

## PREVALENCE AND RISK FACTORS OF ANTITUBERCULAR DRUG-INDUCED HEPATITIS IN URBAN POPULATION OF BAHAWALPUR DISTRICT, PUNJAB-PAKISTAN

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### ABSTRACT

**Introduction:** Tuberculosis (TB) infects one third of population, world over. Anti-tubercular like isoniazid, rifampicin and pyrazinamide are highly effective but hepatotoxic. Data on prevalence of anti-TB drug-induced hepatitis and contributing risk factors are scarce in Bahawalpur. This cross-sectional study was designed to look at the prevalence and promoting risk factors of drug-induced hepatitis in the urban population of Bahawalpur district, Punjab-Pakistan.

**Methods:** We examined a total of 1161 peoples (>15 years; 589 male and 572 female); divided into 3 groups *i.e.*, young (15≥35 years), mature (35≥50 years) and old (>50 years). Population was compared in terms of demographical data and risk factors, such as age, gender, hepatitis B/C carrier, and pretreatment liver biochemistries (serum albumin, globulin, aspartate aminotransferase, alanine aminotransferase and bilirubin). Data was evaluated by 95% confidence interval. Differences were considered significant at  $p < 0.05$  and highly significant at  $p < 0.001$ .

**Results:** Out of 146 TB patients, 21 developed hepatitis. The prevalence of drug-induced hepatitis was 14.38%. Lower serum albumin ( $p < 0.05$ ), higher serum globulin ( $p < 0.05$ ), tuberculosis, hepatitis B/C and poverty were significant risk factors.

**Conclusion:** ATB-induced hepatotoxicity was significantly frequent among the patients treated with ATB.

**Keywords:** anti-tuberculosis drugs, drug induced hepatitis, extrapulmonary tuberculosis, hepatotoxicity, isoniazid, pyrazinamide, rifampin, toxic hepatitis

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**Running title:** Prevalence and risk factors of antitubercular drug-induced hepatitis

## INTRODUCTION

Tuberculosis (TB) is a global pandemic and the incidence is on rise (Snider Jr and Roper, 1992). WHO declared TB a global emergency in 1993, since then efforts have been made to expand partnerships and bring all stakeholders on board in order to control this disease more effectively (WHO, 2010). High number of tubercular cases occurs in the Southeast Asia region, which accounts for about a one third of global prevalence (WHO, 2010).

TB occurs frequently in Pakistan and unfortunately it has been one of the neglected health issues in the past. The disease prevalence of 263/100 000 has been reported in Pakistan, (Ejaz et al., 2010). Pakistan ranks sixth in the world in terms of TB-burden (Javaid et al., 2008). About 44% of TB-burden is contributed by Pakistan in the Eastern Mediterranean Region while TB is responsible for 5.1% of the total national disease-burden in Pakistan. TB-impact on socio economic status is substantial (Tanveer et al., 2008; Hussain et al., 2003).

The treatment of TB by using chemotherapeutic agents like rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin proves often successful. However drug-induced hepatotoxicity poses a real problem. Occasionally, this hepatotoxicity is predictable and dose dependent, but for most, it may be idiosyncratic and dependent on other factors like drug dosage, age, gender, and body mass index (BMI) (Aithal et al., 1999; Björnsson et al., 2007). Underlying renal and/or liver diseases, the concurrent use of certain food and drugs as well as pregnancy may also play a significant role. Anti-TB drug induced-hepatotoxicity is variable and its occurrence is high in the developing countries; 2%-28%, in comparison to the developed countries; 3%-4%, despite similar regimens used (Tostmann et al., 2008).

A number of risk factors have been implicated, including older age, female gender, poor nutritional status, high alcohol intake, pre-existing liver disease, hepatitis B carriage, increased prevalence of viral hepatitis in developing countries, hypoalbuminaemia and advanced TB (Faustini et al., 2006). Inappropriate use of drugs, acetylator status and immunogenetic factors, have also been implicated (Sharma et al., 2002). Viral infections like hepatitis C and human immunodeficiency virus (HIV) have also been reported to increase such risk (Padmapriyadarsini et al., 2006).

A hospital-based prospective survey in Malaysia, indicated lower mean BMI, lower serum albumin and higher serum globulin, relating-factors in those who developed hepatitis by using anti-TB drugs (Fauzi et al., 2004). Among other reported risk factors, only chronic hepatitis B carrier status remained to be more prevalent. A through review of literature indicates the absence of any known published data on the prevalence of anti-TB drug-induced hepatitis in the urban population of Bahawalpur district, Punjab-Pakistan. Further, there is no data on the significance of multiple risk factors, contributing to the development of anti-TB drug-induced hepatitis in the part of this region. This study was designed therefore to examine these issues.

## **MATERIALS AND METHODS**

This was a population-based cross-sectional study which was carried out from August 10, 2009 to August 09, 2010. 1161 peoples (both sex) of different age and professions of urban areas of Bahawalpur, Pakistan, selected by random sampling were screened out for anti-tubercular drug induced hepatitis and promoting factors (Zaman et al., 2009).

### **Population selection and division criteria**

Selected sample of population of both sex, age;  $\geq 15$  years was divided into three groups *i.e.* young ( $15 \leq 35$  years), mature ( $35 \leq 50$  years) and old ( $> 50$  years). The male and female of same age were grouped together. A willingness certificate for co-operation in carrying out the purpose of present study was obtained, signed by each individual/parents/guardians before his/her inclusion in the study (Zaman, 2006).

### **Interview and blood collection**

All of the participants were interviewed in person at enrollment. Information on socioeconomic characteristics, dietary habits, personal medical and surgical history, family history of major diseases, and anti-T.B. drug treatments were obtained by using a structured questionnaire. A 5-mL blood sample was collected from each participant (Yang et al., 2008; Zaman, 2009).

### **Evaluation of specimen**

All the specimens were evaluated immediately following their collections for liver biochemistries (serum albumin, globulin, aspartate aminotransferase, alanine aminotransferase and bilirubin). Liver function tests (LFT) and HBsAg and Anti-HCV were performed by using commercially available kits. The anti-TB treatment regimens were either a combination of streptomycin, isoniazid, rifampicin and pyrazinamide (SHRZ), or a combination of ethambutol, isoniazid, rifampicin and pyrazinamide (EHRZ) (Behal et al., 2008; Yang et al., 2008; Zaman et al., 2009).

### **Statistical analysis**

The data was analyzed statistically by the application of proportions and confidence interval (CI of 95%) by modified Wald method (Bonett and Price 2006). "P" values were determined. Differences were considered non-significant at  $p > 0.05$ , significant at  $p < 0.05$  and highly significant at  $p < 0.001$  (Zaman et al., 2011).

## **RESULTS**

### **Prevalence of anti-TB drug induced hepatitis**

A total of 1161 peoples ( $> 15$  years; 589 male and 572 female) were included in the study. 148 patients had evidence of hepatitis, but only 146 were eligible and 2 were excluded. Those excluded were with non-specific pretreatment of hepatitis (Table 1).

### **Age specific prevalence**

Over all prevalence of anti-TB drugs induced (ATB) hepatotoxicity (HT) was 14.38% (95% CI; 0.095 to 0.211); maximum 17.54% (95% CI; 0.096 to 0.296) in old group followed by mature (15.09%, 95% CI; 0.076 to 0.273) and young (8.33%, 95% CI; 0.021 to 0.226) groups (Table 1).

### **Gender specific prevalence**

The prevalence of ATB-induced HT in male was 13.58% (95% CI: 0.076 to 0.229) compared to 15.39% (95% CI: 0.084 to 0.263) in female. The difference was found to be statistically insignificant (Table 1).

Table 1: Anti-T.B. Drugs caused-hepatitis in relation with sex and age among human urban population of Bahawalpur-Pakistan

Variables	TB-infected Population (n = 146)	Anti-T.B. Drugs			95% CI
		promoted-hepatitis <sup>a</sup> (n = 13) (8.90%)	induced-hepatitis <sup>b</sup> (n = 8) (5.48%)	caused-hepatitis <sup>ab</sup> (n = 21) (14.38%)	
<b>Age groups</b>					
Young (15≤35)	36	2 (5.56%)	1 (2.78%)	3 (8.33%)	0.0213 to 0.2257
Mature (35≤50)	53	5 (9.43%)	3 (5.66%)	8 (15.09%)	0.0759 to 0.2732
Old (>50)	57	6 (10.53%)	4 (7.02%)	10 (17.54%)	0.0962 to 0.2957
<b>Sex</b>					
Male	81	7 (8.64%)	4 (4.94%)	11 (13.58%)	0.0758 to 0.2287
Female	65	6 (9.23%)	4 (6.15%)	10 (15.39%)	0.0838 to 0.2625

TB, tuberculosis; CI, confidence interval

Table 2: Anti-T.B. drugs caused-hepatitis prevalence according to socioeconomic status of human urban population of Bahawalpur-

Pakistan

Variables	TB-infected Population (n = 146)	Anti-T.B. Drugs			95% CI
		promoted-hepatitis <sup>a</sup> (n = 13) (8.90%)	induced-hepatitis <sup>b</sup> (n = 8) (5.48%)	caused-hepatitis <sup>ab</sup> (n = 21) (14.38%)	
<b>Income</b>					
High	31	02 (06.45%)	01 (03.23%)	03 (09.68%)	00.0256 to 0.2569
Moderate	54	05 (08.26%)	02 (03.70%)	07 (12.96%)	0.0612 to 0.2473
Lower	61	06 (09.84%)	05 (08.20%)	11 (18.03%)	0.1020 to 0.2965
<b>Education</b>					
High	21	01 (04.76%)	01 (04.76%)	02 (09.52%)	0.0145 to 0.3012
Middle	49	04 (08.16%)	02 (04.08%)	06 (12.24%)	0.0536 to 0.2461
Low	76	08 (10.53%)	05 (6.58%)	13 (17.11%)	0.1014 to 0.2724

TB, tuberculosis; CI, confidence interval

### **Socioeconomic status specific prevalence**

The distribution of participants according to socioeconomic status; income and education is shown in Table 2. Maximum prevalence was observed in the peoples with low income and low education (18.03%, 95% CI: 0.102 to 0.297 and 17.11%, 95% CI: 0.101 to 0.272 respectively).

### **Medical illness and treatment regimens specific prevalence**

Slightly greater prevalence was found in the non-diabetics in comparison to the diabetics (14.67%, 95% CI: 0.082 to 0.246 verses 14.08%, 95% CI: 0.076 to 0.242) while hepatitis B and/or hepatitis C carriers developed HT by ATB, 100% (95% CI: 0.718 to 1.000). The prevalence was slightly greater with EHRZ than SHRZ treatment regimens (14.49%, 95% CI: 0.079 to 0.249 and 14.29%, 95% CI: 0.080 to 0.240) (Table 3).

### **Anti-TB drugs-induced changes in biochemical parameters**

ATB slightly reduced mean serum albumin levels both in hepatitis B and/or C careers and non-hepatitis careers before against after treatment for 21 days (Table 4). While serum globulin, serum ALT, serum AST and serum total bilirubin levels were highly significantly ( $p < 0.001$ ) increased in hepatitis B and/or C careers as well as non-hepatitis careers, pre-treatment versus post-treatment with ATB (Table 4).

## **DISCUSSION**

Hepatotoxic side effect of anti-TB drugs (ATB) has been under extensive discussion and studies to confirm their frequency and outcome in patients, all over the world (Tariq et al., 2009).

The prevalence of ATB-induced hepatitis observed in the present study was 14.38%, comparable with those reported in other Asian countries, ranging from 8% to 39% (Parthasarathy, et al., 1986; Türkteş et al., 1994). The observed prevalence is high as compared to those of developed countries; around 3%-4% (Combs et al., 1990). Possibly due to higher viral hepatitis prevalence in developing countries (Parthasarathy, et al., 1986; Türkteş, et al., 1994; Kumar, et al., 1991).

Table 3: Anti-T.B. drugs caused-hepatitis prevalence in relation to medical illness and treatment regimens of human urban population of Bahawalpur-Pakistan

Variables	Population (n = 146)	Anti-T.B. Drugs			95% CI
		promoted-hepatitis <sup>a</sup> (n = 13) (8.90%)	induced-hepatitis <sup>b</sup> (n = 8) (5.48%)	caused-hepatitis <sup>ab</sup> (n = 21) (14.38%)	
<b>Diabetes mellitus</b>					
Yes	71	06 (08.45%)	04 (5.63%)	10 (14.08%)	0.0764 to 0.2422
No	75	07 (09.33%)	04 (5.33%)	11 (14.67%)	0.0822 to 0.2456
<b>Hepatitis B and/or Hepatitis C carrier</b>					
Yes	12	12 (100%)	00 (%)	12 (100%)	0.7180 to 1.0000
No	134	01 (0.75%)	08 (5.97%)	09 (06.72%)	0.0341 to 0.1243
<b>Treatment regimens</b>					
SHRZ	77	07 (09.09%)	04 (05.19%)	11 (14.29%)	0.0799 to 0.2397
EHRZ	69	06 (08.70%)	04 (05.80%)	10 (14.49%)	0.0787 to 0.2486

S: streptomycin; H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol.



*Table 4: Anti-T.B. drugs caused changes in biochemical parameters in the human urban population of Bahawalpur-Pakistan*

Variables	Anti-T.B. Drugs Treatment in						
	Hepatitis virus-infected			95% CI	Hepatitis virus non-infected		
	Pre-treatment	Post-treatment	95% CI		Pre-treatment	Post-treatment	95% CI
Serum albumin (g/dL)	4.5±0.09	3.0±0.07**	1.4813 to 1.5187	4.8±0.82	3.1±0.90	1.5017 to 1.8983	
Serum globulin (g/dL)	3.8±0.02	2.0±0.02**	-3.105 to -3.095	3.7±0.03	2.5±0.04**	-1.208 to -1.192	
Serum ALT (U/L)	11.64±1.12	53.37±3.74**	-42.366 to -41.094	12.76±0.75	33.81±1.93**	-21.387 to -20.713	
Serum AST (U/L)	26.54±2.41	47.38±4.46**	-21.666 to -20.014	14.15±0.91	31.76±2.26**	-18.007 to -17.213	
Serum bilirubin (mg/dL)	1.94±0.05	4.32±0.28**	-2.426 to -2.334	1.99±0.02	2.65±0.03**	-0.666 to -0.654	

Pre-treatment: compared with post-treatment, Mean ± S.E.M = Mean values ± Standard deviation of means.

The findings of present study showed that there was a direct relationship between the hepatitis B and/or hepatitis C infection with the development of hepatotoxicity (Table 3). All the patients with positive hepatitis B and/or hepatitis C markers developed hepatotoxicity by ATB treatment and prevalence was 100% (95% CI: 0.718 to 1.000). However, data indicated almost similar prevalence in diabetics compared with non-diabetics (14.08%, 95% CI: 0.076 to 0.242 and 14.67%, 95% CI: 0.082 to 0.246 respectively). Similarly, both the treatment regimens, tested in this study; SHRZ (streptomycin, isoniazid, rifampicin, pyrazinamide) and EHRZ (ethambutol, isoniazid, rifampicin, pyrazinamide) showed slightly different prevalence (14.29%, 95% CI: 0.080 to 0.240 and 14.49%, 95% CI: 0.079 to 0.249 respectively) (Table 3). This finding is in accord with the reports of Chang et al., (2008); Lee et al., (2005); Kishore et al., (2007).

Socioeconomic parameters like income and education level of population have also been reported to be important in determining the prevalence of hepatitis (Zaman, 2009; Zaman et al., 2009). The study showed maximum prevalence (18.03%, 95% CI: 0.102 to 0.297) in the minimum followed by moderate and high income groups. Low educated people also exhibited highest prevalence (17.11%, 95% CI: 0.101 to 0.272) and minimum in the high educated population (Table 2).

The study showed that hepatotoxicity was more common in females (15.39%, 95% CI: 0.084 to 0.263) in comparison to male in tested population and this matches other studies conducted (Teleman et al., 2002; Shakya et al., 2006). This increased incidence in females is mainly due to differences in pharmacokinetics and slow acetylator status (Naz et al., 2010). Regarding age, study showed increased incidence in old (17.54%, 95% CI: 0.096 to 0.296) followed by mature and young groups (Table 1). Finding strengthened previous studies (Masako, 2005; Tariq et al., 2009). It may be due to aging factor where decline of drug metabolism is a contributory factor (Masako, 2005).

In a study by Shakya et al., (2006) ATB was found to be associated with derangement of hepatic function, resulting in elevation of liver enzymes where 2 times increase in ALT was observed in 38% of patients and more than 3 times elevation in 30% patients within 12–60 days (Tariq et al., 2009). Data of present study showed a highly significantly increase in ALT ( $53.37 \pm 3.74$ , 95% CI: -42.366 to -41.094) in hepatitis B and/or hepatitis C positive population, similarly a highly significantly increase in ALT ( $33.81 \pm 1.93$ , 95% CI: -21.387 to -20.713) in hepatitis B and/or hepatitis C negative population by ATB (Table 4). The study further indicated similar findings in serum AST and Bilirubin in hepatitis B and/or hepatitis C positive and negative volunteers (Table 4). Finding is in accord with the reports of Masako, (2005) and Marzuki et al., (2008).

Nutritional status (serum albumin) of tested population showed poor normal albumin level ( $3.5 \pm 0.09$  in hepatitis and  $3.8 \pm 0.82$  in normal population). It may be one of the risk factor for the ATB-induced hepatotoxicity (Shakya et al., 2006). The patients showed highly significant hypoalbuminaemia post-treatment in comparison with pretreatment both in hepatitis B and/or hepatitis C positive and negative population (Table 4). In malnutrition, glutathione stores are depleted which makes one vulnerable to oxidative injury. In a malnourished person liver metabolizes drug like ATB at a slower rate (Shakya et al., 2006; Lin et al., 2010). It was found that poor nutritional status increases the risk of hepatotoxicity. Decreased glutathione stores

and slower rate of liver metabolism are the possible causes of increased vulnerability among malnourished individuals (Naz et al., 2010).

The data further showed a highly significant change in serum globulin (Table 4); post-treatment in comparison with pretreatment both in hepatitis B and/or hepatitis C positive and negative patients. The observation was consistent with the findings of Marzuki et al., (2008) and Adhvaryu et al., (2007).

In conclusion, the prevalence of anti-TB drug-induced hepatitis in tested population 14.38% may be associated with lower pretreatment serum albumin, higher pretreatment serum globulin, hepatitis viral infection and poverty.

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