RESEARCH ARTICLE

Factors contributing to development of multidrug-resistant tuberculosis

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ABSTRACT

Background: Several factors have been identified in the causation of multidrug-resistant tuberculosis (MDR-TB). The most important is previous inadequate treatment. Other factors include coinfection with HIV, diabetes mellitus, socioeconomically deprived groups, intravenous drug abusers, and other immunocompromised states. This study was planned to find out contributing/associated factors for the development of MDR-TB, specifically patients related factors. **Aims and Objectives:** The present study was conducted among MDR-TB patients to get the information regarding sociodemographic profile, present and history of TB, problems faced during treatment, and drug resistance pattern. **Materials and Methods:** A prospective, cross-sectional study was undertaken in a tertiary care teaching hospital. A total of 50 cases were included in the study who fulfilled inclusion criteria. All information was collected by studying the patients' treatment record and by personal interview of each of the study participants using case record form. **Results:** Middle age groups (21–30 years and 31–40 years) were most commonly affected with MDR-TB. It was found that 44% of patients were smoker, 34% of patients were alcoholic, and 36% of patients were addicted to tobacco chewing, and 96% of patients have a body mass index below the normal range. Most of the patients were from lower socioeconomic status - Class V followed by class. Most of the patients (44) are of secondary MDR-TB and while only 6 patients are of primary MDR-TB. Out of 44 secondary cases of MDR-TB total, 16 cases are due to not completion of the treatment, the reasons were poor adherence, adverse drug reactions, and substance abuse, etc., four patients were living with HIV/AIDS, and 3 patients were suffering from diabetes mellitus. **Conclusion:** There are causative factors and several risk factors associated with the development of MDR-TB has been found in the study. The strategy must be planned for incorporation of these factors in deciding treatment of MDR-TB.

KEY WORDS: Factors; Tuberculosis; Multidrug-Resistant; Association

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is defined as resistance to both Isoniazid and Rifampicin and may be any number of other drug(s).[1] The emergence of resistance to drugs used to treat TB and particularly MDR-TB has become a significant public health problem and an obstacle to effective TB control in countries like India. According to the WHO, the median prevalence of primary and acquired MDR-TB globally was 2.9% and 15.3%, respectively.[2] In India, the available information from the several drug resistance studies suggests that the rate of MDR-TB is relatively low in India.[3] The prevalence of MDR-TB is 1–3% in new cases and around 12% in re-treatment cases in India[3] while in Gujarat, the prevalence of MDR-TB was found 2.4% in new cases and around 17.4% in previously treated cases.[4]

Several contributing factors have been identified in the causation of MDR-TB of which the most important is previous treatment with antitubercular drugs which may be inadequate [Table 1].[3] Other factors include coinfection with HIV, patients with diabetes mellitus, socioeconomically deprived groups in slums, intravenous drug abusers, and other immunocompromised states.[5]

Adequate information required for control and effective treatment of MDR-TB. The present study was conducted among MDR-TB patients to get the information regarding sociodemographic profile, present and history of TB, problems faced during treatment, and drug resistance pattern.

MATERIALS AND METHODS

A prospective, cross-sectional study was undertaken from April to September 2016, in Civil Hospital, Gandhinagar, a teaching hospital attached to GMERS Medical College, Gandhinagar. The protocol was approved by the Institutional Ethics Committee.

SITE: This study was conducted at the Department of Pharmacology and Department of TB and Chest, GMERS Medical College and Civil Hospital, Gandhinagar.

Study Duration

This study duration was April–September 2016.

Sample Size

Considering, the prevalence of MDR-TB (1–3% in new cases and around 12% in re-treatment cases) in India, the sample size calculated is 8 for new cases and 41 in re-treatment cases, using following formula:

$$n = \frac{Z^2 P (1 - P)}{d^2}$$

Where,

	New cases	Re-treatment cases
Z=Z statistics for level of confidence (95%)	1.96	1.96
P=Expected prevalence (%)	0.02 (=2)	0.12 (=12)
D=Precision	0.01 (=10)	0.01 (=10)

Inclusion Criteria

The following criteria were included in the study:
- Patients of all age groups and both gender
- Confirmed MDR-TB case.

Definition of confirmed MDR-TB case: [3] An MDR-TB suspect who is sputum culture positive and whose TB is due to *Mycobacterium* TB that is resistant *in vitro* to at least isoniazid and rifampicin (the culture and DST result being from an RNTCP accredited laboratory).

Exclusion Criteria

As such there are no exclusion criteria.

Collection of Data

The study was conducted for patients meeting the inclusion criteria. Patients were recruited in the study on Pro rata basis, and all the patients participating in the study were explained clearly about the purpose and nature of the study in the language they can understand and written informed consent was taken before including them in the study.

All information to accomplish objectives was collected by studying the patients' treatment record and by personal interview of each of the study participants for 5–10 min using case record form (CRF). The CRF was comprising for details regarding sociodemographic profile; present history including symptoms; history regarding treatment of TB and factors responsible for inadequate treatment; TB contact history; history of HIV and diabetes mellitus; sputum examination including drug sensitivity pattern, pre-treatment investigations, and other relevant information.

Definition of TB Contact

A close contact is defined as living in the same household or frequent contact with a source case (e.g., caregiver) with sputum smear-positive TB.[6]

Statistical Analysis

The data will be subjected to statistical analysis using the

Table 1: Causes of inadequate treatment [3]		
Providers/programs: Inadequate regimens	**Drugs: Inadequate supply/quality**	**Patients: Inadequate drug intake**
Absence of guidelines or inappropriate guidelines	Non-availability of certain drugs	Poor adherence (or poor DOT)
Non-compliance with guidelines	(stock-outs or delivery disruptions)	Lack of information
Inadequate training of health staff	Poor quality	Non-availability of free drugs
No monitoring of treatment	Poor storage conditions	Adverse drug reactions
Poorly organized or funded TB control programs	Wrong dosages or combination	Social and economic barriers
		Malabsorption
		Substance abuse disorders

SPSS software package. Data will be expressed as absolute numbers with or without percentages, as means with standard deviation or as medians with ranges.

RESULTS

A total of 50 patients with MDR-TB were included in the study who were fulfilled the provided criteria and after obtaining informed written consent from them. The sociodemographic characteristics were described in Table 2. Age group of 21–30 years has the maximum number 15 (30%) of patients with MDR-TB followed by the 24% of patients belong to the age group of 31–40 years. The mean age of the patients with MDR-TB was 28.43 ± 14.32 years. Out of total 50 patients, 28 (56%) patients were males as compared to 22 (44%)

patients were females.

On eliciting a history of addiction, it was found that 22 (44%) patients were smoker, 17 (34%) patients were alcoholic, and 18 (36%) patients were addicted to tobacco chewing. Many patients 8 (16%) from above-stated patients were addicted all three. Out of total 50 patients, 48 (96%) patients have a body mass index (BMI) that is below the normal range. A majority of the patients (44, 88%) were belong to vegetarian group. Most of the patients were from lower socioeconomic status - Class V: 15 (30%) patients and Class IV: 14 (28%) patients [Table 2].

In the present study, we have found most of the cases 44 (88%) of secondary TB and only 6 patients with primary MDR-TB. Out of 44 secondary cases of MDR-TB total 28 patients have completed their anti-TB drugs (AKT), though there is recurrence, and they have suffered from MDR-TB, and rest of the 16 cases are due to not completion of the treatment, the reasons were poor adherence (may be due to disappearance of symptoms), certain adverse drug reactions or substance abuse disorders, etc., [Figure 1 and Table 3].

Out of the total 50 patients, 4 (8%) patients were living with HIV/AIDS, and 3 patients were suffering from diabetes mellitus. In all cases of MDR-TB, the drug sensitivity pattern was done and it was found that 3 patients have resistance of

Table 2: Sociodemographic characteristics of patients with MDR-TB (*n*=50)

Sociodemographic characteristics	Number of patients (%)
Age (years)	
1–10	1 (2)
11–20	6 (12)
21–30	15 (30)
31–40	12 (24)
41–50	7 (14)
51–60	5 (10)
>61	4 (8)
Mean age	28.43±14.32
Gender	
Male	28 (56)
Female	22 (44)
Addiction	
Smoking	22 (44)
Alcohol	17 (34)
Tobacco chewing	18 (36)
Diet	
Vegetarian	44 (88)
Non-vegetarian/mixed	6 (12)
Socioeconomic class*	
I	4 (8)
II	7 (14)
III	10 (20)
IV	14 (28)
V	15 (30)
BMI (kg/m^2)	
<18.5	48 (96)
18.5–24.9	2 (4)
>25	0 (0)

BMI: Body mass index. *Prasad's social classification: Per capita income per month (in Rs.)
(Calculated from http://prasadscaleupdate.weebly.com/) [8],
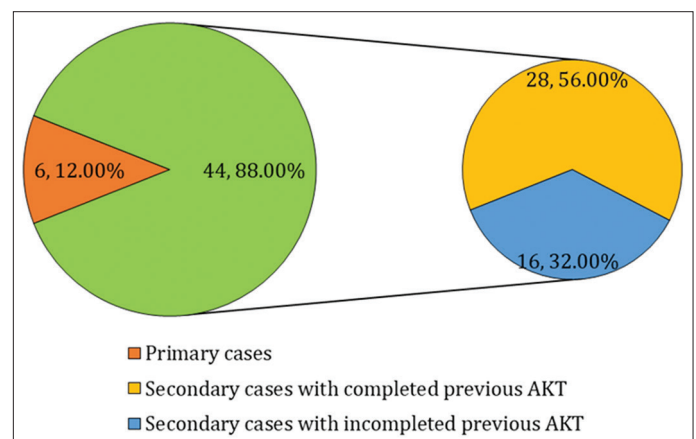MDR-TB: Multidrug-resistant tuberculosis

Figure 1: Types of multidrug-resistant tuberculosis (TB) cases with previous history of anti-TB treatment in second case (*n* = 50). AKT: Antituberculosis drugs

Table 3: Reasons for incomplete treatment in patients with MDR-TB cases with previous history of anti-TB treatment in secondary case (*n*=16)

Reasons for incomplete treatment	Number of patients (%)
Poor adherence	10 (63)
ADRs to anti-TB drugs	3 (19)
Substance abuse disorders	3 (19)
Total	16 (100)

ADRs: Adverse drug reactions, MDR-TB: Multidrug-resistant tuberculosis

Table 4: Resistance pattern of drugs in patients with MDR-TB (*n*=50)	
Resistance pattern	Number of patients (%)
Isoniazid	50 (100)
Rifampicin	50 (100)
Pyrazinamide	0 (0)
Ethambutol	2 (4)
Streptomycin	0 (0)
Kanamycin	3 (6)
Fluoroquinolones	0 (0)

MDR-TB: Multidrug-resistant tuberculosis

kanamycin and 2 patients have resistance of ethambutol in addition to resistance to isoniazid and rifampicin [Table 4].

According to Table 5, many patients (24, 48%) with MDR-TB was mild anemic. Leukocytosis has been found in 26 (52%) patients in the present study. Majority of the patients (37, 74%) have normal platelet count, but more than half of the patients have higher blood urea level. If we see the level of the liver enzymes, abnormal serum glutamic-pyruvic transaminase level has been found more in patients as compared to serum glutamic oxaloacetic transaminase level.

DISCUSSION

India accounts for a quarter of the world's annual incidence of TB.[7] India also ranks second in harboring MDR-TB cases in the world.[9] MDR-TB is a major hurdle in effective control of the disease. Prompt and appropriate management of MDR-TB cases, including strict adherence to therapy, is required to achieve control over the disease. Based on the study criteria, a total of 50 patients with MDR-TB were included in the present study from them we have gathered the information to achieve our aims and objectives.

In the present study, middle age groups (21–30 years and 31–40 years) with a mean age of 28.43 ± 14.32 years were commonly affected as compared to other age groups. Similar findings have been reported from different studies. Age group of 21–30 years with mean age of 32.52 years was commonly affected with MDR-TB in the study done by Mukherjee *et al.*[10] Similar age groups with mean age were also commonly affected in studies by Gaude *et al.*,[9] Kapadia and Tripathi,[11] and Sharma *et al.*[12] More involvement of the middle age group may be due to this age group is more active in life and come across different people with varying diseases.

Out of the total 50 patients, 28 (56%) patients were males as compared to 22 (44%) patients were females in the present study. Male dominated involvement has been found in various studies done by Mukherjee *et al.*,[10] Kapadia and Tripathi,[11] Sharma *et al.*,[12] and Datta *et al.*[13] Male dominance can be

Table 5: Laboratory parameters of patients with MDR-TB (*n*=50)	
Laboratory parameters	
Hb level (mg/dL)	Number of patients (%)
Normal (>13.0)	3 (6)
Mild anemia (11.0–13.0)	24 (48)
Moderate anemia (8.0–10.9)	17 (34)
Severe anemia (<8.0)	6 (12)
Total WBC count (per cmm)	
Normal (4,000–11,000)	24 (48)
Leukocytosis (>11000)	26 (52)
Platelet count (per cmm)	
Normal (1,50,000–4,50,000)	37 (74)
Thrombocytopenia (<1,50,000)	1 (2)
Thrombocytosis (>4,50,000)	12 (24)
Blood urea (mg/dl)	
Normal (7.0–20.0)	21 (42)
Abnormal	29 (58)
Serum creatinine (mg/dl)	
Normal (0.5–1.5)	49 (98)
Abnormal	1 (2)
SGOT (units)	
Normal (5–40)	44 (88)
Abnormal	6 (12)
SGPT (units)	
Normal (7–56)	34 (68)
Abnormal	16 (32)

Hb: Hemoglobin, WBC: White blood cells, SGPT: Serum glutamic-pyruvic transaminase, SGOT: Serum glutamic oxaloacetic transaminase, MDR-TB: Multidrug-resistant tuberculosis

justified by their involvement in more outdoor activities as compared with females.

For people suffering from a potentially fatal and highly contagious disease, addiction can lead to irregular medication use, which can lead to drug-resistant strains of TB. On eliciting a history of addiction in the present study, patients were addicted to it was found that many patients were addicted to smoking (22, 44%), alcohol (17, 34%), and tobacco chewing (18, 36%). Our findings are in consonance with such observations made by Gaude *et al.*[9] and Mukherjee *et al.*[10] In 2007, Partners in Health, Russia has started integrating alcohol treatment with the treatment of TB in 200 patients. The study was successful in terms of improvement in outcomes TB.[14]

Both tobacco smoking and TB are major global public health problems.[15] It is estimated that smokers have approximately twice the risk of both *M.* TB infection[16] and active TB.[17] It was also found that the risk of a poor TB treatment outcome was 70% greater in current smokers compared to never smokers.[15] A retrospective cohort study with a large sample

of 5,567 TB patients was carried out in Taiwan from 2005 to 2010. The researches have followed each patient whom had TB confirmed through bacteriologic testing and went on to successfully complete TB treatment. Of those patients, 1.5% developed a recurrent case of TB, with regular tobacco smokers twice as likely to develop recurrent TB compared with former smokers and with individuals who had never smoked tobacco.[18] Hence, smoking is an independent risk factor for poor TB treatment outcomes, recurrence, and drug resistance. Smoking cessation programs need to be targeted at TB patients.

In the present study, 48 (96%) patients have a BMI that is below the normal range. Majority of the patients with MDR-TB were also found to have BMI below 18.5 kg/m² in studies done by Mukherjee *et al.*,[10] Kapadia and Tripathi[11] BMI <18.5 kg/m² is also associated with poor outcome.[19] This indicates that most of the patients suffering from MDR-TB are malnourished, and diet plays a major role here. Malnutrition and TB are both problems of considerable magnitude in the developing countries like India.[20] Undernutrition increases the risk of TB, and in turn, TB can lead to malnutrition.[21] It has been also found that malnourished TB patients have delayed recovery and higher mortality rates. It has been demonstrated that undernutrition is a risk factor for progression from TB infection to active TB disease and severe form, namely MDR-TB and extensively drug-resistant (XDR)-TB.[22] There are several second-line drugs used to treat MDR-TB can interfere with food intake by producing significant anorexia, nausea, vomiting, and diarrhea which further aggravating malnourished state. Therefore, nutritional support is an essential part of the care and management of patients with MDR-TB.

On eliciting diet history, a majority of the patients (44, 88%) were belong to vegetarian group in the present study. The importance of good nourishment in MDR-TB has been already discussed in the previous paragraph. There are numerous studies dealing with the effects of different diets on TB patients, and widely divergent and contradictory claims have been made.[20] In study by Strachan *et al.* conducted in London, it was found that Hindu Asians had more chances of developing TB as compared with Asians Muslims. As such, religion had no relation with TB and MDR-TB, but Hindu Asians were more prone because of vegetarianism common among them.[23] There was a trend of increasing risk of TB with decreasing frequency of meat or fish consumption. Decreased immunocompetence associated with a vegetarian diet may result in increased mycobacterial reactivation.

Most of the patients were from lower socioeconomic status - Class V: 15 (30%) patients and Class IV: 14 (28%) patients in the present study. Similar findings were observed in studies done by Gaude *et al.*[9] and Mukherjee *et al.*[10] Low socioeconomic status consisting of low monthly income; lack of social security and employment; and residency in a

rural area increased the risk of MDR-TB around 6-fold.[24] Moreover, all this factors lead to poor adherence to treatment. MDR-TB often develops in patients who do not adhere to or complete the proper treatment for regular.

In the present study, we have found most of the cases 44 (88%) of secondary TB and only 6 patients with primary MDR-TB. In the study done by Gaude *et al.*,[9] out of total 46 patients, six patients had primary drug resistance, while the rest of 40 patients had acquired/secondary drug resistance. The similar distribution of the patients also has been reported in previous studies from different parts of India.[4,25-27] These findings point out inthe absence of a good effective national TB-control program and improper use of anti-TB drugs.

In the present study, out of 44 secondary cases of MDR-TB total 28 patients have completed their AKT, though there is recurrence and they have suffered from MDR-TB, and rest of the 16 cases are due to not the completion of the treatment. The reasons for incomplete treatment may be varied such as poor adherence (may be due to disappearance of symptoms), certain drug reactions, or substance abuse disorders. The literature strongly suggests that the most powerful predictor of the presence of MDR-TB is a history of treatment of TB.[9] Irregular, incomplete, inadequate treatment is the most common cause of secondary drug-resistant organisms.[9] Patients' poor compliance with treatment is also a major factor in the development of secondary MDR-TB. It was found that only 43% of the patients receiving short-course treatment and 35% of those receiving standard chemotherapy completed 80% or more of their treatment in one the study of south India.[28] The other reasons for default, including travel to different places, symptom relief, adverse drug reactions, and inability to afford treatment, are also documented in literature.[29]

Out of the total 50 patients, 4 (8%) patients were living with HIV/AIDS, and 3 patients were suffering from diabetes mellitus in the present study. Similar type of TB and HIV association has been found in different Indian studies.[10-13] An African study has recorded HIV seroprevalance rates of 50–70% in patients with TB[30] while in some East European countries, MDR rates are double the normal in HIV-positives cases.[2] In patients with HIV/AIDS, there is an increased vulnerability, increased opportunity to acquire TB and malabsorption of anti-TB drugs resulting in suboptimal therapeutic blood levels in spite of strict adherence to treatment regimen. All these factors have been postulated as the possible causes for increased risk of acquiring MDR-TB.[31-34]

In the present study, it was found that 3 patients have a resistance of kanamycin and 2 patients have resistance of ethambutol in addition to resistance to isoniazid and rifampicin. Hence, in our study sparing isoniazid and rifampicin, there was very less resistance to first-line anti-TB drugs. Although higher prevalence of resistance to first line anti-TB drugs have been observed in other studies.[35-37] The

high rate of drug resistance to the first-line drugs reflects the absence of a good effective TB control program.

Many patients 24 (48%) with MDR-TB were mild anemic in the present study. It may be due to the high prevalence of malnourished patients in the present study and TB itself lead to malnourishment and nutrition deficiency anemia. Leukocytosis has been found in 26 (52%) patients in the present study which is the obvious sign of ongoing infection in the body.

There are several limitations of the present study. The present study was on patients presented to our center. Hence, the exact prevalence of primary drug resistance may not be applicable to the general population as a whole. The findings of this study are based on very small numbers of patients. Hence, the results presented here should be interpreted with caution and cannot be generalized to the entire country. However, this study has highlighted the potential factors which may contribute to the development of MDR-TB, even for XDR-TB. This type of data may strengthen the RNTCP's preventive activities against the development of MDR-TB cases.

CONCLUSION

A major challenge for the program in achieving the goal of TB control is MDR-TB (MDR-TB). Although the prevalence of MDR-TB in terms of percentage is quite small, these rates translate into a large absolute number. Moreover, MDR-TB patients often live a number of years before succumbing to the disease. Thus, maintaining the chain of transmission of the drug-resistant strains. Drug resistance develops either due to infection with a resistant strain, or as a result of inadequate treatment, poor patient compliance, use of inappropriate non-standardized treatment regimens, irregular drug supply, poor drug quality, or rarely erratic absorption of medications. There are also several risk factors associated with the development of MDR-TB has been found in the study. The strategy must be planned for incorporation of these risk factors in deciding treatment of MDR-TB.

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