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Original Article

Pattern of Adverse Effects of Drugs Used To Treat Multi Drug Resistant Tuberculosis

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During treatment of multi drug resistant tuberculosis (MDR-TB), patients suffer from many adverse effects. Severe adverse effects may lead to refusal and discontinuation of treatment. Though national tuberculosis control programs are generally well structured, they do not collect information on adverse effects of drug directly. This study had been designed to observe the pattern of adverse effects of MDR-TB drugs in Bangladesh. This observational and descriptive type of longitudinal study was carried out at the in-patient department of the National Institute for Diseases of the Chest and Hospital, Dhaka, Bangladesh. The total number of subjects included was 64. The data collection was carried out with pretested questionnaire. After the interview at the initial stage, the respondents had to take part in interview again at one month interval up to the end of the 3rd month of treatment. The collected data was analyzed in terms of descriptive method. The mean age of respondents was 34.76 ± 12.98 years. 20-60 years age group comprised80% of respondents. Male to female ratio was 2:1. Regarding the adverse effects of MDR-TB drugs, 80% of respondents suffered from arthralgia, 59% from anorexia, 52% from dizziness, 44% from nausea/vomiting and 44% from sleep disturbances. Gastritis, hypothyroidism and psychological disorders were each observed in 19% of patients. 17% developed impaired hearing. Peripheral neuropathy was developed by 28% of respondents. Serum creatinine level was raised in 3% of respondents. Hypocalcemia had been developed in 6% of respondents. Among psychological disorders, 67% consisted of depression, 25% were anxiety, and 8% were psychosis. The mean number of adverse effects that the respondents had to suffer from was 5 (range 1 -11). Uninterrupted treatment had been continued in 86% of cases. Drug dose had to be reduced in 11% of cases and drug had to be stopped in 3% of cases. The findings of this study may provide baseline information in Bangladesh on adverse effects of MDR-TB drugs. The information may help minimizing the treatment interruption and thus preventing propagation and dissemination of MDR-TB.

Keywords: MDR-TB (Multi drug Resistant Tuberculosis)

Tuberculosis (TB) is a major public health problem in Bangladesh since long. Of all countries, there are 22 that are referred to by World Health Organization (WHO) as high TB burden

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countries. Bangladesh is in the fifth position among the top five high burden countries (1).

In 1993, WHO declared TB as global emergency. Nearly one third of global population is infected with *Mycobacterium tuberculosis* (2). In spite of strong TB control program, under close supervision of government and WHO, Bangladesh fails to escape from the claw of multidrug resistant TB (MDR-TB), caused by the strains of *Mycobacterium tuberculosis* resistant to the effects of isoniazid and rifampicin with or without resistance to any other drug (3).

Though the causes are microbial, clinical and programmatic, MDR-TB is essentially a man-made phenomenon (4). Ongoing transmission of established MDR-TB strains in population may further contribute to new primary drug resistant cases (5).

In 2008, WHO ranked Bangladesh as 9th among 25 high priority MDR-TB countries (6). The occurrence of total MDR-TB is about 4000 each year in Bangladesh which was 3000 approximately in 2007 (3, 7). To achieve millennium development goal, Bangladesh is addressing not only TB but also MDR-TB. The national TB control program of Bangladesh (NTP) has launched a program in 2008 to treat MDR-TB.

According to national guidelines and operational manual for programmatic management of drug resistant TB (2013) in Bangladesh, MDR-TB treatment regimen consists of two phases: intensive phase and continuation phase. Duration of intensive phase is at least 8 months provided 4 months past culture conversion, and continuation phase is at least 12 months. The total treatment duration is 20 - 22 months (5).

In both phases, drugs are administered for at least 6 days per week under strict directly observed therapy (DOT) either in a hospitalized state at National Institute for Diseases of the Chest and Hospital, Dhaka, a tertiary level hospital and research institute for the chest diseases including Pulmonary TB and the central point of treatment of drug resistant TB in Bangladesh, or at community level where DOT, short-course (DOTS) is provided by trained DOTS provider (6, 8).

Five anti-TB drugs used in intensive phase are pyrazinamide, kanamycin, ofloxacin, ethionamide, and cycloserine. The drug dosages are determined by body weight of the patient. Among the drugs, kanamycin is the only injectable one. In continuation phase kanamycin is no longer used (4).

In MDR-TB due to treatment with more toxic drugs, patients suffer from many adverse effects (9). The common possible adverse effects include anorexia, nausea/vomiting, diarrhea, gastritis, allergic reaction, skin rash, hepatitis, peripheral neuropathy, hearing and visual disturbances, nephrotoxicity, hypothyroidism, psychological disorders like psychosis, depression, anxiety, suicidal ideation, seizures, arthralgia, electrolyte imbalance, dizziness, vertigo, tinnitus, headache, sleep disturbance etc (3-5).

Severe adverse effects may lead to refusal and discontinuation of treatment before smear conversion. There may be occurrence of concomitant transmission of resistant strains of *Mycobacterium tuberculosis* to the community as well. This may lead to a burden to the economy as patients of MDR-TB are treated for a long period with less potent, more toxic and much more expensive drugs.

Though national TB programs are generally well structured, they do not collect information on adverse effects of drugs directly. In Bangladesh, adverse effects of drugs used in MDR-TB is scantly reflected in published information on subject. In this regard, pharmacovigilance needs to be an integral component for TB control program (10).

The present study had been designed to observe the pattern of adverse effects of MDR-TB drugs in Bangladesh with the objective to provide information for patients as well as health workers and organizations concerned with the activities for prevention, control and management of MDR-TB.

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Materials and methods

Study design

This observational and descriptive type of longitudinal study has been carried out at the in-patient department of the National Institute for Diseases of the Chest and Hospital (NIDCH), Dhaka, Bangladesh. MDR-TB patients from all over the country, mostly referred cases, attended this health care facility. Thus, patients visiting this hospital provided the reflection of MDR-TB situation in Bangladesh. The study was approved by the Ethical Review Committee of Dhaka Medical College, Dhaka, Bangladesh. Permission for data collection was obtained from the authority of NIDCH, Dhaka, Bangladesh. Informed written consent was taken from all participants before the interview.

The duration of the study was one year extending from July 2013 to June 2014. The study population comprised all the patients of MDR-TB admitted in NIDCH from December 2013 to February 2014 which was a total of 110 where there were 32, 32, and 46 patients in December, January, and February, respectively. Purposive sampling has been done to fill up the target respondents. Diagnosed and registered MDR-TB patients with a DOTS identification number who were admitted and had to stay at least three months in NIDCH were included in the study. The total number of subjects included in the study regarding inclusion and exclusion criteria was 64.

The data collection had been carried out with a predesigned pretested questionnaire containing both open and closed ended questions. Data was collected through face to face interview and data regarding supporting physical and laboratory findings were obtained from DR-TB treatment card, physical examination and laboratory reports of the respondents after taking informed written consent. After the interview at the initial stage of treatment, the respondents had to take part in interview again at one month interval up to the end of the 3rd month of treatment.

The data included information regarding the identification of respondents, their socio demographic background, co-morbidity, smoking habit, site of TB, treatment protocol, history of contact with TB or MDR-TB patients, previous history of TB treatment along with adverse effects of first line anti-TB drugs, adverse effects in MDR-TB treatment, supporting physical and laboratory findings. Checking regarding weight, anemia, jaundice, vision, hearing, mental status, and peripheral numbness was done at base line and at one month interval up to the end of 3rd month of MDR-TB treatment. Also, the data containing information about laboratory findings of hemoglobin level, cell count, serum bilirubin, alanine aminotransferase (ALT), serum creatinine, random blood sugar (RBS), serum potassium was collected at base line and then monthly up to the end of the 3rd month of treatment. Data about thyroid stimulating hormone (TSH) was recorded at base line and at second month.

Statistical analysis

The quality of data was ensured at field level. After scrutiny, the completed questionnaire was reviewed to ensure the completeness and consistency of the collected data. The collected data was classified. The edited data had been entered into computer through Excel program. Then the data was analyzed in terms of descriptive method which includes percentage, frequencies, means with standard deviation of findings.

Results

A total of 64 respondents participated in the study. The study revealed that the mean age of respondents was 34.76 ± 12.98 years. 16% of respondents were below the age of 20 years. 5% were above the age of 60 years and the rest (44%+36%) 80% (51/64) were between 20 to 60 years.

Among the respondents, 66% were male and 34% were female with a male to female ratio of 2:1. Table 1 shows the distribution of subjects

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according to sex, living place, education, and marital status. Among the respondents 59% (38/64) had been living in urban. Among the female respondents 77% (17/22) had been living in urban area, while half of male subjects (21/42) leaved in urban area. 25% (16/64) of respondents were illiterate. Females were non-smoker, while 79% (33/42) of male respondents were smoker.

9% (6/64) of participants were farmers and students, 19% (12/64) were house wives, and 27% (17/64) and 22% (14/64) were involved in service and business, respectively. 14% (9/64) were involved in other works like driving, etc. Among the service holders 47% (8/17) were garments worker and 41% (7/17) had been working in offices, and 12% (2/17) had history of working abroad. Among the working respondents 30% (14/46) had monthly income below 5000/- taka. Most of them, 43% (20/46), had monthly income of 5000-10000/- taka, and 9% (04/46) had 15000/- taka and above. Mean income was 10,859/- taka per month. Most participants were married.

There had been history of TB in family among 17% of respondents. 72% of respondents were free from co-morbidities. 14% (9/64) had been suffering from diabetes mellitus (DM), 6% (4/64) from bronchial asthma, and 3% (2/64) from chronic obstructive pulmonary disease (COPD). Hypertension and others consisted each 2% (1/64) of cases. 98% of respondents had been suffering from pulmonary TB, and the remaining 2% had extra pulmonary TB. Among the respondents, 25% were susceptible to TB (had close contact with TB patient), 11% were susceptible to MDR-TB (had close contact with MDR-TB patient) and 3% were susceptible to both TB & MDR-TB. 39% of susceptible respondents had close contact with siblings, next 26% with father, 22% with others but none had close contact with spouses having TB or MDR-TB.

69% of respondents had been informed about adverse effects of 1st line anti-TB drugs. Adverse effects had occurred in 27% of respondents. During

Table 1. Distribution of respondents according to sex, living place, educational qualification, and marital status

Variables	Characteristics	Female (n=22)	Male (n=42)
		n (%)	n (%)
Living place	Urban	17 (77)	21 (50)
	Rural	5 (23)	21 (50)
Educational qualification	Illiterate	8 (36)	8 (19)
	Below class Vl	5 (23)	8 (19)
	Below SSC	7 (32)	17 (40)
	SSC	1 (5)	6 (14)
	HSC	1 (5)	1 (2)
	Graduation and above	0 (0)	2 (5)
Marital Status	Married	12 (55)	27 (64)
	Unmarried	6 (27)	15 (36)
	Separated	2 (9)	0 (0)
	Widow	2 (9)	0 (0)
Smoking	Smoker	0 (0)	33 (79)
	Non smoker	22 (100)	9 (21)

SSC: secondary school certificate; HSC: high school certificate.

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treatment with 1st line anti-TB drugs 94% had been suffering from vomiting and 88% from arthralgia. 18% and 12% had been suffering from tinnitus and allergic reaction, respectively. Jaundice, impaired vision, hearing loss and peripheral neuropathy occurred each in 6% of respondents. 3% of respondents had to discontinue TB treatment due to adverse effects of 1st line anti-TB drugs. The discontinuation of TB treatment was only temporary with duration of 7-14 days.

Treatment relapse and failure

The distribution of patients according to relapse and failure categories was investigated. 28% (18/64) of respondents belonged to relapse of category 1 (cat-l) regimen which corresponds to first-line drugs treatment. 19% (12/64) and 14% (9/64) belonged to treatment failure of cat-l and cat-ll (retreatment with first-line drugs) regimen, respectively. Again 8% (5/64) and 6% (4/64) were delayed converter (persistent positivity after 2 months treatment) of cat-l and cat-ll, respectively. 17% (11/64) were from relapse cat-ll and 5% (3/64) from default cat-l. 3% (2/64) of patients were case of showed primary MDR-TB.

Body weight and hemoglobin levels

During the first three months of MDR-TB treatment, mean weight was between 39.77 and 40.68 kg in females, and between 45.61 and 47.66 kg in males. The average weight gain was 1 kg and 2 kg in females and males, respectively. Mean hemoglobin level varied between 11.40 and 11.92 g/dl in females, and between 12.79 and 12.96g/dl in males. Table 2 represents the mean body weight and hemoglobin levels of the respondents during the first three months of treatment.

Adverse effects

Regarding the adverse effects of MDR-TBdrugs, 80% (51/64) of respondents suffered from arthralgia. Other common adverse effects were anorexia (59%), dizziness (52%), nausea/vomiting (44%), and sleep disturbances (44%). Table 3 represents different observed adverse effects andtheir frequencies in respondents.

During the treatment of MDR-TB jaundice appeared in 2nd month in one patient and in 3rd month in another patient. Peripheral neuropathy developed in 28% (18/64) of respondents with half of them (9/64) being diabetic. Out of 12 cases presenting psychological disorders, 67% (8/12) suffered from depression, 25% (3/12) from anxiety, and 8% (1/12) from psychosis (figure 1).

23% (15/64) respondents had to suffer from 4 adverse effects, 16% (10/64) from 3 adverse effects, 14% (9/64) each from 5 or 6 adverse effects, and 2% (1/64) from 11 adverse effects. The mean number of adverse effects that the respondents had to suffer from was 5 (range 1 -11). Uninterrupted treatment had been continued in 86% (55/64) of cases. Drug dose had to be reduced in 11% (7/64) of cases and drug had to be stopped in 3% (02/64) cases.

Biochemical evaluation

81% (52/64) of respondents were non diabetic, 14% (9/64) had co-morbidity with DM, and 5% (3/64) developed impaired glucose tolerance. Serum creatinine level was normal in 97% of respondents and elevated in 3% of cases during their treatment. Serum TSH level was normal in 81% of respondents and was raised in 19% of cases during their treatment. Hypocalcemia had developed in 6% of respondents. Serum potassium level was normal in 94% of cases.

Table 2. Mean body weight and hemoglobin level of the respondents

Variables	Month	Female	Male
Body weight Mean ± SD (kg)	0	39.77±4.61	45.61±6.8
	1	39.81±4.43	46.45±6.8
	2	40.18±4.4	47.02±6.95
	3	40.86±4.6	47.66±9.3
Hb level Mean ± SD (g/dl)	0	11.4±0.69	12.79±1.43
	1	11.45±0.77	12.94±1.20
	2	11.71±0.65	12.94±0.95
	3	11.92±0.57	12.96±1.94

Hb: hemoglobin

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Table 3. Distribution of respondents by adverse effects of MDR-TB Drugs (n =64)

Adverse effects	Frequency	%
Anorexia	38	59
Nausea/vomiting	28	44
Skin rash	3	5
Hepatitis	2	3
Peripheral neuropathy	18	28
Impaired hearing	11	17
Nephrotoxicity	1	2
Gastritis	12	19
Hypothyroidism	12	19
Psychological Disorders	12	19
Arthralgia	51	80
Electrolyte imbalance	4	6
Dizziness/vertigo	33	52
Tinnitus	21	33
Headache	13	20
Sleep disturbance	28	44
Allergic reaction	10	16

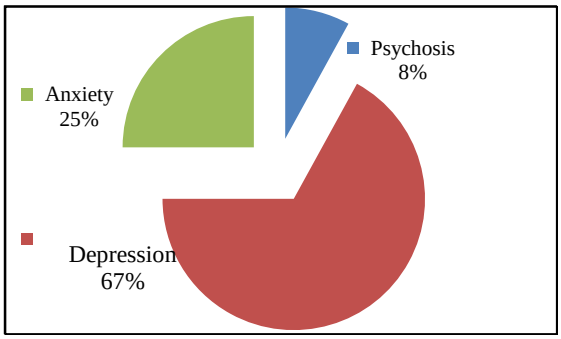

Figure 1. Distribution of respondents by type of psychological disorder (n =12).

Discussion

Demographic analyzes of respondents showed that 20-60 years age group comprised 80% of cases, which indicates that the most valuable working period of life could not escape from the claw of MDR-TB and it affects the main contributors of gross domestic product (GDP) (11).

Regarding educational qualification, 25% of respondents were illiterate. 36% of females were illiterate and none of them had graduation or higher degree, indicating that in education women still lag behind. It was most alarming that 83% of respondents did not complete the level of SSC. Most respondents (27%) were service holder. Among them 47% were garments worker and 12% had history of working abroad. 55% of women were house wives. The mean income of the working respondents was 10,859/- taka per month. 73% had monthly income below 10,000/- taka which indicates the low socioeconomic status of the patients. A study in Turkey suggested that 56.7% of MDR-TB cases occurred among those with poor economic status (12). Result of population prevalence survey regarding TB in Bangladesh also showed that poor, less educated, and worker class contribute to the higher prevalence of the disease (13).

In the present study 61% of cases were married. But married people were not contaminated from their spouse though they could have contaminated their healthy spouse. Among the respondents, 25% had history of contact with TB patients which mean that they were susceptible to TB. Again 11% were susceptible to MDR-TB and 3% had history of contact with both TB and MDR-TB patients. Most of them (39%) had contact with siblings, 26% with fathers, 9% with mothers and 4% with offspring. 22% had contacts with others like uncle, mother-in-law and roommate as well, which corresponds to close contact, that is living in the same house hold or spending several hours per day together with the patient in the same indoor living or working space (5). The contact period was from 15 days to 1 year. Among male respondents 79% were smokers though smoking increases risk of infection, progression of TB and death (14). None of the women was smoker or pregnant.

72% of respondents were free from co-morbidities like hypertension, DM, bronchial asthma, COPD, chronic kidney disease, or chronic

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lung disease. 14% had been suffering from DM, 6% from bronchial asthma, and 3% from COPD. A meta-analysis revealed that DM patients had 1.55 to 3.59-fold increased risk of developing active TB (15). All respondents were HIV negative. In the first Bangladesh national tuberculosis drug resistance survey among 1468 respondents, only one had been found HIV positive (7).

Regarding treatment of TB with 1st line anti-TB drugs 31% of respondents (20/64) were not informed about the adverse effects but it occurred in 27% of cases. 94 % and 88% had the history of vomiting and arthralgia respectively. Similarly, an ambispective cohort study in Chinese population revealed that the 2 most common adverse events associated with MDR-tuberculosis were arthralgia (67.5%) and gastrointestinal disorders (65.4%) (16).3% had history of discontinuation of treatment which was only temporary and the duration of interruption was 7 days to 14 days. In case of MDR-TB treatment all patients had been informed about the adverse effects of the drugs.

98% (63/64) of cases had pulmonary TB, and the remaining had extra pulmonary TB with the site being cervical lymph node. In both cases treatment regimen was almost the same (5). Among the respondents 28% belonged to relapse cat-I. 19% and 14% were from treatment failure cat-I and cat-II, respectively. The frequency of relapse cat-II was 17%. Delayed converter group consisted of 14% of respondents. 3% of cases belonged to the group of primary MDR-TB while incidence of MDR-TB among new cases is 1.4% in Bangladesh (7). Among the 2 primary MDR-TB cases, one had the history of contact with a MDR-TB patient.

As dosing of anti-TB drugs is based on the weight of the patients, monthly weight monitoring had been done. From base line to the end of the 3rd month, average weight gain (2 Kg and 1 Kg in males and females, respectively) did not require to move into higher weight class to adjust the medication dose as well (5) . Again the mean weight of the patients (at baseline 39.77 Kg in female, and 45.61 Kg in male) has indicated their poor nutritional status.

Regarding the adverse effects of MDR-TB drugs, 80% had suffered from arthralgia. Study in Canada also revealed the same type of finding (82%) (17). 59% had anorexia and 44% had nausea and vomiting. Study in China among 273 MDR-TB patients also found the occurrence of vomiting in 45% of cases (18). Dose of kanamycin had been reduced in 11% (7/64) of cases but serum level of the drug was not measured to evaluate whether the serum concentration of the drug was sufficient to kill the bacilli or not. 3% developed hepatitis which had been noticed through scheduled monitoring. But treatment was not interrupted as treatment would not be changed immediately only when ALT, AST, total bilirubin is elevated to greater than 2 times (18). 3% developed nephrotoxicity, and due to high serum creatinine level kanamycin was stopped. 19% of patients developed gastritis. Hypothyroidism was observed in 19% of cases. An Indian study on MDR-TB had also noticed the occurrence of hypothyroidism in 23% of cases (19). 44% and 19% of respondents suffered from sleep disorders and psychological disorders. Fortunately none suffered from suicidal ideation. As TB patients are perceived as a source of infection resulting in their social rejection and isolation, the disease and drugs lead to a long term impairment of their psychosocial wellbeing. (12, 13). One patient developed psychosis and cycloserine had been stopped for 2 weeks. The mean number of adverse effects that MDR-TB patients had to suffer from was five, and the highest number was 11 with nobody without suffering from any adverse effects. The same trend had been observed in Canadian and South African studies (7, 20).

Uninterrupted treatment had been continued for 3 months in 86% of respondents. The dose of drug (kanamycin) had to be reduced in 11%, and stopped in 3% of respondents. Cycloserine was stopped temporarily for 2 weeks and then re-introduced after improvement of sign symptoms of

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psychosis in case of one respondent (21). On the other hand during the study period, kanamycin could not be reintroduced after discontinuation as sign symptoms and laboratory findings of nephrotoxicity were not adequately improved.

There are some limitations to the present study. Correspondingly, only the hospital admitted MDR-TB patients were included in the study, but those who had been treated at community level through community based programmatic management of drug resistant TB (cPMDT) could not be included. It was not mentioned whether the patients were smear positive or negative which would provide an idea regarding the severity of chance of spread of MDR-TB. Also, due to the lack of facilities baseline audiometry was not performed. Finally, patients were observed for 3 months only.

In conclusion, treatment of MDR-TB requires prolonged therapy with multiple drugs which leads to adverse reactions in a significant number of patients. Adverse effects lead to treatment interruption, drug discontinuation and drug dose reduction. The findings of this study may provide baseline information in Bangladesh on adverse effects of MDR-TB drugs.

Further long term studies involving large number of MDR-TB patients (hospital admitted patients as well as patients treated under cPMDT program) are needed to learn more about the adverse effects of MDR-TB drugs along with its management. Basic pharmacological research and pharmacovigilance is needed to shed light on the treatment of MDR-TB so that the therapy could be continued in doses that will render effective drug level yet minimizing the adverse effects.

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Conflict of interest

The authors declared no conflict of interest.

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