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Anti-Tuberculosis Therapy Induced Liver Injury in Children

Muhammad Akhter Sultan, Hira Asim, Seemin Saleem, Asim Umar, Saifullah Sheikh, Muhammad Asghar Butt

ABSTRACT

Introduction: Tuberculosis has remained and is one of the major issues of the under developed world including Pakistan. About 10-11% cases of tuberculosis are from pediatric population. Isoniazid, rifampicin and pyrazinamide constitutes generally used therapeutic regime. Directly observed treatment short course (DOTS) is now much popular strategy. Ant tuberculosis drug-induced liver injury creates obstacles in treatment and also exerts socioeconomic strain on resources. **Objective:** To determine the frequency, severity and pattern of the Anti-tuberculosis Drug-Induced Liver Injury in children under 14 years of age. **Study Design:** Case series study. **Duration of Study:** 02-10-2015 to 03-10-2016. **Setting:** Department of Pediatric Medicine Unit-1, Allied Hospital, Faisalabad. **Sample size:** The total sample size is 100 cases. **Sampling Technique:** Non-probability purposive sampling. **Methodology:** Total of 100 patients with either sex from 1 to 15 years of age, on anti-tuberculosis therapy due to any variety of tuberculosis having normal liver anatomy and function initially were studied. Patients already having hepatobiliary disease regardless of etiology were not enrolled in study. Initial diagnosis was confirmed using set criteria. All patients underwent detailed medical history and physical examination followed by investigations. Data comprising age, sex, type of tuberculosis, treatment interval, and hepatotoxicity etc. was collected using designed Performa by the researcher. The data was analyzed through SPSS-20 by means of descriptive statistic. **Results:** In our study, out of 100 children, minimum age was 6 months and maximum age was 156 months and Mean ± SD was calculated as 38.07±37.368 months, 51 (53.1%) were male and 45 (46.9%) were females, ventilator associated pneumonia was recorded in 19 (19.8%) while 77(80.2%) had no findings of the ventilator associated pneumonia. **Conclusion:** The frequency of TB DILI was 14.0% in this study, indicating the importance of keeping index of suspicion high for the development of hepatotoxicity with anti-tuberculosis therapy in children being treated for any variety of tuberculosis.

Keywords: Tuberculosis, drug induced liver injury, anti-tuberculosis therapy, hepatotoxicity

Corresponding Author
Dr. Muhammad Akhter Sultan
Medical officer, Pediatrics Unit-1
Allied Hospital, Faisalabad.
Contact: +92 345-7829369
Email: akhterdr@live.com

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INTRODUCTION

Tuberculosis (TB) caused by mycobacterium tuberculosis is both preventable and treatable.[1] Considered as a disease of past in industrialized world[2], tuberculosis remains a noteworthy infectious disease and elucidates a worth mentioning socioeconomic burden in underdeveloped countries.[3]This is due to poor screening, late case detection and lack of treatment facilitation in these resource depleted countries.[2] Only six countries contributes almost 60% of the tuberculosis cases occurring globally.[4] About 10-11% cases of tuberculosis are from pediatric population. According to WHO data, almost 1 million children had tuberculosis infection each year and 210 000 children lost their life during the course of illness.[1] In Pakistan, disease prevalence is documented to be almost 350 (158 - 618)[3] securing a place in the top 6 nations with the maximum burden of disease.[4] In liaison with the world health organization and national Tuberculosis treatment guidelines, directly observed treatment short course (DOTS) now considered foundation stone of tuberculosis control programs.[5] Globally an uprising trend in the tuberculosis control is observed, by putting into practice the directly observed treatment short courses (DOTS). Despite aforementioned strategy, pediatric TB remains a leading cause in addition; to various other causes of illness and death of youngsters of underdeveloped nations including Pakistan.[6] The situation is further worsened by the tuberculosis treatment associated problems like nephrotoxicity, ototoxicity, hepatotoxicity etc.[7] Almost every foreign substance ingested is metabolized in the liver. True is the case with anti-tuberculosis chemotherapy.[8] Directly observed treatment short-course (DOTS) strategy recommended by the World Health Organization (WHO), include Isoniazid, rifampicin and pyrazinamide as pivotal components and hepatotoxicity has been experienced with 4,5 each of them.[8] Drug induced liver injury is one of the most serious and commonly observed side effect of the anti-tuberculosis therapy thereby limiting usefulness of therapeutic regimes4,5.[9] Problem got further exacerbated by the epidemic of human immunodeficiency virus (HIV) , causing an increase in the no of cases and deaths associated with tuberculosis particularly in the Africa. In association with HIV infection, failure in decreasing incidence of TB and profound increase in conversion from latent to active tuberculosis is observed. Hasty commencement of anti-tuberculosis therapy is warranted for the active disease.[6] In general, first line chemotherapeutic agents i.e. Isoniazid, rifampicin, pyrazinamide etc. in combination, are used after detection of active tubercular disease .All these mentioned drugs had got well recognized hepatotoxic profile.[11] Anti-tuberculosis drug-induced liver injury (TB DILI), by definition, is hepatic injury due to anti-tuberculosis drugs as

suggested by the international DILI Expert Working Group and American Thoracic society. Multifactorial etiology is considered in the pathogenesis TB DILI, taking into account HLA association, idiosyncrasy and various free radicals production. Toxic metabolites are generated, by the virtue of idiosyncratic response to INH and in the face of oxidative stress; they lead to key organelle damage. This key concept can be used to demonstrate enhanced risk of hepatotoxicity in settings of concomitant rifampicin and pyrazinamide intake.[12] Presence of certain factors like drug abuse, older age, underlying chronic liver disease and metabolic disorder have been linked with more chances of evolving anti-TB drug-induced hepatic injury (DIH) 3, 6.[13]

Tuberculosis had remained and is one of the major issue of the poorly developing countries including Pakistan. According to world health organization Pakistan is included in top ranked countries with major burden of TB in the world and almost (1%) population is suffering the disease. Pakistan's Annual incidence of tuberculosis is reported to be 510,000 including 46000 children under 14years of age. Treatment success rate is 93%among newly diagnosed cases. National TB budget costs 62 US$ millions and funding source include <1% domestic, 65% international, 35% unfunded. The new cases reported are almost 3 million per annum with almost 80/100,000 sputum proved cases.[14] Allergic and skin reactions, gastrointestinal upsets, neurological problems, nephrotoxicity and hepatotoxicity are commonly reported adverse events seen with anti-tuberculosis chemotherapy. Amongst them hepatic injury is the utmost grave and so is the center of the current analysis.[15]

Pakistan is highly prevalent area of tuberculosis with significant resultant mortality and morbidity.[16] In such settings liver injury from tuberculosis therapy further exacerbates the problem by contributing to resistance and may eventually leads to failure of TB eradication goal. Taking into consideration the gravity of issue, better concept of symptomatology of TB DILI like expected time of onset, severity grade, initial clinical features and biochemical features are of utmost significance in recognition of the toxic effects of therapy with requirement for timely intervention. A primary health care facility physician must have knowledge when to halt therapy if DILI is detected and when to resume it. Otherwise situation will further worsen in our country. Our study is designed to assess the exact burden, provides insight to the severity and pattern of liver injury resulting from ATT, so that resulting resistance to ATT and morbidity associated with this problem can be minimized.

METHODOLOGY

Study Design: Case series study.

Setting: Out-patient department of Pediatrics Medicine Unit-1, Allied Hospital, Faisalabad.

Duration of study: 02-10-2015 to 01-09-2016.

Sample size: Sample size was calculated by using WHO sample size calculator;

It will be 100 by keeping prevalence of ATT induced hepatitis 36.8[2], Absolute precision required 10%, Confidence level at 95%.

Sampling technique: Non probability purposive sampling technique

Inclusion Criteria: Pediatric population of either gender having age between 1 to 15 years and on ATT.

Exclusion Criteria: Included

Hepatitis A infection (anti HAV IgM antibody)
Hepatitis B infection (anti-Hbs Ag)
Hepatitis C infection (anti-HCV IgM antibody)
Biliary obstruction (confirmed by ultrasound)
Congestive Hepatomegaly
History of hepatotoxic drug intake
Liver abscesses or nay focal lesions (confirmed by ultrasound).
Any other apparent cause for the elevation of liver chemistries

Methods: 100 Children fulfilling the inclusion criteria with informed consent of their parents were studied after ethical review committee approval. All the children on ATT were closely monitored for any feature suggestive of drug induced liver injury, especially nausea, vomiting, anorexia, dizziness, abdominal pain, jaundice, encephalopathy. Monitoring was scheduled as weekly for the first month followed by biweekly schedule for next month and monthly later on till completion of therapy. Liver function tests (including aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum bilirubin & alkaline phosphatase (ALP) were performed ahead of starting anti-tuberculosis therapy and repeated at weekly interval for first two weeks followed by two weekly interval for next two weeks & 2monthly till completion of treatment. Afore ascribing DILI to anti-TB drugs, additional causes of liver diseases were ruled out by biochemistry, viral serology i.e HbSAg, anti-HCV IgM, anti-HAV IgM, abdominal ultrasound (for any local mass, abscess, hepatic texture changes suggestive of chronic liver disease). All necessary investigations including complete blood counts, erythrocyte sedimentation rate, X-ray chest were done. Data gathering was done with the help of specifically drafted Performa by the researcher.

Tuberculosis Infection: WHO criteria was used for diagnosing tuberculosis comprising; Mycobacterium tuberculosis growth on culture media, no growth but suggestive clinical and radiological features along with, anti-tuberculosis therapy response.[17]

Defining Drug Induced Liver Injury:

Done by the demonstration of any single of the underlying criteria:

1. Transaminases level rise by ≥5 times above the normal serum value (taking normal ranges of SGPT & SGOT at 7-41 U/L and 12-38 U/L respectively).
2. An increase of value more than 1.47 mg/ dL of total serum bilirubin
3. Clinical features of nausea, jaundice, dark colored urine and anorexia plus any degree of rise in serum baseline values of transaminases.[18]

Establishing Pattern of DILI: was defined by using following criteria
R = (ALT/UNL)/(ALP/UNL)
Hepatocellular Pattern of DILI = R ≥ 5
Mixed Pattern of DILI = R>2 and < 5
Cholestatic pattern of DILI = R ≤ 2 [19]

Severity Indexation of DILI:
Categorized according to WHO definition:
Grade 1 (mild) <2.5 times ULN (ALT 51–125 U/L)
Grade 2 (mild) 2.5–5 times ULN (ALT 126–250 U/L)
Grade 3 (moderate) 5–10 times ULN (ALT 251–500 U/L)
Grade 4 (severe) >10 times ULN (ALT > 500 U/L)[15]
Finally, the results were entered and analyzed with the help of SPSS version 20. Frequencies along with mean ± SD were used for expressing data. Tables were used for showing qualitative variables results. Effect modifiers like age and gender were controller by stratification. Post stratification chi-square test was applied. The value of P < 0.05 was taken significant statistically. Data were compared through Student's t-test and $\chi 2$ analysis for continuous variables and proportions, respectively.

Abbreviations:
ALT (alanine aminotransferase), ULN(upper limit of normal, i.e. 50 U/L),ALP(Alkaline Phosphatase) SGPT(serum glutamic pyruvic transaminase),SGOT(serum glutamic oxaloacetic transaminase),DILI(drug induced liver injury),HAV(hepatitis A virus),HBV(hepatitis B virus),HCV(Hepatitis C virus)

RESULTS

100 patients with confirmed diagnosis of tuberculosis and taking anti-tuberculosis therapy were included in our study from Oct 2015 to September 2017. Ages range between 1 to 15 years with Mean ±SD calculated as 6.378±4.3778 years (Table 1).

Table 1: Clinical Variable of Study Subjects (n=100)

	n	Minimum	Maximum	Mean	Std. Deviation
AGE	100	1	15	6.378	4.3778

Out of 100 patients, 51 (51.0%) were between 1 – 5years, 23(23.0) were between 6 – 10 years and 11 – 15 years calculated in 26 (26.0%) (Table 2).

Table 2: Age Distribution (n=100)

Age	Frequency	%age
1-5 years	51	51.0%
6-10 years	23	23.0%
11-15 years	26	26.0%
Total	100	100%

Amongst 100 patients, 55 (55.0%) were male and 45 (45.0%) were females (Table 3),

Table 3: Sex distribution of study subjects (n=100)

Gender	Frequency	Percent
Female	45	45.0
Male	55	55.0
Total	100	100.0

14 (14.0%) patients fulfilled the criteria of TB DILI while 86(86.0%) patients did not developed liver injury. (Table 4).

Table 4: Distribution of TB DILI according to study subjects (n=100)

TB Drug Induced Liver Injury	Frequency	Percent
No	86	86.0
Yes	14	14.0
Total	100	100.0

Amongst these 14 cases of TB DILI 08 were male while females were 6 (Table 5)

Table 5: Distribution of TB DILI according gender (n=100)

Gender	TB DILI		Total
	NO	Yes	
Male	47	08	55
Female	39	06	45
Total	86	14	100

Chi-square value: 0.30, p-value: 0.862

TB DILI frequency amongst 51, 23 and 26 patients belonging to1 – 5, 6 – 10 and 11 – 15 years was 1, 6 and 7 respectively. (Table 6).

Table 6: Distribution of TB DILI to age group (n=100)

		TB Drug Induced Liver Injury		Total
		No	Yes	
Age grouping	1 – 5 years	50	1	51
	6 – 10 years	17	6	23
	11 – 15 years	19	7	26
Total		86	14	100

Chi-square value: 12.537, p-value: 0.002

Pulmonary TB (55%) was the commonest variety followed by disseminated (14%), meningeal (14%), lymph nodes (11%) and abdominal TB (3%). (Table 7)

Table 7: Distribution of TB Variety according to study subjects (n=100)

Type of tuberculosis	Frequency	Percent
abdominal tuberculosis	3	3.0
tuberculosis meningitis	14	14.0
disseminated tuberculosis	14	14.0
intestinal tuberculosis	3	3.0
lymph nodes tuberculosis	11	11.0
pulmonary tuberculosis	55	55.0
Total	100	100.0

Among 14 patients with TB DILI Nausea, vomiting were most common followed by anorexia, abdominal pain and pruritus. (Table No. 8)

Table 8: Symptomatology in study subjects with TB DILI (n=14)

Clinical Symptoms	Frequency	Percentage
Abdominal pain	3	21.42
Anorexia	4	28.57
Dizziness	3	21.42
Pruritus	3	21.42
Nausea	6	42.85
Vomiting	5	35.71
Jaundice	1	7.14

Hepatocellular pattern (64.2%) turned out to be commonest type of TB DILI among study subjects followed by mixed and cholestatic pattern (21.4%) and (14.2%). (Table 9)

Table 9: Patterns of DILI among study subjects with TB DILI (n=14)

Pattern of DILI	Frequency	Percent
Cholestatic	2	14.2
Hepatocellular	9	64.2
Mixed	3	21.4
Total	14	100.0

Most of the patients with TB DILI have mild grade of injury (42.85%) followed by moderate and sever (35.71%) and (21.42%). (Table 10)

Table 10: Severity of TB DILI among study subjects with TB DILI (n=14)

Severity of DILI	Frequency	Percent
Mil d	6	42.85
Moderate	5	35.71
Severe	3	21.42
Total	100	100.0

Among the 14 patients of TB DILI, 50% have disseminated TB, 35.71% have pulmonary TB and 14.28% have extra pulmonary TB. (Table 11)

Table 11: Distribution of DILI according to verity of tuberculosis (n=14)

Type of tuberculosis	Frequency of DILI	Percent
Pulmonary	5	35.71
Extra pulmonary	2	14.28
Disseminated	7	50.00
Total	14	100.0

DISCUSSION

A combination of at least 3 or 4 drugs for initial intensive phase with essential first-line therapy is recommend in the treatment of childhood tuberculosis by WHO and National TB Control Program to overcome expected drug resistance[20]. According to Frydenberg et al anti-TB drugs are very well tolerated by the children if used according to pediatric recommended dosage[21]. Liver being metabolic factory of body is responsible for the drug metabolism and thereby more vulnerable to drug induced liver injury. All 3 essential first line anti-tubercular drugs (isoniazid, rifampicin and pyrazinamide) have the potential to cause liver injury[22,23]. with severity ranging between only liver enzymes level rise with no clinical symptomatology to overt hepatic failure. Increased chances of hepatotoxicity are present with higher than recommended dosage administration[24]. Usually diagnosis of TB DILI is based on suggestive clinical features in the presence of drug intake and their resolution with drug withdrawal[21]. TB DILI is quite alarming and require immediate discontinuation and replacement of the offender drugs[25]. Thus follow-up requires screening for any hepatotoxicity besides general wellbeing of the patient helping in early detection and intervention that will reduce the risk of hepatic injury but also treatment failure. The incidence of DIH depends upon various risk factors like age, patient built-up, underlying liver pathology, type and seriousness of disease itself; and dosage of drugs to name a few[26-30].

Being tuberculosis prevalent area, we designed our study to observe the effect of anti-tuberculosis therapy especially for hepatotoxicity in our population as no such previous data is available in our setup. Results of this study will be helpful not only in minimizing mortality and morbidity associated with this particular issue but also in reducing drug resistance as well as treatment failure by framing local protocols helpful in timely detection and prompt introduction of intervention in our patients. In this study, comprising of total 100 cases, ages range between 1 to 15 years with Mean ±SD calculated as 6.378±4.3778 years, 51 (51.0%) were between 1 – 5 years, 23 (23.0%) were between 6 – 10 years and 11 – 15 years was calculated in 26 (26.0%), 55 (53.1%) were male and 45 (45.0%) were females, TB DILI was seen in 14 (14.0%) while 86(86.2%) did not developed liver injury. . A similar percentage of DIH was seen in a study conducted at Karachi National Institute of Child Health[6]. A review study of Donald PR reported incidence of about 10% in children taking ATT due to TBM.11 Data from to local studies showed percentage of 8.4% to 20% in adult population which is also consistent with our study results.[27] Initial phase of therapy comprised majority of the TB DILI reported cases, a finding similar to most of the studies[31-34]. Highest percentage of patient developing TB DILI belongs to younger age group. This had been observed in various other studies also[28,29]. In this study patients who developed TB DILI had mean age of 2.5 + 1.3 yrs.' which was consistent with Mansukhani results of vulnerability at younger age i.e. (<3.5 yrs.) and different to 5.88 + 3.74 yrs. observed in an Indian study[35]. Among the 14 patients of TB DILI in current study, 8 were male and 6 were females and have p-value: 0.862, ruling against gender predisposition. A Spanish study by Lucena et al. had revealed comparable results with equal frequency in either gender[36]. In contrast male predilection for TB DILI was observed in a study conducted at Karachi[6].

Acute viral hepatitis as a complicating factor has been implicated by an Indian study[29], but we did not included patients having any liver pathology (acute or chronic) in our study. Pulmonary tuberculosis was the commonest type in our study which is consistent with a study by I. H. Naqvi et al[3]. Among 14 patients with TB DILI Nausea & vomiting were most common followed by anorexia, abdominal pain and pruritus. Results being congruent to one of the study conducted in china[37]. Hepatocellular pattern (64.2%) turned out to be commonest type of TB DILI among study subjects followed by mixed and cholestatic pattern (21.4%) and (14.2%). Ghabril et al. reported similar results in his study.[38]. However, this is in contrast to a study conducted in adult patient reporting highest proportion of cholestatic pattern. Most of the patients with TB DILI have mild grade of injury (42.85%) followed by moderate and sever (35.71%) and (21. 42%).Similar incidence of DILI severity was observed in a study from Ethiopia[39]. Among the 14 patients of TB DILI, 50% have disseminated TB, 35.71% have pulmonary TB and 14.28% have extra pulmonary TB. Comparable results were reported in a study by Hassen Ali et al. depicting disseminated tuberculosis being most vulnerable variety for developing tuberculosis[10].

No mortality was observed in our study in contrast to high mortality percentage reported in various other studies[32, 35, 40]. Difference can be attributed to early detection and prompt intervention in the form of alternative therapy introduction in patients of TB DILI.

CONCLUSION

Anti-tubercular drug-induced hepatotoxicity was observed in 14% of children with tuberculosis on treatment. Most of the patients developed ATDIH in the intensive phase of chemotherapy comprising of first line anti-tuberculosis drugs. We recommend keeping index of suspicion high, for TB DILI, in the presence of any suggestive clinical features with regular monitoring of serum alanine transaminase levels for timely diagnosis and speedy therapeutic intervention to prevent and minimize morbidity and mortality seen with TB DILI, hence also preventing treatment failure which may choke the national TB control program. It is also suggested to incorporate these recommendations in your local guide lines for monitoring of patients on anti-tubercular therapy to have better surveillance for at least a duration of intensive phase of therapy.

REFERENCES

1. World Health Organization: Tuberculosis. WHO Fact Sheet. Revised 2016.
2. Parsons LM, Somoskövi A, Gutierrez C, Lee E, Paramasivan CN, Abimiku A, Spector S, Roscigno G, Nkengasong J. Laboratory diagnosis of tuberculosis in resource-poor countries: challenges and opportunities. Clin Microbiol Rev. 2011;24(2):314-50.
3. Naqvi IH, Mahmood K, Talib A, Mahmood A. Antituberculosis drug-induced liver injury: an ignored fact, assessment of frequency, patterns, severity and risk factors. Open J Gastroenterol. 2015;5:173-84.
4. World health organization (2016) Global Tuberculosis Control: WHO report 2016.
5. Saha A, Shanthi FXM, Winston AB, Das S, Kumar A, Michael JS, Balamugesh T. Prevalence of hepatotoxicity from antituberculosis therapy: a five-year experience from South India. J Prim Care Community Health. 2016;7(3):171-4.
6. Hotchandani H, Moorani NK, Kazi Y. Anti-tuberculosis therapy induced hepatotoxicity in children. Pak Pediatr J. 2013;37:117-22.
7. Mohan N, Kumar J, Chakrawarty A, Ranjan P. Comprehensive review of anti-tubercular treatment induced liver injury. Int J Basic Clin Pharmacol. 2015;4:397-403.
8. Shamra SK, Mohan A. Antituberculosis treatment-induced hepatotoxicity:from bench to bedside. Medicine Update. 2005:479-84.
9. Jeong I, Park JS, Cho YJ, Yoon HI, Song J, Lee CT, Lee JH. Drug-induced Hepatotoxicity of Anti-tuberculosis Drugs and Their Serum Levels. J Korean Med Sci. 2015;30(2):167–72.
10. Ali AH, Belachew T, Yami A, Ayen WY. Anti-tuberculosis drug induced hepatotoxicity among TB/HIV co-infected patients at Jimma University Hospital, Ethiopia: nested case-control study. PLoS One. 2013;8(5):6462-72.
11. Kumar R, Shalimar, Bhatia V, Khanal S, Sreenivas V, Gupta SD, Panda SK, Acharya SK. Antituberculosis therapy-induced acute liver failure: magnitude, profile, prognosis, and predictors of outcome. Hepatology. 2010;51(5):1665-74.
12. Huang YS, Chern HD, Su WJ, Wu JC, Lai SL, Yang SY, Chang FY, Lee SD. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. Hepatology. 2002;35(4):883-9.
13. Ungo JR, Jones D, Ashkin D, Hollender ES, Bernstein D, Albanese AP, Pitchenik AE. Antituberculosis drug-induced hepatotoxicity. The role of hepatitis C virus and the human immunodeficiency virus. Am J Respir Crit Care Med. 1998;157:1871-6.
14. Ansari S, Bawany MD. Hayat AS, Munir A, Khahro AA, Naz F. Drug induced hepatitis; does hepatitis b and hepatitis c co-infection increases the risk during anti tuberculous chemotherapy. Prof Med J. 2014;21:49-54.
15. Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. J Gastroenterol Hepatol. 2008;23(2):192-202.
16. World Health Organization (2012) Global Tuberculosis Control: WHO Report 2012. http//apps.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf.
17. National Guidelines for Control of Tuberculosis in Pakistan, January 2015. http://ntp.gov.pk/uploads/NATIONAL_GUIDELINE_ON_TB_CASE_MANAGEMENT_REV_JAN_2015.pdf.
18. Steele MA, Burk RF, Des, Prez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. Chest. 1991;99(2):465-71.
19. Aithal GP, Watkins PB, Andrade RJ, et al. Case Definition and Phenotype Standardization in Drug- Induced Liver Injury. Clin Pharmacol Ther. 2011;89(6):806-15.
20. Marais BJ, Gupta A, Starke JR, El Sony A. Tuberculosis in women and children. Lancet. 2010;12;375(9731):2057-9.
21. Frydenberg AR, Graham SM. Toxicity of first line drugs for treatment of tuberculosis in children: Review. Trop Med Int Health. 2009;14(11):1329-37.

22. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006;15;174(8):935-52.
23. Singla R, Sharma SK, Mohan A, et al. Evaluation of risk factors for anti-tuberculosis treatment induced hepatotoxicity. Indian J Med Res. 2010;132:81-6.
24. Yew WW, Leung CC. Anti-Tuberculosis Drugs and Hepatotoxicity. Invited review. Respirology. 2006;11(6):699-707.
25. Perez – Velez CM, Marais BJ. Tuberculosis in children. N Engl J Med. 2012;26;367(4):348-61.
26. Tostmann A, Boeree MJ, Aarnoutse RE, et al. Anti- tuberculosis drug-induced hepatotoxicity: Concise up-to-date review. J Gastroenterol Hepatol. 2008;23(2):192-202.
27. Donald PR. Antituberculosis drug- induced hepatotoxicity in children. Pediatr Rep 2011;3(2):51-64.
28. Shakya R, Rao BS. Incidence of hepatotoxicity due to antitubercular medicines and assessment of risk factors. Ann Pharmacother. 2004;38(6):1074-9.
29. Sarda P, Sharma SK, Mohan A, et al. Role of acute viral hepatitis as a confounding factor in antitubercular treatment- induced hepatotoxicity. Indian J Med Res. 2009;129(1):64-7.
30. Singla R, Sharma SK, Mohan A, et al. Evaluation of risk factors for anti-tuberculosis treatment induced hepatotoxicity. Indian J Med Res 2010;132:81-6.
31. Yew WW, Leung CC. Anti-Tuberculosis Drugs and Hepatotoxicity. Invited review. Respirology. 2006;11(6):699-707.
32. Ohkawa K, Hashiguchi M, Ohno K, et al. Risk factors for antituberculous chemotherapy- induced hepatotoxicity in Japanese pediatric patients. Clin Pharmacol Ther. 2002;72(2):220-6
33. Memon JI, Almani SA, Burney AA, et al. Ant tuberculosis drug induced hepatitis. Med Channel 2006;12(1):49-51.
34. Shaikh MA, Yakta DE, Shaikh D. Frequency of Hepatotoxicity during anti-tuberculosis treatment at Medical Unit of LUMHS Sindh. Med Channel. 2012;18(1):20–3.
35. Mansukhani S, Shah I. Hepatic Dis-function in children with tuberculosis on treatment with anti-tubercular therapy. Ann Hepatol. 2012;11(1):96-9.
36. Younossian AB, Rochat T, Ketterer JP, Wacker J and Janssens JP. High hepatotoxicity of pyrazinamide and ethambutol for treatment of latent tuberculosis Eur Respir J. 2005;26(3):462-4.
37. Shang P, Xia Y, Liu F, Wang X, Yuan Y, Hu D, Tu D, Chen Y, Deng P, et al. Incidence, clinical features and impact on anti-tuberculosis treatment of anti-tuberculosis drug induced liver injury (ATLI) in China. PLoS One. 2011;6(7):e21836.
38. Ghabrila M, Chalasania N, and Björnssonb E. Drug-induced liver injury: a clinical update. Curr Opin Gastroenterol. 2010;26(3):222-6.
39. Yimer G, Gry M, Amogne W, Makonnen E, Habtewold A, Petros Z, et al. Evaluation of Patterns of Liver Toxicity in Patients on Antiretroviral and Anti-Tuberculosis Drugs: A Prospective Four Arm Observational Study in Ethiopian Patients PLoS One. 2014;8;9(4): e94271.
40. Devarbhavi H, Karanth D, Parasanna KS, et al. Drug induced liver injury with Hyper sensitivity features has better outcome: a single center experience of 39 children and adolescents. Hepatology. 2011;54(4):1344-50.

AUTHORSHIP AND CONTRIBUTION DECLARATION

AUTHORS	Contribution to The Paper	Signatures
Dr. Muhammad Akhter Sultan Medical officer, Pediatrics Unit-1 Allied Hospital, Faisalabad.	Contribution of the completion and design, acquisition of data, analysis of interpretation of data	
Dr. Hira Asim House Officer, Department of Surgery-II Bahawal Victoria Hospital, Bahawalpur	Contributed in completion and interpretation of data and give her expert opinion of manuscript designing	
Dr. Seemin Saleem Lecturer University of Faisalabad, Faisalabad	Drafting the article and share her expert research opinion and experience in formatting the manuscript	
Dr. Asim Umar Medical officer, Pediatrics Unit-1 Allied Hospital, Faisalabad.	Collection of data	
Dr. Saifullah Sheikh Assistant Professor, Pediatrics Unit-1 Allied Hospital, Faisalabad	Data analysis and Interpretation	
Prof. Dr. Muhammad Asghar Butt Head of the Department of Pediatrics Unit-1 Faisalabad Medical University, Faisalabad.	Supervised the study and contributed in conception and shares its expert research opinion