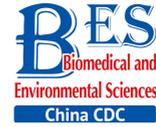## Letter to the Editor

Prevalence and Risk Factors Associated with Adverse Drug Reactions among Previously Treated Tuberculosis Patients in China[*]

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We assessed the incidence of adverse drug reactions (ADRs) with anti-TB medications and evaluated the risk factors for developing ADRs in previously treated tuberculosis patients in China. All patients received the first-line anti-TB regimen (2HREZS/6HRE) as recommended by the national guidelines. Clinical and laboratory evaluations were performed once a month. Out of the 354 participants, 262 (74.0%) experienced ADRs such as hyperuricemia (65.0%, 230/354), hepatotoxicity (6.2%, 22/354) and hearing disturbances (4.8%, 17/354). ADRs were significantly associated with diabetes mellitus [OR (95% *CI*): 15.5 (2.07-115.87)]; however, weight more than 50 kg [OR (95% *CI*): 0.41 (0.22-0.85)] was a protective factor for occurrence of ADRs. Hyperuricemia is the most common adverse event but, most patients with hyperuricemia showed increased tolerance for high uric acid levels. Low body weight and diabetes mellitus increased the risk of the occurrence of ADRs during anti-TB treatment.

Key words：Tuberculosis; Adverse drug reactions; Anti-TB medications; Tuberculosis treatment

Tuberculosis (TB) is a major public health threat globally[1]. According to the World Health Organization (WHO), approximately 10.40 million tuberculosis cases were globally diagnosed in 2015[2]. China has the third highest TB burden worldwide accounting for 11% of the global tuberculosis incidence[2]. Despite the successful control and prevention of tuberculosis in last 20 years, the incidence of pulmonary tuberculosis in China still remains at 68 cases per 100,000 people[2].

TB patients with a history of drug treatment always have worse outcomes than patients never treated before, because of high rates of drug resistance. Hence, further treatment of previously treated non-multiple drug resistance (MDR) patients requires extended treatment with isoniazid (INH, H), rifampicin (RMP, R), ethambutol (EMB, E), pyrazinamide (PZA, Z), and streptomycin (SM, S) according to the National Tuberculosis Program (NTP) of China. Although first-line anti-TB drugs are less toxic than second-line drugs, adverse reactions to INH, RMP, and EMB are well documented by previous studies[3]. Considering the prolonged anti-TB treatment with first-line drugs, the high rate of adverse drug reactions (ADRs) is expected among previously treated patients. Unfortunately, limited data on the adverse effects of these drugs among such patients is available in China. In this study, we enrolled the previously treated TB patients who had received the standard first-line anti-TB regimens in four specialized TB hospitals in China to determine the incidence of major ADRs associated with first-line anti-TB medications and evaluate the risk factors for developing the side effects with ADRs in this group of patients.

In this retrospective study, ADR was defined as 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product[4]. The diagnostic criteria for hearing disturbances, psychiatric, gastrointestinal disturbances, arthralgia, hepatotoxicity, leucopenia, peripheral neuropathy, and renal toxicity were followed in accordance with the guidelines of WHO[5]. Patients meeting at least one criterion were defined

as previously treated TB patients.

Previously treated TB patients seeking treatment in Beijing Chest Hospital, the Fourth Hospital in Inner Mongolia, the First Affiliated Hospital of Xinxiang Medical College, and the First Affiliated Hospital of Chongqing Medical University were included in this study. In addition to the treatment history the following were the inclusion criteria: ages between 18 to 65 years old, HIV negative, and positive tubercular culture results. The following were the exclusion criteria: extra pulmonary manifestations of TB, resistance to both isoniazid and rifampicin determined by phenotypic drug susceptibility testing, smear negative results, infection with non-tuberculous mycobacteria (NTM), patients with severe cardiac arrhythmia, patients with severe liver dysfunction, patients with severe kidney dysfunction, and patients with gout.

All patients received the first-line anti-TB regimen (2HREZS/6HRE) recommended by the national guidelines. The protocol applied in this study was approved by the Ethics Committees of Beijing Chest Hospital. All patients enrolled in this study provided written informed consent.

During the 5-year (2009-2013) study period, a total of 591 previously treated TB patients seeking treatment in four hospitals agreed to take part in this study. Of the 591 patients, 237 (40.1%) were excluded because of MDR-TB (20.0%, 118/591), NTM infection (1.9%, 11/591), negative sputum culture (12.4%, 73/591), severe comorbidities (4.2%, 25/591), and failure to follow-up (1.7%, 10/591). Hence, data from 354 previously treated patients were used for further analysis. The demographic and clinical characteristics are summarized in Table 1.

Majority of the participants were male (77.4%, 274/354), and weighed above 50 kg (67.5%, 239/354). The most common age group was 50-59 years (26.3%, 93/354). Eighty-nine patients (25.1%) had comorbidities other than tuberculosis.

As seen in Table 2, 262 patients (74.0%) had obvious side effects. The mean time of the occurrence of ADRs after anti-TB treatment was 1.9 ± 1.6 months. The three most common adverse events were hyperuricemia (65.0%, 230/354), hepatotoxicity (6.2%, 22/354), and hearing disturbances (4.8%, 17/354).

Although 65% (230/354) patients had hyperuricemia during anti-TB treatment, only 4.8% (11/230) patients (with pain or swelling in the joints) required modification of the treatment regimen. For patients suffering from hepatotoxicity, the symptoms improved with additional medication or withdrawal of any one of the anti-TB drugs in 22 cases, addition of a hepatoprotective drug in 12 cases, withdrawal of PZA in 8 cases, and withdrawal of RMP in 2 cases. In addition, all 17 patients complaining of hearing disturbances were attributed to SM and the symptoms were controlled after the withdrawal of SM.

We further analyzed the percentage of patients experiencing ADRs among different characteristics (Table 3). Multivariate logistic regression analysis found that ADRs was significantly associated with diabetes mellitus (*OR* 15.5; 95% *CI*, 2.07-115.87; *P* = 0.008). However, weight of more than 50 kg (*OR* 0.41; 95% *CI*, 0.22-0.85; *P* = 0.012) was a protective factor for occurrence of ADRs.

Table 1. Characteristics of Previously Treated Tuberculosis Patients

Characteristic	*n*	%
Age (y)		
< 30	55	15.5
30-39	48	13.6
40-49	85	24
50-59	93	26.3
≥ 60	73	20.6
Gender		
Male	274	77.4
Female	80	22.6
Weight (kg)		
< 50	115	32.5
≥ 50	239	67.5
Comorbidity		
No	265	74.9
Diabetes mellitus	56	15.8
Others	22	6.2

Table 2. Frequency of Adverse Events among 354 Previously Treated Patients

Adverse Event	Patients Experiencing Each ADR *n* (%)
All adverse events	262 (74.0)
Type of adverse event	
Hyperuricemia	230 (65.0)
Hepatotoxicity	22 (6.2)
Hearing disturbances	17 (4.8)
Arthralgia	15 (4.2)
Gastrointestinal disturbances	9 (2.5)
Allergic reaction	9 (2.5)
Dermatological effects	7 (2.0)
Renal toxicity	6 (1.7)
Leucopoenia	4 (1.1)
Psychiatric	4 (1.1)
Visual disturbance	2 (0.6)
Achilles tendinitis	2 (0.6)

The adverse reaction associated with anti-TB treatment is considered to be the major contributor towards treatment discontinuation, thereby, resulting in treatment failure. In our study, we found a higher rate of the ADRs among TB patients as compared to previous similar studies[3]. Gastrointestinal (GI) side effects and hepatotoxicity are the most frequent ADRs associated with anti-TB treatment, while the incidence of hyperuricemia ranges from 2.2% to 47.1% in previous studies[6-7]. In contrast, our study results reveals that hyperuricemia is the most frequent ADRs among previously treated TB patients. A similar study by Romanillos et al. also found that 83% of the patients under the treatment regimen containing PZA, led to an increase in the serum concentration of uric acid[8]. Despite the hyperuricemia, patients in our study showed better tolerance for increased uric acid, majority of whom did not develop arthralgia. Considering the crucial role of PZA in shortening the course of anti-TB treatment, our experience suggests that the occurrence of hyperuricemia should not be used as an indicator for withdrawing PZA from treatments unless the patients exhibit the symptoms of arthralgia. Hepatotoxicity was identified in 22 patients (6.2%), which is lower than that found in a study conducted in Japan (18.3%)[9]. There were several potential reasons behind this. Continuous INH therapy is associated with hepatic damage, whereas, the acetylation of INH in the liver serves as a potential mechanism for INH hepatotoxicity. In contrast to other ethnic groups, Chinese people are more likely to be rapid acetylators, resulting in low incidence of INH induced hepatotoxicity[10]. PZA is another important contributor to drug induced hepatotoxicity but PZA-associated hepatotoxicity is thought to be time-dependent[8]. Hence, short treatment with PZA for 2 months instead of long-term regimen may be the reason for low prevalence of hepatotoxicity in this study.

This study also revealed that being underweight is an important factor for being at a high risk for developing ADRS in this cohort of TB patients. The study cohort received the standard regimen for previously treated patients as recommended by the NTP irrespective of their body weights. This led to a higher serum drug concentration in patients with low body weight resulting in higher ADRs as compared to patients with higher body weight. Hence, our study findings highlight the fact that body weight should be considered in calculating the effective dose of anti-TB regimen to reduce incidence of ADRs.

DM has recently demonstrated to be a potential confounder affecting the course of TB infection, disease presentation, and clinical outcome. In our series, DM is associated with increased risk for the occurrence of ADRs during anti-TB treatment. The chronic hyperglycemia during diabetes is responsible for long-term damage, dysfunction, and failure of different organs, especially the kidneys, nerves, and eyes. As the kidneys are the primary site of drug metabolism renal damage will undoubtedly cause reduced metabolism of anti-TB drugs. The longer

Table 3. Risk Factors Associated with Developing ADRs

Characteristics	Patients Experiencing Each ADR		Univariate Analysis	Multivariate Logistic Regression	
	n	%	P value	adjusted OR (95% CI)	P value
Age (y)					
18-29 (n = 55)	42	76.4	-		
30-39 (n = 48)	40	83.3	0.383		
40-49 (n = 85)	69	81.2	0.493		
50-59 (n = 93)	75	80.6	0.537		
≥ 60 (n = 73)	67	91.8	0.02		
Gender					
Male (n = 274)	225	82.1	-		
Female (n = 80)	68	85	0.549		
Weight (kg)					
< 50 (n = 115)	103	89.6	-	Reference	-
≥ 50 (n = 239)	183	78.9	0.016	0.41 (0.22-0.85)	0.012
Diabetes mellitus					
Yes (n = 56)	55	98.2	0.01	15.5 (2.07-115.87)	0.008
No (n = 298)	238	79.9	-	Reference	-

half-lives of these drugs enable a higher serum drug concentration for a longer period of time leading to high prevalence of ADRs. Therefore, the control of hyperglycemia in DM patient is an important factor associated with the potential occurrence of ADRs and the treatment outcome.

In order to improve the health care service for TB patients in China, the TB diagnosis and treatment of TB patients have transferred from local CDC or TB dispensary to TB specialized hospitals since 2010. Because the TB specialized hospitals are more capable of ADRs surveillance than the public health system, the routine follow-up surveillance for TB patients will have a major impact on the control of ADRs. In addition, prevention of ADRs is always more effective than intervening after the ADRs have occurred. Hence, preventing the occurrence of ADRs in high risk previously treated TB patients will go a long way to improve the adherence to the extended treatment regimen.

Our study has several limitations. First, some demographic and life style factors such as profession, educational level, attainments, nationality, smoking, and drinking may be related to the occurrence of ADRs. Unfortunately, because data of above factors was incomplete of patients, and thus could not be assessed in the study. Second, only body weight instead of Body Mass Index (BMI) is included as a risk factor in the study as data regarding heights of many patients is missing in the study. This could have resulted in potential confounding as BMI is a risk factor for development of ADRs and not weight. Third, a small proportion of the patients in this study might have received a short-term anti-TB treatment prior to the enrollment in the study, leading to the increased frequency of ADRs while participating in the study. In addition, because of the long-term follow-up period, the clinical outcome of these previously treated patients is not analyzed.

Despite these limitations, our study has several strengths. To the best of our knowledge, this is the first study to investigate the prevalence and risk factors associated with ADRs due to first-line anti-TB regimen among non-MDR previously treated TB patients in China. Our study data demonstrate that hyperuricemia is the most common adverse effect among these patients because of the long-term treatment with PZA. However, majority of these patients with hyperuricemia showed good tolerance for increased uric acid levels thereby limiting the withdrawal of PZA from the treatment regimen. In addition, low body weight and DM are associated with increased risk for the occurrence of ADRs during anti-TB treatment. Our findings highlight that the body weight should be considered in calculating the effective anti-TB drugs doses in the regimen for lowering the risk of occurrence of ADRs.

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