Abstract

Background: To investigate the factors affecting treatment outcome of extensively drug resistant tuberculosis (XDR-TB) in Gujarat, India. Methods: A prospective, observational study was conducted on patients with XDR TB from January 2012 to October 2016. Details of demography, clinical symptoms, sputum/culture and radiological examination, drug treatment, adverse drug reactions (ADRs) and treatment outcome were recorded in pretested case record form (CRF). Data was analyzed using Fisher’s exact test and paired student’s t test. Results: Out of 112 patients, 83 (74%) were men and 29 (26%) were women and majority of belonged to age group of 16 – 45 years. Majority of patients (79%) received standardized treatment. A total of 61 (54%) patients converted to sputum culture negative by 12 months and out of these, 49 turned sputum culture negative within initial 6 months of treatment. Successful treatment outcome was seen in 29 (25.89 %). Age ≤40 years ($P < 0.05$), body mass index > 18.5 ($P < 0.05$) and sputum/culture conversion at three month ($P < 0.001$) were positive predictors for successful treatment outcome, while tobacco chewing habit ($P < 0.05$) and alcohol consumption ($P < 0.05$) were negative predictors for the successful treatment outcome. Out of 83 (74.1 %) patients with unsuccessful treatment outcome, 58 (51.78 %) died, 11 (9.82 %) were defaulter and 10 (8.92 %) were treatment failure. Factors positively associated with death were very low BMI (< 18.5), concomitant diseases and harmful personal habits. Conclusions: Treatment outcome of XDR TB patients is extremely poor with high mortality rate.

Keywords: Correlation, extensively drug resistant tuberculosis, treatment outcome

Introduction

Drug-resistant tuberculosis (DR-TB) is a major threat to public health and a challenge for whole of medical fraternity. Poor adherence to drug treatment, nonuniformity of treatment, poor drug administration, frequent treatment interruptions due to adverse drug reactions (ADRs), and lack of resources also contribute to DR-TB. Resistance to first-line anti-TB drugs (isoniazid and rifampicin) leads to DR-TB known as multidrug-resistant TB (MDR-TB), while resistance to second-line drugs leads to a new entity of DR-TB known as extensively drug-resistant tuberculosis (XDR-TB) which involves resistance to the isoniazid, rifampicin, any of the fluoroquinolones (ofloxacin, levofloxacin, or moxifloxacin [Mfx]) and at least one of three injectable second-line anti-TB drugs (kanamycin, amikacin, or capreomycin [Cm]). XDR-TB is a recent development in timeline of TB, involving the use of multiple drugs with high incidence of ADRs and less clinical experience. A standardized treatment regimen including initial intensive phase (IP) (6–12 months) and continuation phase (CP) (18 months) had been advocated since its existence from 2012. In spite of multiple drug administration for prolonged periods, the incidence of XDR-TB is increasing at an alarming rate. Subsequent to the first case reported in Iran, XDR-TB cases have been reported by 117 countries till 2016. In 2015, highest number of XDR cases reported were in India (2130) followed by Ukraine (1206), the Russian Federation (1205), South Africa (719), and Middle Eastern (719) countries. Globally, in 2015, numbers of XDR-TB cases were 7579 and out of them 7234 patients with XDR-TB were enrolled on treatment. In 2015, XDR-TB
treatment was initiated for 2130 registered cases in India. Among six countries with highest XDR-TB burden, mortality was highest (>40%) in India and South Africa. 

In 2012, XDR-TB treatment was included in DOTS-Plus program under Category V regimen under Revised National TB Control Programme (RNTCP) in India. In spite of such a heavy burden of the disease with a very high mortality, very few studies have been carried out around the world and in India on XDR-TB. The present study was conducted to evaluate the treatment outcome of XDR-TB.

**METHODS**

This prospective, observational, continuous, single-centered study was approved by the Institutional Ethics Committee of B. J. Medical College, Civil Hospital, Ahmedabad. Prior permission to conduct the study was obtained from the Head of Pulmonary Medicine Department and relevant authorities concerned with RNTCP.

All patients diagnosed and treated for XDR-TB (except pregnant patients) from January 2012 to March 2014 under Category V regimen of RNTCP from Gujarat in Western India were enrolled and followed up till the end of the treatment (October 2016).

The baseline data of the patients were recorded in pretested case record form. Patients enrolled in the study were treated with daily supervised standardized regimen consisting of an IP of 6–12 months with seven drugs, namely, Cm, para-aminosalicylic acid (PAS), Mfx, high-dose isoniazid (high-dose H), clofazimine (Cfz), linezolid (Lzd), and amoxicillin + clavulanic acid (Amx + Clv). This was followed by a CP of 18 months with six drugs, such as PAS, Mfx, high-dose H, Cfz, Lzd, and Amx + Clv. Pyridoxine was administered to all patients as a supplement. Clarithromycin and thiacetazone were substituted in case of intolerance [Table 1].

Each patient was followed up every month for clinical assessment (body weight), sputum culture examination, chest X-ray, and monitoring of ADRs till completion of 30 months. Two early morning sputum specimens were examined for sputum smear microscopy and culture during each follow-up. For the first 6 months, hematological and biochemical tests (liver and renal function tests) were done every month and thereafter as and when required.

Treatment outcome was categorized as cured, treatment completed, defaulted, failure, and death as per the RNTCP guidelines. A patient was declared cured after complete treatment for at least 24 months with consecutive five sputum culture negative in last 12–15 months. However, patients having two or more of last five cultures positive were considered as failure while patients who did not meet the criteria for cure or failure due to lack of bacteriological

### Table 1: Treatment regimen of XDR-TB with follow-up and investigations

| Regimen                      | Dose           | Remarks                                                                 |
|------------------------------|----------------|-------------------------------------------------------------------------|
| **Intensive phase (6-12 months)** |                |                                                                         |
| Drugs                        |                |                                                                         |
| Capreomycin (Cm)             | 1000 mg        | Those having weight <45 kg were given lower doses of the mentioned drugs  |
| Para amino salicylic acid (PAS) | 12 gm         |                                                                         |
| Moxifloxacin (Mfx)           | 400 mg         |                                                                         |
| High dose isoniazid (High dose H) | 900 mg     |                                                                         |
| Clofazimine (Cfz)            | 200 mg         |                                                                         |
| Linezolid (Lzd)              | 600 mg         |                                                                         |
| Amoxicillin + clavulanic acid (Amx + Clv) | 875/125 mg |                                                                         |
| **Follow-up**                 |                |                                                                         |
| **Continuous phase (18 months)** |                |                                                                         |
| Drugs                        |                |                                                                         |
| Para amino salicylic acid (PAS) | 12 gm         | Those having weight <45 kg were given lower doses of the mentioned drugs  |
| Moxifloxacin (Mfx)           | 400 mg         |                                                                         |
| High dose isoniazid (High dose H) | 900 mg     |                                                                         |
| Clofazimine (Cfz)            | 200 mg         |                                                                         |
| Linezolid (Lzd)              | 600 mg         |                                                                         |
| Amoxicillin + clavulanic acid (Amx + Clv) | 875/125 mg |                                                                         |
| **Follow-up**                 |                |                                                                         |
| Investigations               |                |                                                                         |
| Smear, Culture, Radiological examination, Hematological and biochemical examinations | At every follow up liquid culture was done |
| **Liquid culture**           |                |                                                                         |
| Heamatological and biochemical investigations were done as per requirement |

Note: Amx + Clv was administered twice daily, while all other drugs were prescribed once daily. All patients also received pyridoxine 100mg daily. In case of intolerance to any drug, patients were administered clarithromycin (500mg BD) or thiacetazone (150mg OD)
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RESULTS

Baseline characteristics

A total of 112 patients were enrolled during the study. Of these, 83 (74.1%) were male and 22 (25.8%) were female, with a male: female ratio of 2.9:1 (m:f). The mean age of patients was 33 ± 18.47 years. The majority of patients belonged to the age group of 16–45 years. Mean weight of patients at baseline was 41.93 ± 10.53 kg and mean height was 158.53 ± 9.94 cm. Mean baseline body mass index (BMI) of patients was 16.79 ± 3.66 kg/m² (mean ± standard deviation). Of 112 patients, 35 patients had habit of tobacco chewing followed by smoking (25) and alcohol consumption (5). Forty patients had more than one habit, i.e., tobacco chewing, smoking, and alcohol consumption. Of 112 patients, 89 were previously treated with Category I, while 48 patients were treated with Category II. All patients (112) were previously treated with Category IV regimen (MDR-TB). Family history of TB was also positive in 18 (16%) patients. Of 112 patients, 23 patients had 27 different comorbid conditions. Among them, the most common was hypothyroidism (6) followed by decreased hearing (4), diabetes mellitus (2), ischemic heart disease (2), and severe anemia (2). One patient was HIV positive and one was pregnant at the time of diagnosis of XDR-TB. A drug sensitivity pattern in XDR-TB patients showed that of 112 patients, majority (95, 85%) were resistant to 4 drugs, i.e., isoniazid (H), rifampicin (R), kanamycin (Km), and ofloxacin (O) while 4 (3.6%) patients were mono-resistant to kanamycin and 13 (11.6%) to only ofloxacin.

Outcome of regimen

Clinical assessment

A periodical increase in mean body weight of 2.07 ± 0.9 kg was observed at the end of the study as compared to baseline weight. However, this increase was not statistically significant ($P > 0.05$, Fisher’s exact test) [Figure 1].

Bacteriological improvement

Of 112 patients, sputum culture examination turned negative in 61 patients during first 12 months of treatment. Of these 61 patients, 26 turned sputum negative in first 3 months and remaining 35 turned negative by the end of 12 months of treatment. However, in remaining 51 patients, sputum culture examination was not done or result was not available due to death, defaulted, transferred out, or lost to follow-up [Figure 2].
Safety assessment

Of 112 patients, 58 (51%) patients developed 85 ADRs due to 116 causal drugs. Causal drug was withdrawn temporarily in 32 adverse events and permanently stopped in five adverse events. Of 85 ADR reports, 27 were serious, while 58 were nonserious in nature [Figure 3]. Most common serious ADRs were related to gastrointestinal system, decrease in hearing, and jaundice. Common causal drugs were clofazimine, Cm, linezolid, and PAS. Causality assessment based on WHO-UMC and Naranjo’s scale showed that majority of ADRs were possible in nature (61) and 55 ADRs were probably due to the suspected drug. It was observed that majority of ADRs were mild (54) followed by moderate ADRs (30) based on modified Hartwig and Siegel scale. Of 85 ADRs, 38 ADRs were not preventable, 35 were probably preventable, and 12 were definitely preventable based on Schumock and Thornton preventability scale.

Tuberculosis treatment outcomes

The present study observed that of the 112 patients, 58 (51.78%) patients died and 29 (25.89%) had successful outcome, i.e., 17 (15.17%) were cured and 12 (10.71%) completed the treatment. Of remaining 83 (74.1%) patients, 58 (51.78%) patients died during the treatment, 10 (8.92%) were treatment failure, 11 (9.82%) were defaulter, and treatment outcome of four patients was not available as 3 (2.67%) were transferred out of the state and one was lost to follow-up [Figure 4].

Treatment correlation

An attempt was made to find out the relationship between different variables and treatment outcome in XDR-TB patients. There was direct correlation between age (P < 0.05), BMI >18.5 (P < 0.05), and sputum/culture conversion at 3 months (P < 0.001) with successful treatment outcome, while tobacco chewing habit (P < 0.05) and alcohol consumption (P < 0.05) were commonly related to unsuccessful treatment outcome. Unsuccessful outcome was also more common in patients with history of TB treatment failure or those who were sputum culture positive at the 6th month of treatment with MDR-TB (P > 0.05) [Table 2]. Further, sputum culture conversion patients having successful treatment outcome were significantly quicker as compared to those having unsuccessful treatment outcome (P < 0.001). Some factors, which had no correlation with treatment outcome, include gender, concomitant disease, habit of smoking, and radiological extent of the disease [Table 2].

Predictors of death

A total of 58 patients died while on XDR-TB treatment. Of them, 40 (68.96%) were male and 18 (31.03%) were female. The majority of these patients (50, 86.2%) belonged to the age group of 16–45 years in both genders. Positive predictors

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Table 2: Correlation of various factors associated with successful treatment outcome in extensively drug-resistant tuberculosis patients (n=112)

| Characteristic factors                  | Successful (29) | Not successful (79) |
|-----------------------------------------|-----------------|---------------------|
| Gender                                  |                 |                     |
| Male                                    | 21              | 59                  |
| Female                                  | 8               | 20                  |
| Age (years)                             |                 |                     |
| ≤40                                     | 3*              | 25                  |
| >40                                     | 26*             | 54                  |
| BMI                                     |                 |                     |
| <18.5                                   | 17*             | 12                  |
| ≥18.5                                   | 60*             | 19                  |
| Concomitant disease                     |                 |                     |
| Yes                                     | 3               | 20                  |
| No                                      | 26              | 59                  |
| Personal habits                         |                 |                     |
| Yes                                     | 19              | 77                  |
| No                                      | 10              | 2                   |
| Smoking                                 |                 |                     |
| Yes                                     | 14              | 39                  |
| No                                      | 15              | 40                  |
| Tobacco                                 |                 |                     |
| Yes                                     | 11              | 49**                |
| No                                      | 18              | 30**                |
| Alcohol                                 |                 |                     |
| Yes                                     | 1               | 19**                |
| No                                      | 28              | 60**                |
| Radiological extent of disease          |                 |                     |
| Cavitary lung lesion                    |                 |                     |
| Yes                                     | 12              | 39                  |
| No                                      | 17              | 40                  |
| Bilateral/unilateral involvement        |                 |                     |
| Bilateral                               | 17              | 43                  |
| Unilateral                              | 12              | 36                  |
| Culture conversion within 3 months      |                 |                     |
| Yes                                     | 14*             | 10                  |
| No                                      | 15*             | 69                  |

Values are absolute numbers. *P<0.05 as compared to Group II, **P<0.001 as compared to Group II, ***P<0.05 as compared to Group I (Fisher’s exact test). BMI: Body mass index
for the death were BMI <18.5 ($P < 0.001$), concomitant disease/s ($P < 0.05$), and habit of smoking ($P < 0.05$) while negative predictor for death was sputum/culture conversion at 3 months ($P < 0.05$) [Table 3]. Gender, age, habit of tobacco chewing and alcohol consumption, and radiological extent of the disease had no correlation.

**DISCUSSION**

The present study was conducted on adult XDR-TB patients treated in RNTCP under standard programmatic settings in India. A large number of XDR-TB patients are treated under RNTCP, not much is known about factors that influence treatment outcome. The relationship between various patient-, disease-, and drug-related factors to good treatment outcome is intricate. The present study examined the relationship between different variables to successful treatment outcome.

Our study showed that treatment outcome of XDR-TB patients despite being on long-term regular treatment was low (26%) with late culture conversion (12 months) and high proportions of death occurring in the first 12 months. Age, BMI, sputum culture conversion, tobacco chewing, and alcohol consumption were important factors that had an impact on treatment outcome.

Although the number of patients cured or completing treatment was comparable to the WHO global TB report (2016), unfortunately, the treatment outcome of this study was lower as compared to other studies [Table 4]. Second, in spite of higher sputum culture conversion in our study, the treatment outcome remained poor as compared to other published reports. We observed that a small proportion of patients (29) had successful treatment outcome among culture-converted XDR-TB patients (61). This indicates need of in-depth analysis of treatment failures and defaulters. Although a gap or discrepancy between sputum culture conversion and successful treatment outcome of 8%–10% has been reported by other studies, the present observed a wide gap of about 50% which warrants further research. This also emphasizes the need for more stringent follow-up, monitoring, and patient education in CP to ensure adherence and complete treatment.

In our study, age (<40 years) was positively associated with better treatment outcome. This may be due to the absence of other comorbidities or better compliance with the treatment regimen.

**Table 3: Correlation of factors associated with death of extensively drug-resistant tuberculosis patients ($n=112$)**

| Characteristic factors                  | Death ($n=58$) | Alive ($n=50$) |
|----------------------------------------|---------------|----------------|
| Gender                                 |               |                |
| Male                                   | 40            | 40             |
| Female                                 | 18            | 10             |
| Age (years)                            |               |                |
| $\leq 40$                               | 14            | 36             |
| $>40$                                   | 44            | 14             |
| BMI                                     |               |                |
| $<18.5$                                 | 50**          | 27             |
| $\geq 18.5$                             | 8**           | 23             |
| Concomitant disease                    |               |                |
| Yes                                    | 16*           | 7              |
| No                                     | 42*           | 43             |
| Personal habits                        |               |                |
| Yes                                    | 58            | 38             |
| No                                     | 0             | 12             |
| Smoking                                |               |                |
| Yes                                    | 33*           | 20             |
| No                                     | 25*           | 30             |
| Tobacco                                |               |                |
| Yes                                    | 36            | 24             |
| No                                     | 22            | 26             |
| Alcohol                                |               |                |
| Yes                                    | 13            | 7              |
| No                                     | 45            | 43             |
| Radiological extent of disease         |               |                |
| Cavitary lung lesion                   |               |                |
| Yes                                    | 27            | 23             |
| No                                     | 31            | 27             |
| Bilateral/unilateral involvement       |               |                |
| Bilateral                              | 32            | 27             |
| Unilateral                             | 26            | 23             |
| Culture conversion within 3 months     |               |                |
| Yes                                    | 7             | 17*            |
| No                                     | 51            | 33*            |

Values are absolute numbers. *$P<0.05$ as compared to Group II, **$P<0.001$ as compared to Group II, $P<0.05$ as compared to Group I (Fisher’s exact test). BMI: Body mass index

**Table 4: Comparison of XDR-TB patients’ treatment outcome in different studies (%)**

| Outcome of treatment | Present study ($n=112$) | WHO global TB report, 2016 ($n=4236$) | Pietersen E et al., 2014 ($n=114$) | Migliori GB et al., 2007 ($n=64$) | Leimane V et al., 2010 ($n=48$) | Shah NS et al., 2008 ($n=83$) | Mitnick CD et al., 2008 ($n=48$) | Jeon DS et al., 2009 ($n=176$) |
|----------------------|-------------------------|---------------------------------------|-----------------------------------|---------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Cure                 | 15.17                   | 28                                    | 5                                 | 34                             | 37                            | 0                             | 60                            | 15                            |
| Completed treatment  | 10.71                   | 7                                     | 3                                 | 0                              | 33                            | 0                             | 3                             | 3                             |
| Failure              | 8.92                    | 21                                    | 10                                | 19                             | 48                            | 0                             | 10                            | 40                            |
| Defaulter            | 9.82                    | 0                                     | 4                                 | 12                             | 6                             | 0                             | 6                             | 9                             |
| Death                | 51.78                   | 27                                    | 73                                | 22                             | 8                             | 26                            | 23                            | 23                            |
| Transfer out         | 2.67                    | 2                                     | 3                                 | 0                              | 0                             | 0                             | 0                             | 10                            |
| Lost to follow up/   | 0.89                    | 23                                    | 4                                 | 12                             | 0                             | 24                            | 0                             | 10                            |

NA: Not available
of concomitant diseases in young patients and lack of major physiologic changes expected with aging that may unfavorably affect the ability to withstand drug concentration and its metabolism. In addition, BMI (>18.5) had a significant impact on successful outcome. This can be attributed to better nutrition and immunity.[17]

Further, we also found that the period for sputum culture conversion occurring within the first 3 months was positively associated with successful outcome. Earlier sputum culture conversion indicates effective drug levels at the infection site. Decreased drug concentration, below the expected range, has been observed to take longer time to culture conversion and treatment failure.[19] Furthermore, tobacco chewing and alcohol consumption were found to be negative predictors of successful treatment outcome which may be due to suppression of immunity by nicotine[19] and altered drug metabolism. This may adversely affect plasma levels and increase frequency of ADRs. Frequent ADRs have a propensity to drug interruptions and discontinuation which in turn increase chances of unsuccessful outcome.

The treatment regimen for XDR-TB patients in our study was standardized and was designed according to the WHO guidelines based on the accumulated experience and evidence of RNTCP-programmatic management of drug-resistant TB efforts. In the present study, drug sensitivity testing (DST) was done only for the second-line drugs ofloxacin and kanamycin. Unfortunately, facility for sensitivity testing of the other second-line drugs was not available that could have led to unnecessary administration of ineffective drugs. This calls the need for establishment of infrastructure and laboratory facilities with latest technology to test drug sensitivity. As compared to other studies, the treatment regimen in our study was fixed and less flexible. Thus, resistance to any of the drugs prescribed in Category V may have remained undetected and promoted further drug resistance.[20] Another possible reason for poor treatment outcome could be due to altered microbiology of the tubercle bacilli, i.e., the presence of pili or alternate efflux pump mechanism.[21,22] Unsuccessful treatment outcome was seen in 79 patients (70.5%) in our study, which is higher as compared to other studies [Table 4].[15-16]

An attempt was made to analyze details of patients with fatal outcome. Alarmingly, our study found that a large proportion of patients met with fatal outcome (52%), which was significantly higher than WHO global report (27%) and other studies.[13,14,16,23,24] The majority of these patients died within the first 3 months of starting treatment, whereas mean time required for sputum culture conversion is 4 months. Interestingly, all these patients were previously treated for MDR-TB. Moreover, these patients were treated with fixed standardized regimen in programmatic settings where DST was limited to kanamycin and ofloxacin. Early fatal outcome despite good adherence and intensive therapy with seven drugs is alarming and indicates high-grade resistance. However, influence of other factors, contributing to death, like low BMI (<18.5), concomitant diseases, and harmful personal habits (smoking, tobacco chewing) cannot be ruled out. This further emphasizes the need for new intensive regimen and mobilization of resources to improve DST and individualized treatment as per DST.

Ours was a prospective and retrospective study over a period of 24 months, wherein all the information was recorded precisely. The number of patients included in our study (n = 112) represent a sufficiently good sample size considering low prevalence of XDR-TB. The strength of our study includes recruitment of XDR-TB patients with complete follow-up for entire treatment duration. Second, the patients were observed for clinical symptoms and objective tests such as body weight, sputum smear and culture examination, radiological examination and correlated with treatment outcome.

However, like any other study, there were certain limitations. Ours was an observational study conducted at single center. The patients received treatment at peripheral DOTS center and data were retrieved from treatment card every week. Thus, mild ADRs that did not require any intervention could not be assessed. We were not able to distinguish between deaths related to TB and those attributable to other causes. Further, causality assessment of death due to underlying disease or otherwise was not possible due lack of information.

Conclusions

Treatment outcome of patient treated with Category V regimen of XDR-TB is poor. Although the treatment was well tolerated by majority of the patients, only 26% of XDR-TB patients had the successful treatment outcome, which is not satisfactory. The long duration of treatment (27–30 months), previous frequent defaulted and failure of anti-TB treatment, higher number of ADRs, lack of supportive health-promoting measure, high pill count per day and lack of education, awareness among patients are major obstacles for successful outcome. As most of the patients are treated at peripheral DOTS center, there is a need to develop strategy to strengthen the coordination between RNTCP center and district/peripheral centers. There is also a need to design treatment regimen with decreased duration of treatment and number of pills per day. Individualized treatment and DST-guided regimens provide better treatment outcomes.

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Conflicts of interest
There are no conflicts of interest.

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