Adverse Drug Reactions of Anti-Tuberculosis Treatment among Children with Tuberculosis

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Abstract

Background: The frequency, severity, and the nature of anti-tuberculosis (TB)-induced adverse drug reactions (ADRs) have always been the matter of concern. The present study was, therefore, aimed to study the incidence, risk factors, and effect of anti-tuberculosis treatment (ATT) among TB children. Methods: A prospective longitudinal study was conducted in the Sindh province, Pakistan. A total of 508 TB children in multicenter hospitals under ATT were assessed for ADRs. Naranjo Causality Assessment and Hartwig’s Severity Assessment Scale were used. Results: A total of 105 ADRs were reported in 67 (13.2%) of 508 patients. Gastrointestinal disorders were the most frequently observed ADRs (65.7%), followed by arthralgia (24.8%). Around 65 (61.9%) of ADRs were identified as probable and 78 (74.3%) as mild severe ADRs during the study. A total of four cases of mild hepatotoxicity were observed among children. On multivariate analysis, the independent variables which had statistically significant positive association with ADRs were female (OR; 2.66, $P = 0.004$), retreatment (OR; 22.32, $P = 0.001$), and absence of BCG scar (OR; 17.84, $P = 0.001$). Conclusions: The finding of the current study suggests that close monitoring of females, patients with previous TB treatment, and those without BCG is warranted at the study site.

Keywords: Adverse drug reactions, children, risk factors, tuberculosis

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INTRODUCTION

The frequency, severity, and the nature of anti-tuberculosis (TB)-induced adverse drug reactions (ADRs) have always been the matter of concern. Studies have shown that multidrug regimens can cause undesirable ADRs such as arthralgia, allergic reactions, hepatotoxicity, neurological, and gastrointestinal disorders.[11] Since ever ADRs of anti-TB treatment (ATT) remained as main concern, in terms of mounting treatment costs, visits to health facilities and hospitalizations in case of severity. Repercussions of ADRs result in the treatment disruption, following treatment failure and acquired resistance, adding up to the number of TB cases and more infrequently in the number of deaths.[2] The overall incidence of ADRs caused by ATT ranges from 5.1% to 83.5%.[3]

Generally, ADRs are less frequent in children than in adults. The most severe ADR is hepatotoxicity, caused by isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA). Hepatitis is the grievous ADR of INH, almost definitely as a result of reactive metabolites of acetyl hydrazine, which may be toxic to tissues through free radical generation. PZA reveal hepatotoxicity that may be dose dependent and idiosyncratic. By interfering with nicotinamide acetyl dehydrogenase levels, PZA may result in the generation of free radical species injurious to cells.[4] Long-term exposure to ATT increases the risk of ADRs. These ADRs might be gentle and in addition deadly. An extreme ADR against one of the primary anti-TB drugs, which prompts the discontinuation of that drug, has several complications including an increased morbidity and mortality. In the meantime, use of alternative agents may bring

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about more prominent issues of lethality and compliance. Subsequently, the risk of treatment failure and relapses are higher. Familiarity with the risk groups is in this way vital as it might diminish the cost and additionally the occurrence of serious drug-related ADRs. Some of the factors significantly associated with ADRs reported in previous studies include female, having previous history of ADRs, alcoholism, HIV co-infection, genetic factors, nutritional deficiencies, age >50 years, smoking, previous history of TB treatment, and comorbidities.

ADRs are a major reason of morbidity and mortality. Thus, it is essential to recognize ADRs and to ascertain an underlying relationship between the drug and an adverse event. Causality assessment of ADRs is a method used for estimating the strength of relationship between drug (s) exposure and occurrence of ADRs whereas severity of ADRs is related to the extent to which the ADRs affect the daily life of patients. The frequency, severity, and the nature of anti-TB-induced ADRs have always been the matter of concern. However, limited data is available about the incidence of ADRs among children. The present study was, therefore, aimed to study the incidence, risk factors and effect of anti-tuberculosis treatment (ATT) among TB children.

**METHODS**

**Study design**

A prospective longitudinal study was performed in children ≤14 years at five DOTS centers in three cities of Pakistan namely Hyderabad, Jamshoro, and Matiari. A total of 508 children registered for TB treatment from June 2016 to November 2016 were assessed for ADRs of ATT. Patients were examined for the incidence of ADRs on each monthly visit or caregivers of children were asked to consult the clinician at any time in case of any ADR. For assessment and management of ADRs in the study population, their laboratory reports and medical charts were evaluated for prescribing the auxiliary drugs. The occurrence of ADRs was based on laboratory reports (hematologic disorders and liver dysfunction), and symptomatic events (gastrointestinal disorders, allergic reactions, arthralgia, and neurological disorders) reported from caregivers and physical examination by clinician and pediatrician (if ADRs could not be identified by laboratory reports).

For ADRs which can be certified by laboratory reports, one abnormal value was regarded as sufficient for defining the result (Hartwig et al., 1992). Causality assessment of ADRs was measured in study participant using Naranjo scale and probability of ADRs was assigned as definite, probable, possible, or doubtful. In addition, the severity of effects was measured using ADRs Hartwig’s Severity Assessment Scale and ADRs were recorded as mild, moderate, and severe. All PTB and EPTB cases were treated with the same standardized first-line anti-TB regimen. Treatment was free and was only provided by the DOTS program for all TB patients. The treatment of all new TB cases (Category-I, with no previous history of TB treatment) was comprised of INH, RIF, and PZA for 2 months intensive phase followed by INH and RIF for 4 months continuation phase. For category-II patients (relapse, failure and default), INH, RIF, PZA, and EMB were given for 3 months intensive phase and INH and RIF for 5 months continuation phase. Based on the pretreatment weight, children were assigned to one of 4 pretreatment weight bands (5–7 kg, 8–14 kg, 15–20 kg, and 21–30 kg). They were treated on the basis of prefixed weight band dosage. Patients weighing <5 kg were treated with individualized dosages while those weighing more than 30 kg were treated using adult dosages. As improvement in weight was observed during monthly visits, dose of ATT was then adjusted accordingly.

**Adverse drug reactions definition**

ADR was defined as “noxious or unintended response of drug at doses normally used for prophylaxis, diagnosis, treatment of disease or for modification of physiologic function.” Arthralgia: Pain or swelling in joints as reported by patients and recognized by clinician with/without the presence of arthritis with elevation of uric acid levels of more than 7 mg/dL. Hepatotoxicity: Increase in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) of more than three times the upper normal limit in the presence of symptoms such as anorexia, abdominal pain, nausea, vomiting or increase of transaminases of more than five times the upper normal limit without symptoms, and/or in total bilirubin to >2 mg/dL. Jaundice: Yellowing of skin, mucous membranes, and sclera due to the deposition of bilirubin. It appears when bilirubin level exceeds 34.2 µmol/L or 2 mg/dL. Dermatologic reactions: Flushing and/or itching of the skin with or without a rash. Anemia: Was defined as more than 1 g/dL drop in hemoglobin concentration after starting treatment.

For causality and severity assessment, all the suspected ADRs were discussed with the treating practitioner, pediatrician and local specialist. Once a suspected ADR was identified, these were recorded, and the patient was followed until ADR was resolved or end of TB treatment course. ADR patients modified their DOTS therapy additionally got symptomatic treatment as indicated by the seriousness of the ADR. Various possible risk factors responsible for developing ADRs were likewise studied. The severity of hepatotoxicity was classified according to the WHO Toxicity Classification Standards. As LFT is not practiced as baseline test in TB patients at the all the five studied hospitals, it was therefore not possible to record normal values of ALT and AST before the ATT began. However, when no other possible causative factors were identified, hepatotoxicity was considered to be caused by the concomitant ATT as per suggestion of health practitioners.

**Statistical analysis**

SPSS Statistics 24 (IBM) was used for data analysis. All the extracted information was coded into variables and cases were entered according to their serial numbers used throughout the data collection. Categorical variables were accounted as...
frequencies and percentages (%) while continuous variables were reported as means ± standard deviation and medians. Determinants of ADRs were evaluated using logistic regression analysis. Variables measured in univariate analysis were based on literature review and those suggested by advisory committee and clinical team at the study site. All the variables significant in univariate analysis were included in multivariate analysis. Odds ratios (ORs) with their 95% confidence intervals (CIs) were estimated for each independent variable. \( P < 0.05 \) was considered statistically significant.

**Ethics approval and consent to participate**

Ethical approvals were issued by the relevant Institutional Research and Ethics Boards of Shah Bhitae Hospital Latifabad, Hyderabad Liaquat University Hospital Hyderabad/Jamshoro, Sindh Government Hospital Qasimabad, Hyderabad, Sayed Baqadar Shah Civil Hospital Matiari, and Institute of Chest Diseases, Kotri Sindh, Pakistan, (Vide Letter No: SBGH/L. ABAD HYD-1575; dated: April 13, 2017, LUI/Estt/-23176/14; dated: August 06, 2016, MS-SGHQ/HYD/2187: dated: April, 13, 2017, CS/CH/MAT: 1761; dated: May 18, 2016 and ICDK/771; dated: April 12, 2017, respectively). Oral informed consent assent was acquired from every caregiver of children upon enlistment because of their illiterate status. During data collection, oral informed consent was obtained from all guardians after they were introduced to the purpose of the study. To keep confidentiality, names or other identities of study participants were avoided in the questionnaires and reporting the results of the study.

**Results**

A total of 105 ADRs were reported in 67 (13.2%) of 508 patients. The types, incidence, and onset time of ADRs due to DOTS therapy are listed in Table 1. Gastrointestinal disorders were the most frequently observed ADRs (65.7%), followed by arthralgia (24.8%). The least frequently observed ADR was anemia (1.9%). A total of 441 (86.8%) patients experienced no ADRs while 38 (56.7%), 22 (32.8%) and 7 (10.4%) experienced 1, 2 or 3 or more ADRs, respectively.

The causality assessment of ADRs results revealed that 34 (32.4%) were identified as possible, 65 (61.9%) as probable and 6 (5.7%) as definite [Table 2]. None of the ADRs was reported as doubtful. A total of 53 (79.1%) patients with ADRs had extra clinic visits and had to bear additional expenses.

Details of the severity assessment are given in Table 3. On assessment of the severity of ADRs by Hartwig scale, it was apparent that most of the ADRs reported were of mild severity (74.3%) and no any case of severe ADR was observed during the study. In most of the cases, ADRs belonged to level 1 (56.7%) followed by level 2 (28.4%) and 3 (14.9%).

In terms of the severity of hepatotoxicity, all the four cases had mild hepatotoxicity, one (25%) of these had Grade 1 and three (75%) had Grade 2 hepatotoxicity, while no case of severe hepatotoxicity was observed [Table 4]. Among all the four cases, nausea, vomiting, and jaundice were the frequently reported symptoms.

**Management of adverse drug reactions**

All ADRs were monitored and managed according to the WHO guidelines. The general principle for management of ADRs at five hospitals was the pharmacological supportive therapy. Every possible effort was made to stay away from any modification in ATT. Permanent discontinuation of offending drug was set as a last choice. Initially each patient was counseled and encouraged. When severe ADRs occurred, the drug responsible was recognized either by terminating the suspected drug alone or by discontinuing all three drugs, followed by a gradual restoration of drugs.

**Predictors of adverse drug reactions in study participants**

The independent variables which had statistically significant positive association with ADRs in univariate analysis [Table 5] included females (OR; 2.00, \( P = 0.012 \)), age 6–10 years (OR; 1.70, \( P = 0.050 \)), EPTB (OR; 2.42, \( P = 0.002 \)), and absence of BCG scar (OR; 10.92, \( P \leq 0.001 \)).

On multivariate analysis [Table 6], the independent variables which had statistically significant positive association with ADRs were female (OR; 2.66, \( P = 0.004 \)), and absence of BCG scar (OR; 17.84, \( P = 0.001 \)).

**Treatment outcomes**

Table 7 represents the treatment outcomes of all the registered patients. Patients with ADRs have increased risk of treatment failure as reported in previous phase of our study.[10] The rate of failure, death, lost to follow-up, and transferred out was reported higher among those with ADRs. Patients who were transferred out were finally recorded as TB-resistant patients.

**Discussion**

A total of 105 ADRs were observed among 67 (13.2%) of 508 patients. Overall, 411 (86.8%) patients experienced no ADRs, while 38 (56.7%), 22 (32.8%) and 7 (10.4%)
Table 2: Causality assessment of adverse drug reactions of anti-tuberculosis treatment in tuberculosis children using Naranjo scale

| Type of ADRs                      | Doubtful, n (%) | Possible, n (%) | Probable, n (%) | Definite, n (%) |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|
| 1. Gastrointestinal disorders    |                 |                 |                 |                 |
| Nausea and vomiting              | -               | 13 (34.2)       | 25 (65.8)       | -               |
| Anorexia                         | -               | 8 (61.5)        | 5 (38.5)        | -               |
| Abdominal pain                   | -               | 6 (33.3)        | 12 (66.7)       | -               |
| 2. Arthralgia                    | -               | 6 (23)          | 17 (65.4)       | 3 (11.5)        |
| 3. Hepatotoxicity                | -               | -               | 2 (50)          | 2 (50)          |
| 4. Dermatologic reaction (rash/itching) | -               | -               | 3 (75)          | 1 (25)          |
| 5. Anemia                        | -               | 1 (50)          | 1 (50)          | -               |
| Total                            | -               | 34 (32.4)       | 65 (61.9)       | 6 (5.7)         |

*From the start of treatment. IQR: Interquartile range, ADRs: Adverse drug reactions

Table 3: Assessment of severity of adverse drug reactions of anti-tuberculosis treatment in tuberculosis children using Hartwig scale

| Type of ADRs       | Number of ADRs (%) |
|--------------------|--------------------|
| Mild               | 78 (74.3)          |
| Moderate           | 27 (25.7)          |
| Severe             | -                  |

ADRs: Adverse drug reactions

Table 4: Cases of hepatotoxicity among tuberculosis children based on WHO classification

| Grade          | Value relative to ULN | Patients (%) |
|----------------|------------------------|--------------|
| Grade 1 (mild) | <2.5 times ULN (ALT 51-125 U/L) | 1 (25)       |
| Grade 2 (mild) | 2.5-5 times ULN (ALT 126-250 U/L) | 3 (75)       |
| Grade 3 (moderate) | 5-10 times ULN (ALT 251-500 U/L) | -            |
| Grade 4 (severe) | >10 times ULN (ALT >500 U/L) | -            |

ALT: Alanine aminotransferase, ULN: Upper limit of normal, i.e. 50 U/L

Patients who developed gastrointestinal symptoms were reassured and managed symptomatically with supplementary drugs. All the 38 patients with nausea and vomiting were advised to take ATT after a meal. In addition, appetizers and anti-emetic (dimenhydrinate) were added to their regimen. Metronidazole was prescribed by the paediatrician for the relief of abdominal pain. Nausea, vomiting, abdominal pain, and anorexia have previously been reported in studies conducted in children and attributed with the use of INH and RIF.[19] Majority of the children in our study were underweight due to which might have not tolerated the multidrug regimen. The symptoms were resolved once the ancillary drugs were given along with ATT after meal.

A remarkable proportion of current cohort (24.8%) experienced arthralgia without arthritis. This was consistent with the incidence of arthralgia in 22% of adult TB patients in India[20] and 17.6% in Japan.[21] However, comparatively lower level of arthralgia has been reported by.[11] Use of PZA has been reported to be the main cause of arthralgia in TB patients.[1,2,22] During ATT, arthralgia is renowned ADR of PZA. Pyrazinoic acid, a metabolite of PZA, inhibits the renal tubular secretion of uric acid and thereby increases its serum concentration. The subsequent hyperuricemia can result into arthralgia and very occasionally to arthritis.[23] Patients with arthralgia were prescribed with ibuprofen and termination of PZA was not necessarily required in any patients except that the dose was adjusted in 11 patients. In contrast,[5] Gülbay et al., have reported discontinuation of PZA in patients of arthralgia with hyperuricemia.

Though ATT has the ability to kill Mycobacterium tuberculosis effectively, nevertheless they are responsible to induce various ADRs containing hepatotoxicity, gastrointestinal, and neurological disorders as well as skin reactions. Anti-TB drug-induced hepatotoxicity (ATDH) is one of the most significant that reduces the effectiveness of ATT, by way of nonadherence, and further leads to treatment failure, recurrence or the emergence of drug-resistance. All these deleterious atermaths may possibly impair the effects of TB epidemic control.[23] The incidence of hepatotoxicity varied between 3.5% and 16.2% in published studies from...
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various countries (McNeill et al., 2003; Schaberg et al., 1996; Teleman et al., 2002). Compared to study conducted in Japanese children, our study showed a low incidence of hepatotoxicity (3.8%) but higher than that reported by Yiyuan et al. [17]

In the current study, hepatotoxicity was classified on the basis of WHO criteria. [21] The median interval between the initiation of ATT and the detection of ATDH for all patients was 37 (IQR: 26–71 days). In terms of the severity of ATDH, 1 (25%) cases had mild Grade 1 hepatotoxicity and 3 (75%) had mild Grade 2 hepatotoxicity. The median onset time for ATDH in our study was also longer than that stated in a study in Singapore [26] and China. [23] Patients with ATDH in our study experienced nausea, vomiting and anorexia which might help clinicians to be more vigilant about ATDH. Moreover, this may perhaps be supportive to clinicians in developing countries as laboratory

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### Table 5: Univariate analysis of risk factors for adverse drug reactions of anti-tuberculosis treatment in tuberculosis children (n=508)

| Variables                  | ADRs         | OR (95% CI) | P      |
|----------------------------|--------------|-------------|--------|
|                            | Yes, n (%)   | No, n (%)   |        |
| Gender                     |              |             |        |
| Male                       | 22 (9.2)     | 218 (90.8)  | 1      |
| Female                     | 45 (16.8)    | 223 (83.2)  | 2.00 (1.16-3.44) | 0.012** |
| Age (years)                |              |             |        |
| ≤2                         | 21 (12.1)    | 153 (87.9)  | 1      |
| 3-5                        | 15 (12.5)    | 105 (87.5)  | 0.92 (0.49-1.70) | 0.799 |
| 6-10                       | 25 (18)      | 114 (82)    | 1.70 (0.99-2.92) | 0.050** |
| 11-14                      | 6 (8)        | 69 (92)     | 0.53 (0.22-1.27) | 0.156 |
| Residence                  |              |             |        |
| Urban                      | 37 (12.3)    | 265 (87.7)  | 1      |
| Rural                      | 30 (14.6)    | 176 (85.4)  | 1.22 (0.72-2.04) | 0.450 |
| Type of TB                 |              |             |        |
| PTB+                       | 6 (20.7)     | 23 (79.3)   | 1      |
| PTB−                       | 9 (17.3)     | 43 (82.7)   | 1.43 (0.66-3.10) | 0.356 |
| PTBNS                      | 27 (8.6)     | 288 (91.4)  | 0.35 (0.21-0.60) | <0.001** |
| EPTB                       | 25 (22.3)    | 87 (77.7)   | 2.42 (1.40-4.18) | 0.002** |
| Weight (percentiles)       |              |             |        |
| Underweight*               | 59 (12.9)    | 398 (87.1)  | 1      |
| Normal weight              | 8 (15.7)     | 43 (84.3)   | 1.25 (0.56-2.80) | 0.579 |
| Registration category      |              |             |        |
| New                        | 54 (11.1)    | 431 (88.9)  | 1      |
| Retreated♣                 | 13 (56.5)    | 10 (43.5)   | 10.37 (4.34-24.80) | <0.001** |
| Baseline X-ray             |              |             |        |
| Normal                     | 8 (6.1)      | 123 (93.9)  | 1      |
| Abnormal                   | 42 (13.2)    | 276 (86.8)  | 1.00 (0.59-1.70) | 0.987 |
| Not done                   | 17 (28.8)    | 42 (71.2)   | 3.23 (1.71-6.09) | <0.001** |
| BCG scar                   |              |             |        |
| Present                    | 33 (7.6)     | 403 (92.4)  | 1      |
| Absent                     | 34 (47.2)    | 38 (52.8)   | 10.92 (6.09-19.57) | <0.001** |
| TST                         |              |             |        |
| Positive (≥10 mm)          | 25 (9.3)     | 243 (90.7)  | 1      |
| Negative (<10 mm)          | 42 (17.5)    | 198 (82.5)  | 1.55 (0.92-2.60) | 0.097 |

*<5 percentiles, ♣Relapse, default and failure patients with previous TB treatment, **P value indicates factors significantly associated with ADRs.

TB: Tuberculosis, PTB−: Smear negative pulmonary TB, PTB+: Smear positive pulmonary TB, PTBNS: Pulmonary TB with no sputum examination, EPTB: Extra-pulmonary TB, ADRs: Adverse drug reactions, OR: Odds ratio, CI: Confidence interval, BCG: Bacillus Calmette-Guérin, TST: Tuberculin skin test

### Table 6: Multivariate analysis of risk factors for adverse drug reactions of anti-tuberculosis treatment in patients (n=508)

| Variables                  | β     | SE    | OR (95% CI) | P  |
|----------------------------|-------|-------|-------------|----|
| Female                     | 0.979 | 0.349 | 2.66 (1.35-5.23) | 0.004** |
| 6-10 years                 | 0.573 | 0.372 | 1.77 (0.85-3.67) | 0.123 |
| PTBNS                      | -1.229 | 0.461 | 0.29 (0.11-0.72) | 0.008 |
| EPTB                       | -0.060 | 0.525 | 0.94 (0.33-2.63) | 0.909 |
| Retreated patients         | 3.019 | 0.569 | 22.32 (7.44-66.95) | <0.001** |
| Normal X-ray               | -1.166 | 0.469 | 0.31 (0.12-0.78) | 0.013 |
| X-ray not done             | 0.450 | 0.521 | 1.56 (0.56-4.36) | 0.388 |
| BCG scar absent            | 3.062 | 0.394 | 17.84 (8.64-36.82) | <0.001** |

**P-value indicates factors that have significantly positive association with ADRs. TB: Tuberculosis, B: Beta, SE: Standard error, CI: Confidence interval, OR: Odd ratio, ADRs: Adverse drug reactions, PTBNS: Pulmonary TB with no sputum examination, EPTB: Extra-pulmonary TB, BCG: Bacillus Calmette-Guérin...
test may not be available and ATDH diagnosis frequently depend on observation of clinical symptoms.

INH was discontinued in patients who developed hepatitis. Once the laboratory values for liver enzymes became normal and clinical symptoms were resolved, INH was restored. Almost similar findings for INH as an offended drug for hepatitis in children have been confirmed previously.\(^{[19,27]}\) ATDH may be deadly if not documented early or therapy is not stopped early enough. Thus, in order to recognize asymptomatic ATDH, if accessible, monthly liver function monitoring is highly suggested for patients receiving ATT so as to make suitable intervention at correct time. Conversely, this monthly monitoring could add extra costs to patients as well as difficult to perform among all TB patients in Pakistan. Therefore, a more real method is to recognize the individuals presenting the risk factors known to cause ATDH and monitor them carefully. Risk factors for ATDH in adults include females, advanced age, malnutrition, HIV-infection, pre-existing liver disease, alcohol abuse, and parallel use of other hepatotoxic drugs.\(^{[25]}\)

During TB therapy, occurrence of skin reactions is often coupled with RIF\(^{[2,28]}\) and rarely with PZA.\(^{[29]}\) In the present study, rates of skin adverse reaction with ATT were relatively lower (3.8%) than other studies.\(^{[30,31]}\) Contrary to this, a study conducted in Iran has shown rather lower rate of skin reactions.\(^{[1]}\) For the dermatologic reactions, all the four patients were successfully managed with cetirizine (antihistamine) and treatment adjustment was not needed in any of the case. However, an ultimate termination of ATT due to cutaneous reactions was determined by Gülbay et al.\(^{[5]}\) and RIF and PZA were completely withdrawn in a study by Yee et al.\(^{[31]}\)

Anaemia as an ADR of ATT has been reported in studies conducted elsewhere.\(^{[3,32]}\) Use of INH, RIF and PZA has been associated with anaemia.\(^{[32]}\) In our study, challenging drug for anaemia could not be detected and may be additionally linked with poor nutritional and socio-economic status of patients. Instead, multivitamin syrup was given to the patients reported with anorexia and anaemia. Majority of the ADRs are likely to occur in the intensive phase of ATT,\(^{[1,3,31,33]}\) while effects, for instance hepatotoxicity, may come about far along, during continuous phase of treatment.\(^{[34]}\) Correspondingly, in our study, most (87.6%) of the ADRs occurred during the intensive period with 64% in the 1st month of treatment, which may be reasonably due to the fact that the three drugs interrelated with most of the ADRs were used concurrently during that period.\(^{[33]}\)

As per the Naranjo’s Causality Assessment Scale, most of the events in the study participants were identified as probable (61.9%) which is in accordance with the findings of Shang et al. and Damasceno et al.\(^{[23,33]}\) and opposed to Javadi et al. and Chhetri et al.\(^{[6,12]}\) where greater number of events were recorded as possible. Evaluation of the severity of ADRs of ATT in the study cohort using Hartwig’s scale showed that 74.3% of the ADRs were mild. However, no severe ADR was detected during the study.

In the current cohort, modification in ATT due to ADRs was less frequent and symptomatic treatment was major measures in managing ADRs in our study which is in agreement to Lv et al.\(^{[39]}\) As to the impact of ADRs on ATT pattern, 55% patients required adjusting their ATT, including dose adjustment, interruption, changes in administration (taking medicines after a meal instead of on an empty stomach) similar to the study conducted in Iran.\(^{[6]}\) There was no drug replacement or complete withdrawal of any drug reported in the present study. Patients with ATDH, gastrointestinal disorders and arthralgia had to change their ATT pattern, which is in concordance with the study by Breen et al.\(^{[36]}\) The only drug temporarily discontinued was INH that was reintroduced once the symptoms resolved. Contrary to this, complete discontinuation of INH and PZA has been reported by\(^{[31]}\) in ATDH.

During the course of ATT, early identification and proper management of ADRs is necessary for ensuring patient’s compliance and successful treatment outcomes. A better understanding of risk factors for ADRs during ATT gives clinicians an opportunity to identify high-risk patients and helps them in the proper and timely management of ADRs. Very few studies have evaluated the association between occurrence of ADRs during ATT and socio-demographic and clinical characteristics of patients and the rate of such studies are almost negligible in children.\(^{[5,31]}\)

The most important factor which affects the manifestation of ADRs is age. Elderly and paediatric patients are predominantly susceptible to ADRs as drugs are barely studied widely in these patients; moreover, pharmacokinetics is unpredictable and inconsistent in extreme of ages. The lines of evidences propose that infants and very young children are usually at high risk of developing ADRs since their ability to metabolize the drug is not completely evaluated.\(^{[37]}\) Studies conducted for estimating the risk factors of occurrence of ADRs in children have concluded that neonates\(^{[38]}\) and children aged 11–18 years\(^{[39]}\) are at high risk of ADRs.

Previous studies have revealed that females,\(^{[1,6,31]}\) age and smoking,\(^{[32]}\) alcohol use and drug abuse,\(^{[40]}\) co-infection of HIV and other liver diseases,\(^{[25]}\) previous TB treatment,\(^{[1]}\) and ethnic group\(^{[41]}\) would be independent risk factors for the development
of ADRs in adults during ATT. In this study, we were incapable to conclude whether all the risk factors recognized in adult patients would also be applicable in children because none of our patients were co-infected with HIV, had previous hepatitis disorders, and habit of smoking, alcohol and drug abuse.

In the current cohort, female patients were 2.6 times more likely to develop ADRs than male patients. Generally, female patients reported to have a greater risk of developing an ADR compared with male patients. Not clearly understood but this could be due to gender-related differences in pharmacokinetic and immunological as well as hormonal factors. Compared with males, females generally have a lean body mass, reduced hepatic clearance, differences in cytochrome P450 enzyme activity,[42] and different gastric motility and lower glomerular filtration rate.[37] However, how these differences result in an increased risk of ADRs is uncertain.

The most striking finding in our study was the occurrence of ADRs in patients with absence of BCG scar. The exact mechanism for this is not clearly understood, but this can be linked with the effectiveness of BCG vaccine in prevention of TB. Children who do not receive BCG may develop serious form of TB, which ultimately led them to disease progression and factors responsible to bring physiological changes, responsible to cause ADRs in these patients such as weight loss and anemia, previously studied as risk factor for ADRs.[7,37] In the current study, the frequency of ADRs was more in patients with previous ATT, which is in agreement with the previous study conducted in adult TB patients.[1] Of 67 patients, 79.1% successfully completed the treatment. Of the remaining, 4.5% were failure, 9% were default, 4.5% were transferred out (they were diagnosed with resistant TB) and 3% died. Death was associated with the progression of disease and indirectly to ADRs.

The study includes some limitations. First, the laboratory tests, specifically LFT, are not performed at baseline level due to limited resources provided at study sites. Therefore, we could not analyze the significant impact of treatment-related ADRs in patients. Second, because our study focused on three interconnected districts, we could not do the comparative analysis among different regions of country again due to limited resources, which could have shown the pattern of ADRs in response of ATT.

**Conclusions**

The highly frequent ADRs in the current cohort did not result into temporary or permanent deferral of ATT. These findings suggest that ADRs could be better managed by supportive psychological and pharmacological therapy without disturbing the clinical effectiveness of ATT, unless the ADRs are fatal. Females, patients with previous treatment, and those without BCG as risk factors for ADRs should be critically monitored at full length. Participation of clinical pharmacist in the collaborative practices may help caregivers regarding the correct use of drugs, and early detection, prevention, and management of ADRs.
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