of clinical symptoms (either yellowish discoloration of the skin or abdominal pain) along with any one of the following abnormal liver function test values:

- Total bilirubin >1.1 mg/dL
- Alanine aminotransferase (ALT) >50 U/L
- Aspartate aminotransferase (AST) >34 U/L
- Alkaline phosphatase (ALP):
    - 500 U/L for children <12 years
    - 750 U/L for children aged 12–15 years

A child meeting these criteria was labeled as having anti-tuberculosis induced hepatitis.

Data Collection Procedure

After ethical approval, children presenting to the outpatient department for routine follow-up and meeting the inclusion criteria were assessed for eligibility. Details of the study objectives, risks, benefits, and confidentiality measures were explained to parents or guardians. Written informed consent was obtained, and for children aged 7–15 years, assent was also documented.

A structured pre-designed proforma was used to record demographic and clinical information including:

- Age
- Gender
- Weight
- Residence (urban/rural)
- Family monthly income
- Duration of ATT
- Presenting symptoms

A trained phlebotomist collected 5 mL of venous blood using aseptic technique. Blood samples were sent to the hospital laboratory for liver function testing, including total bilirubin, ALT, AST, and ALP. Laboratory reports were reviewed by the investigator, and hepatitis was classified according to the operational definition. All information was recorded confidentially and assigned a serial study number.

Data Analysis

Data were analyzed using IBM SPSS version 26.

Quantitative Variables

Variables such as age, weight, and family income, duration of ATT, bilirubin, ALT, AST, and ALP were summarized as:

- Mean ± standard deviation (SD) for normally distributed data
- Median with interquartile range (IQR) for skewed data

Normality was assessed using the Shapiro–Wilk test.

Qualitative Variables

Variables including gender, residence, presenting symptoms, and presence of hepatitis were expressed as frequencies and percentages.

Stratification and Inferential Analysis

To control for confounders such as age, gender, residence, weight, family income, and duration of ATT, stratification was performed.

After stratification:

- Chi-square test was applied for categorical variables
- Fisher's exact test was used when expected cell counts were <5

A p-value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 186 children diagnosed with tuberculosis and receiving first-line anti tuberculosis therapy (ATT) for at least 4 weeks were included in the study. The demographic characteristics, clinical features, biochemical parameters, frequency of anti-tuberculosis induced hepatitis (ATLI), and stratified analyses are presented below.

Demographic Characteristics

The mean age of the participants was 8.6 ± 3.7 years. Among the total sample, 53.2% were males and 46.8% females. Most children belonged to rural areas (57.5%)**,** and the majority had low

socioeconomic status, with a median family monthly income of PKR 22,000 (IQR: 18,000–28,000). The mean weight of participants was 22.4 ± 6.8 kg.

Clinical Presentation

The most common presenting symptom among children later diagnosed with ATLI was abdominal pain (58.6%), followed by yellowish discoloration of the skin (37.9%). A minority reported nausea, vomiting, or generalized weakness.

Biochemical Findings

Children diagnosed with ATLI had significantly higher liver enzyme levels compared to non-ATLI children. The mean ALT and AST levels among ATLI cases were 92.4 ± 34.1 U/L **and** 71.2 ± 28.3 U/L, respectively.

Frequency of Anti-Tuberculosis Induced Hepatitis

Out of 186 children, 29 developed ATLI, resulting in a frequency of: 15.6%

Most cases occurred between 4 to 8 weeks of treatment initiation. Duration of ATT >6 weeks, rural residence, and low body weight were significantly associated with ATLI ($p \leq 0.05$).

Table 1: Demographic Characteristics of the Study Population (n = 186):

Variable	Mean ± SD / n (%)
Age (years)	8.6 ± 3.7
Weight (kg)	22.4 ± 6.8
Gender	
• Male	99 (53.2%)
• Female	87 (46.8%)
Residence	
• Urban	79 (42.5%)
• Rural	107 (57.5%)
Family Monthly Income (PKR)	Median 22,000 (IQR: 18,000–28,000)
Duration of ATT (weeks)	Median 6 (IQR: 4–8)

Table 2: Clinical Presentations among Children with ATLI (n = 29):

Clinical Feature	N (%)
Abdominal pain	17 (58.6%)
Yellowish discoloration (jaundice)	11 (37.9%)
Nausea/vomiting	6 (20.7%)
Hepatomegaly	4 (13.8%)
Generalized weakness	3 (10.3%)

Table 3: Comparison of Biochemical Parameters between ATLI and Non-ATLI Groups:

Parameter	ATLI (n = 29) Mean ± SD	Non-ATLI (n = 157) Mean ± SD	p-value

Total Bilirubin (mg/dL)	2.1 ± 0.9	0.7 ± 0.3	<0.001
ALT (U/L)	92.4 ± 34.1	32.6 ± 14.8	<0.001
AST (U/L)	71.2 ± 28.3	29.4 ± 12.6	<0.001
ALP (U/L)	612 ± 110	424 ± 87	<0.001

Table 4: Frequency of Anti-Tuberculosis Induced Hepatitis (n = 186):

Hepatitis Status	**n (%)**
Present (ATLI)	29 (15.6%)
Absent	157 (84.4%)

Table 5: Stratification Analysis of Factors Associated With ATLI:

Variable	**ATLI Present (n=29)**	**ATLI Absent (n=157)**	**p-value**
Age >10 years	13 (44.8%)	41 (26.1%)	0.04*
Gender (Male)	16 (55.2%)	83 (52.9%)	0.81
Rural Residence	20 (69.0%)	87 (55.4%)	0.04*
Weight <20 kg	14 (48.3%)	41 (26.1%)	0.02*
Duration of ATT >6 weeks	18 (62.1%)	58 (36.9%)	0.02*

*Statistically significant at $p \leq 0.05$.

Summary of Key Findings

- ATLI frequency**:** 15.6%
- Most affected age group**:** >10 years
- Common symptoms**:** abdominal pain (58.6%), jaundice (37.9%)
- Significant factors**:** duration of ATT >6 weeks, rural residence, low weight
- Biochemical markers**:** significantly higher ALT, AST, bilirubin, ALP in ATLI group

DISCUSSION

This study found that 15.6% of pediatric TB patients developed ATLI, consistent with frequencies reported in regional studies (Mansukhani & Shah, 2012; Sultan et al., 2018). A significant proportion developed hepatotoxicity between the fourth and eighth week of treatment, consistent with findings from Gafar et al. (2019), who identified the intensive phase of ATT as the period of highest risk.

The most common symptoms—abdominal pain and jaundice—align with established clinical patterns described in the literature (Choudhary et al., 2013; Durand & Bernuau, 2002). Elevated liver enzymes and bilirubin levels confirmed hepatocellular and cholestatic injury, consistent with mechanisms of ATT-induced toxicity described by Ramappa and Aithal (2013). Risk factors identified in this study, including rural residence, low body weight, and longer duration of therapy, are similarly reported in other pediatric populations (Malik et al., 2017; Taneja et al., 2017). Malnutrition may impair hepatic metabolism, increasing susceptibility to ATLI (Parkin & Preece, 2002). The implications of ATLI include treatment interruption and risk of drug resistance, emphasizing the need for routine liver function monitoring (Saukkonen et al., 2006;

Devarbhavi et al., 2013). Early recognition and intervention can prevent progression to severe liver injury.

In the present study, the majority of hepatotoxicity cases emerged between 4 to 8 weeks of initiating therapy. This is consistent with global evidence indicating that the intensive phase where children are exposed to multiple potentially hepatotoxic drugs (isoniazid, rifampicin, and pyrazinamide) poses the highest risk of liver injury. Pyrazinamide, in particular, is well-established as the most hepatotoxic first-line drug, and its concurrent administration with isoniazid amplifies the risk due to their synergistic hepatic metabolism pathways (3).

The clinical presentation in this study was dominated by abdominal pain (58.6%) and yellowish discoloration of the skin (37.9%)**,** findings comparable to earlier studies. Many pediatric patients with ATLI may initially present with vague, nonspecific symptoms such as malaise or gastrointestinal discomfort before progressing to overt jaundice. This underlines the challenge clinicians' face in detecting ATLI early, especially in resource-constrained settings where routine laboratory screening may be inconsistent.

Analysis of associated factors revealed statistically significant relationships between ATLI and age >10 years**,** rural residence**,** low body weight**,** and duration of ATT >6 weeks. Rural children may have delayed access to care, poorer nutritional status, or limited follow-up a plausible explanation for higher susceptibility. Low body weight, often a marker of malnutrition, can impair hepatic drug metabolism, increasing vulnerability to toxicity. Similar associations have been reported by studies in South Asia, where malnutrition and socioeconomic deprivation amplify the risk of ATT-related adverse events (8,9).

Gender did not show a significant association with hepatotoxicity in this study, consistent with findings from other pediatric cohorts, although adult studies often report higher susceptibility among females (3,7). This difference may reflect developmental physiology, differences in drug metabolism, and varying exposure patterns. The implications of ATLI extend beyond the immediate hepatic injury. Hepatotoxicity often necessitates temporary cessation or modification of ATT, posing risks of treatment interruption, poor adherence, prolonged infectiousness, and potential development of drug resistance. The findings of this study support the need for routine baseline and periodic liver function testing in all pediatric TB patients, especially during the first 8 weeks of therapy. Strengthening monitoring protocols in outpatient settings, training healthcare providers to recognize early warning signs, and improving follow-up systems may significantly reduce the burden of ATLI. Furthermore, nutritional support programs for underweight children may mitigate risk.

Overall, the findings confirm that anti-tuberculosis induced hepatitis is a significant and preventable complication in children. Early recognition, appropriate laboratory monitoring, and timely intervention can reduce morbidity, ensure treatment adherence, and improve overall outcomes in pediatric tuberculosis management.

CONCLUSION

Anti-tuberculosis drug-induced hepatitis is a significant and clinically relevant complication among pediatric TB patients, with a frequency of 15.6% in this study. Routine biochemical surveillance, particularly during the first 8 weeks of treatment, is essential for early detection. High-risk groups—including underweight children and those residing in rural settings—require closer monitoring. Improved awareness among clinicians can enhance treatment safety and outcomes.

Several factors, including older age (>10 years), rural residence, low body weight, and prolonged duration of therapy (>6 weeks), were significantly associated with an increased risk of

hepatotoxicity. These findings underscore the importance of routine clinical and biochemical monitoring in pediatric TB patients, especially among high-risk groups.

Early detection and timely management of ATLI are essential to prevent treatment interruption, drug resistance, prolonged illness, and increased morbidity. Strengthening monitoring protocols and improving physician awareness can significantly enhance treatment safety and overall TB outcomes in the pediatric population.

RECOMMENDATIONS

1. **Routine Liver Function Monitoring:** Baseline and periodic liver function tests (LFTs) should be incorporated into standard TB management protocols, particularly during the first 8 weeks of therapy.
2. **Focused Monitoring of High-Risk Children:** Children who are underweight, reside in rural areas, or have longer treatment duration should receive more frequent clinical and biochemical assessments.
3. **Strengthening Clinical Awareness:** Healthcare providers should be trained to recognize early signs of hepatotoxicity such as abdominal pain, jaundice, nausea, and unexplained weakness.
4. **Timely Management Protocols:** Standardized guidelines should be implemented to guide clinicians on when to temporarily stop ATT, initiate supportive therapy, and safely reintroduce drugs.
5. **Nutritional Support:** Programs targeting malnutrition and low body weight may reduce the risk of hepatotoxicity and improve overall treatment outcomes.
6. **Improved Follow-Up Systems:** Regular follow-up visits should be ensured through appointment tracking, counseling, and community health worker involvement, especially for rural populations.
7. **Future Research:** Larger multi-center studies, including assessment of drug levels, genetic factors, and long-term outcomes, are recommended to further elucidate risk factors and preventive strategies for ATLI.

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