Research Article

Clinico-epidemiological profile and treatment outcome of drug-resistant tuberculosis patients admitted to drug-resistant-tuberculosis center in a tertiary care hospital in Varanasi

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ABSTRACT

Background: Tuberculosis (TB) is one of the top ten causes of mortality and the leading cause of a single infectious agent. Unfortunately, India is home to approximately one-fourth of drug-resistant (DR)-TB cases globally. Despite all the developments in TB, the disease is becoming an important threat to public health. **Objective:** The present analysis was done to describe the profile and assess and compare the outcome of DR-TB patient admitted in DR-TB ward, Sir Sunderlal Hospital (SSH), Banaras Hindu University (BHU). **Materials and Methods:** Retrospective analysis of data from 2013 to 2018 of multi-DR (MDR)-TB patients admitted in DR-TB ward, SSH, Institute of Medical Sciences, BHU and treatment initiated after pre-treatment evaluation was conducted. Patients were referred from nearby nine districts of Uttar Pradesh. After pre-treatment evaluation treatment was initiated at DR-TB center, SSH as well as in their respective district. **Results:** A total of 3234 (76.7%) MDR-TB patients out of 4216 MDR-diagnosed patients were initiated on standard treatment which has increased from 74% in 2013. More than 93% of the cases were older than 15 years of age with slightly male predominance. The majority (>96%) of the cases were pulmonary TB. In the present analysis conversion of MDR-TB to extensively DR-TB (XDR-TB) was 7.7%. The treatment success rate for XDR-TB had also significantly improved from 11% in 2015 to 34% in 2017. **Conclusion:** Analysis shows 7.7% MDR patients converted into XDR; hence, there is a strong need to explore factors responsible for conversion. 7% of patients were <15 years of age indicating the need for separate pediatric DR-TB ward. 18% of DR-TB patients were defaulters; hence, the reason for it should be sought and addressed. Treatment success rate for MDR-TB has been seen improved from 40% in 2013 to 48% in 2017.

KEY WORDS: Clinical; Epidemiological; Multidrug-Resistant; Patients; Treatment Outcome

INTRODUCTION

Twenty-five years ago, in 1993, the World Health Organization (WHO) declared tuberculosis (TB) a global health emergency.[1] India is a shelter to 27% of drug-sensitive-TB and 24% of drug-resistant (DR)-TB globally.[2] DR TB continues to be a public health crisis. Globally, 3.5% of new TB cases and 18% of previously treated cases had multi-DR (MDR)/resistant to rifampicin (RR)-TB.[2] Among cases of MDR-TB in 2017, 8.5% (95% confidence interval, 6.2–11%) were estimated to have extensively DR-TB (XDR-TB).[2] Worldwide in 2017, 558,000 people (range, 483 000–639 000) developed TB that was RR-TB, the most effective first-line drug, and of these, 82% had MDR-TB.[2,3] Three countries accounted for almost half of the world's

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cases of MDR/RR-TB: India (24%), China (13%), and the Russian Federation (10%).[2,4] Globally, 160,684 cases of MDR/RR-TB were detected and notified in 2017 (a small increase from 153,119 in 2016). Of these, a total of 139,114 people (87%) were enrolled on treatment with a second-line regimen, up from 129,689 in 2016 but still only 25% of the estimated 558,000 people who developed MDR/RR-TB in 2017. China and India alone accounted for 40% of the global gap.[2] As per recent the WHO report 2018 – gaps between the estimated number of new cases and the number actually reported are due to both underreporting of detected cases, and underdiagnosed (either because people do not have access to health care, or because they are not diagnosed when they do). Treatment success remains low (55% globally).[2] Examples of high burden countries in which better treatment success rates are being achieved include Bangladesh, Ethiopia, Kazakhstan, and Myanmar and Vietnam (all of which have rates >70%). In 2017, the proportion of people with TB who died from the disease was 16%, down from 23% in 2000. Worldwide, the TB incidence rate is falling at about 2% per year. Closing gaps in detection and treatment require much higher coverage of drug susceptibility testing among people diagnosed with TB, reducing under-diagnosis of TB, models of care that makes it easier to access and continue treatment, new diagnostics, and new medicines and treatment regimens with higher efficacy and better safety.[2]

As per the WHO, the end TB strategy milestones for 2020 and 2025 can only be achieved if TB diagnosis, treatment, and prevention services are provided within the context of progress toward universal health coverage, and if there is multisectoral action to address the social and economic factors that drive TB epidemics. TB incidence needs to be falling at 10% per year by 2025, and the proportion of people with TB who die from the disease needs to fall to 6.5% by 2025. The funding required for prevention, diagnosis, and treatment continues to rise while the allotted fund falls short of what is being provided. Although the majority of the source of funding is domestic only, the stop TB partnership's global plan to end TB 2016–2020 estimated that US$ 10.4 billion is required in these countries in 2018, leaving a gap of US$ 3.5 billion. Without an increase in funding, the annual gap will widen to US$ 5.4 billion in 2020–at least US$ 6.1 billion in 2022. As in previous years, most of the funding (86%) available in 2018 is from domestic sources. However, this global aggregate figure is strongly influenced by BRICS, in which 96% (range 91–100%) of funding is from domestic sources. In India, domestic funding more than tripled between 2016 and 2018.[2]

A study at the TB research center, Chennai, India, indicated that TB may cause 300,000 children to become orphans and 100,000 Indian women to be rejected by their families each year.[5] Researcher at the TB research center, Chennai, India, found that an average patient suffering from TB incurs a total expenditure of US$ 99 on diagnosis and treatment. This is a prohibitive amount for a daily wage laborer who might hope to earn the equivalent of US$ 200–400 per year.[5] In another study in Andhra Pradesh, India by Ramana *et al*. found that on an average, rural TB patients spent US$ 30/month on TB diagnosis and treatment, while urban patients spent US$ 15/month.[6]

Poverty continues to be the key underlying factor for the spread of TB. Due to poverty, patients are less educated, live in appalling, unhealthy environments are malnourished and thence are unaware of problems relating to health and diseases. In fact, to overcome the expense incurred, Government of India has taken an initiative to provide INR 1000 per patient as an allowance for travel cost and nutrition supplementation on RNTCP registration.

One of the major impediments in the control of TB worldwide is the default (Treatment interruption). It has been repeatedly proven that at least one-third of patients does not take the full course of treatment, despite the fact that medicine is available without any cost, treatment is convenient and adequate health education is given. Various attempts have been made to assess the extent of the problem of treatment interruption by patients and to determine the reason for it.[7,8] These include low literacy rate, low monthly income, large family size, loss of wages, inconvenient clinic timings, long waiting hours, and non-availability of medicines. Other reasons sited include impolite behavior of staff,[9] social belief, social stigma,[10] and poor knowledge about disease among patients and inadequate understanding of the treatment regimens. In addition, discontinuation may be due to the disappearance of symptoms, feeling well, as well as pain and suffering associated with injectables and the side effects. It is only natural to enjoy recovery and stop taking medication.[11,12]

Moreover, concordant with previous surveys, the first national anti-TB drug resistance survey conducted by the Indian Government in collaboration with the WHO and the United States Agency for International Development showed that close to 23% of new cases have resistance to any drug with MDR-TB detected in 3%. The outcome depends on the health profile of patients. Hence, the present analysis was done to assess the clinical, epidemiological profile, and outcome of MDR patient admitted in DR-TB ward, Sir Sunderlal Hospital (SSH), Banaras Hindu University (BHU).

MATERIALS AND METHODS

Retrospective analysis of DR-TB patients admitted from January 2013 to June 2018 was conducted after approval from the Institute Ethical Committee and Department of TB and Respiratory Diseases, SSH, BHU. DR-TB center at SSH is accountable for the management of DR-TB patients from nine heavily populated districts of Uttar Pradesh such as Varanasi (3.67 Million), Jaunpur (4.49 m), Chandauli

(1.95 m), Sant Ravidas Nagar District (1.57 m), Sonbhadra (1.86 m), Ghazipur (3.62 m), Mau (2.20 m), Ballia (3.23 m), Azamgarh (4.61 m), and Mirzapur (2.49 m) comprising approximately 29.69 million populations as per district census report 2011.

All MDR-TB/Rifampicin resistant or XDR-TB cases were diagnosed by molecular technique (Genexpert), and/or line probe assay (LPA) followed by drug sensitivity testing for all Genexpert/LPA positive samples. Patients were evaluated as per standard national protocol before initiating treatment with the conventional World Health Organization (WHO) standard regimen and were followed up as per the guidelines.

RESULTS

A total of 3382 DR-TB cases (3234 MDR-TB patients and 148 XDR patients) were initiated on treatment from January 2013 to June 2018 at DR-TB center SSH, BHU. Furthermore, they were divided into three broad categories based on treatment completion and culture conversion [Figure 1].

As evident from Table 1a, a total of 4216 (12.87%) out of 32,756 turned out to be MDR-TB from a suspected MDR sputum sample which was subjected to Genexpert for a period of 5½ years from January 2013 to June 2018. Furthermore, a total of 3234 (76.70%) out of 4216 MDR-TB positive cases were initiated on a conventional MDR-TB treatment regimen for a period of 5½ years from January 2013 to June 2018.

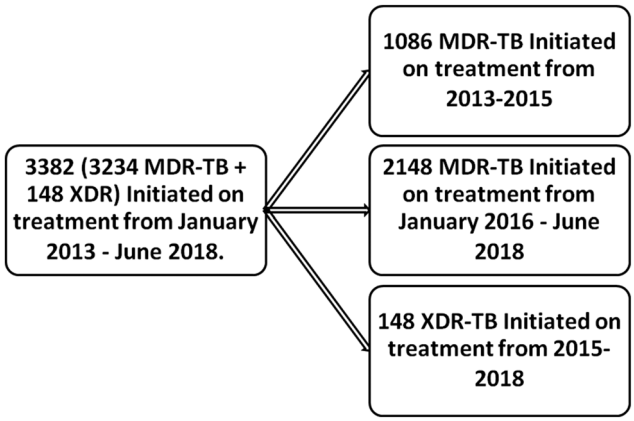

Figure 1: Flow chart of drug-resistant-tuberculosis

Table 1a: Year wise distribution of MDR Patients

Year	Suspected MDR	Diagnosed MDR (%)	Treatment initiated MDR (%)
2013	674	386 (57.27)	255 (66.06)
2014	985	452 (45.88)	327 (72.34)
2015	2892	625 (21.61)	504 (80.6)
2016	5099	843 (16.53)	673 (79.83)
2017	12177	1119 (9.18)	905 (80.87)
2018 (Till June)	10929	791 (7.23)	570 (72.06)
Total	32756	4216 (12.87)	3234 (76.7)

MDR: Multidrug-resistant

Table 1b shows that majority of the DR-TB continues to be male pulmonary MDR-TB >15 years of age which is persistent >90% compared to XDR-TB which continues to be <10%. In fact, most of the DR-TB cases were pulmonary which accounts for approximately 95%, and the majority of them were patients >15 years of age approximately 93% versus 6% among patients <15 years.

During a period of 3 years, i.e., from the year 2013 to 2015, a total of 1463 patients were found to have DR-TB, i.e., 32.14% from a suspected 4551 patients. A standard treatment was initiated on 1086, i.e., 74.23% of MDR-TB patients. A significant proportion of patient (25.73%) was not notified and perhaps was either treated at the private sector or did not receive treatment. Out of the total patients initiated on treatment 196 (18.04%) loss to follow-up, 41 transferred out three stopped treatments due to adverse effects and four due to other reasons.

As evident from Table 2, our treatment success rate (cure + completed) was 40.04% (cured 21.17% + completed 18.87%) till date. However, in 2.57% of patient's treatment failed, 27.16% of patients died during treatment, and 7.73% of patient had developed additional resistance to fluoroquinolones and/or aminoglycosides while on treatment for MDR-TB and was shifted to Pre-XDR/XDR-Regimen accordingly.

Table 3 shows a positive culture conversion (i.e., becoming culture negative) response among 47.25% and 47.84% of the patients on MDR-TB treatment in the year till date among patients initiated on treated in 2016 and 2017.

As evident from Table 4, only 10.81% of XDR-TB patients were successfully treated during 2015 at our center, but the treatment outcome is improving significantly to as high as 34% of patient in 2017 as per the latest outcome report till date as seen from Table 5 with culture becoming negative (i.e., culture conversion) after initiation of treatment. Mortality among XDR-TB was approximately 78.37% in 2015, which had significantly decreased to 46% in 2017.

DISCUSSION

Programmatic management of drug-resistant TB (PMDT) was initiated in 2007 in India to address the emerging problem of DR-TB, and the national PMDT scale-up was achieved by March 2013. A total of 4216 (12.87%) out of 32,756 suspect came out to be positive for MDR-TB from a suspected MDR sputum sample which was subjected to Genexpert for a period of 5½ years from January 2013 to June 2018. A total of 3234 cases (76.70%) out of 4216 MDR-TB positive cases

Table 1b: Clinico-epidemiological profile of DR-TB patient

Variables	Frequency (%)				
	2017	2016	2015	2014	2013
Drug resistance					
MDR	905 (94.8)	670 (91.7)	504 (93.2)	327 (100)	254 (98.8)
XDR	50 (5.2)	61 (8.3)	37 (6.8)	0 (0)	3 (1.2)
Anatomic site P/EP					
Extra-pulmonary	15 (1.6)	18 (2.5)	10 (1.8)	5 (1.3)	2 (0.8)
Pulmonary	938 (98.2)	705 (96.5)	529 (97.8)	373 (98.4)	255 (99.2)
MDR Tb suspect criteria*					
Failure	55 (5.8)	79 (10.8)	50 (8.4)	62 (19)	41 (16)
Re treatment case S+At 4 months	9 (0.9)	24 (3.3)	18 (3.0)	14 (4.3)	13 (5.1)
Contact of known MDR-TB case	19 (2.0)	24 (3.3)	17 (2.9)	5 (1.5)	1 (0.4)
Sputum+ve at diagnosis retreatment Case	85 (8.9)	260 (35.6)	258 (43.3)	230 (70.3)	197 (76.7)
Any follow-up sputum+ve	22 (2.3)	74 (10.1)	63 (10.6)	5 (1.5)	1 (0.4)
Sputum−ve at diagnosis, re-treatment case	57 (6.0)	103 (14.1)	70 (11.7)	0 (0)	1 (0.4)
Age in years					
0–15	64 (6.7)	30 (4.1)	32 (5.9)	23 (7)	18 (7)
>15	891 (93.3)	697 (95.3)	509 (94.1)	304 (93.0)	239 (93)
Sex					
Female	402 (42.1)	292 (39.9)	196 (36.2)	123 (37.6)	108 (42)
Male	553 (57.9)	439 (60.1)	345 (63.8)	204 (62.4)	149 (58)
Total	955 (100)	731 (100)	541 (100)	327 (100)	257 (100)

DR-TB: Drug-resistant-tuberculosis, MDR: Multidrug-resistant EP: Extra-pulmonary, P: Pulmonary, XDR: Extensively drug-resistant

Table 2: DR-TB treatment outcome

TS MDR (2013–2015)	TDx (%)	TI (%)	Cured (%)	Compl. (%)	Default (%)	Died (%)	Failure (%)	XDR (%)
4551	1463 (32.14)	1086 (74.23)	230 (21.17)	205 (18.87)	196 (18.04)	295 (27.16)	28 (2.57)	84 (7.73)

TS MDR: Total suspected multidrug-resistant TB, TDx: Total diagnosed, TI: Total patients in whom treatment was initiated, Compl: Treatment completed, XDR: Extensively drug-resistant, DR-TB: Drug-resistant tuberculosis, TB: Tuberculosis

Table 3: MDR-TB treatment outcome from year 2016 and 2017

TDx	TI (%)	Cured (%)	CN (%)	CP (%)	CU (%)	F	Died (%)	DF (%)	XDR (%)
843	673 (79.83)	18+31 (7.28)	269 (47.25)	67 (9.95)	58 (8.61)	3+	104+15.45	68+10	33+4.9
1119	905 (80.87)	–	433 (47.84)	84 (9.28)	101 (11.16)	–	116+12.81	82+9.06	63+6.96

TS MDR: Total suspected multidrug-resistant TB, TDx: Total diagnosed, TI: Total patients on whom treatment was initiated, Compl: Treatment completed, XDR: Extensively drug-resistant, CN: Culture negative, CP: Culture positive, CU: Culture report unavailable, F: Treatment failed, DF: Default

were initiated on a conventional MDR-TB treatment regimen for a period of 5½ years from 2013 to 2018, June. Male (60.4%) is affected more than female (39.56%). The most frequent criteria to suspect DR-TB which was turned out to be most significant in diagnosing DR-TB were sputum positive at diagnosis of retreatment cases. The majority of the DR-TB continues to be MDR-TB more which is persistent >90 % compared to XDR-TB which continues to be <5%. Treatment success rate for MDR-TB improved from 40.04% in 2013 to 47.25% and 47.84% in the year 2016 and 2017, respectively. In fact, most of the DR-TB cases were pulmonary which accounts for approximately 95%, and the majority of them were patients >15 years of age approximately 93% versus 6% among patients <15 years. 18% of cases initiated on treatment were a defaulter. Conversion of MDR-TB to XDR-TB is

Table 4: XDR-TB cases initiated on treatment originally XDR

Year	Case	Cured	T. completed	Died	Default	T. out
2015	37	4 (10.81)	1 (2.72)	29 (78.37)	2 (5.40)	1
2016	61	2+7*(14.75)	–	36 (59.01)	8 (13.11)	–
2017	50	17* (34)	–	23 (46)	5 (10)	–

*: Culture converted, T. out: Transfer out, T. completed: Transfer completed, XDR: Extensively drug-resistant, TB: Tuberculosis

Table 5: Highlight on local, national, and global treatment outcome[2,3,16]

Indicators	SSH (mean of 2015–2017) (%)	National (%)	International (%)
Cure rate	40.04	46[2,16]	55[2]
Death Rate	27.16	20[2,16]	17[2]
XDR Rate	7.73	8.05[2]	8.5[2]
Proportion of notified patients initiated on treatment	80 (2015–2017)	91.12 (2007–2017)[3]	86.57 (2017)[2]
XDR Success rate	20	28[3]	34[2]

XDR: Extensively drug-resistant, SSH: Sir Sunderlal hospital

lower, i.e., 7.7%. The treatment success rate for XDR-TB had significantly improved from 11% in 2015 to 34% in 2017.

A big gap (i.e., only12.87%) between the number of the suspect and diagnosed cases of MDR; perhaps reflect that the suspect criteria were not followed properly as described in guideline in later years from 2016 to 2018. We found that there were a significant number of MDR-TB diagnosed from 2013 to 2015 (32%) out of suspected cases versus small percentage of 9.76% from January 2016 to 2018 June. Although the author believes that it was done to cover a wide range of population of DR-TB patients/contacts in the community and to prevent further dissemination of the fatal disease. Hence, we reemphasize the need for proper selection of patient before subjecting their sample to Genexpert at present, in view of limited facilities available currently and to enhance the performance and decrease the time duration for reporting. A standard treatment was initiated on 1086, i.e., 74.23% of MDR-TB patients. A significant proportion of patient (25.73%) was not notified and perhaps was either treated at the private sector or did not receive treatment. We believe factors such as less field monitoring, lack of proper counseling, and illiteracy are few important reasons behind missing cases. As per the report available until the preparation of this manuscript, the total enrolled patients on treatment for drug resistance TB, Table 3 shows a positive culture conversion (i.e., becoming culture negative) response among 47.25% and 47.84% of the patients on MDR-TB treatment in the year 2016 and 2017, respectively, against national and international success rate of 46% and 55%, respectively. The success rate and death rate among MDR-TB patients at DR-TB center SSH are 40.04% and 27% until 2015 which is definitely improving as evident from Table 2 compared to national success rate. Moreover, the above data also showed that male (60.4%) is affected more than female (39.56%), i.e., 1.52 times which is comparable to 1.7 times globally[2] though a local study showed male to female ratio was 1:1.17.[13] In fact, sputum Genexpert for MDR-TB positivity at diagnosis in cases of retreatment cases continued to be the most frequent criteria to detect drug resistance. The national treatment success rate remains at 46% and the national death rate of around 20%, respectively, compared to the global treatment success rate of 55% and death rate of 17%.[2] Although a study from Maharashtra[14] showed a significantly higher, i.e., 58% success rate for MDR-TB which is even higher than overall global figure though another study by Vishakha and Sanjay from Ahmedabad showed a success rate of 39%.[15] High rates of treatment failure and deaths are associated with fluoroquinolone resistance (21.82%)[16] in the Indian MDR-TB patients. MDR-TB is a marker of a TB control program's inability to adequately manage drug-susceptible TB. Since culture and drug sensitivity testing are only performed for retreatment cases and patients failing first-line therapy, these numbers are likely a substantial underestimate of the actual current MDR-TB burden. Moreover, the most frequent criteria to suspect DR-TB which was turned out to be most significant in diagnosing DR-TB were sputum positive at diagnosis of retreatment cases, though the yield significantly dropped from 76.7% in 2013 to only 8.9% in 2017 in decrescendo fashion. A big gap (i.e., only 12.87%) between the number of suspect and diagnosed case of MDR; which may reflect that perhaps the suspect criteria were not followed strictly as described in guidelines or possibly because of the national strategy to early detect and treat cases of DR-TB cases in the community. Compared to global data[7,8] of 33% defaulters, we had only 18% of cases initiated on the MDR-TB regimen as a defaulter. The majority of the DR-TB continues to be MDR-TB more which is persistent >90 % compared to XDR-TB which continues to be <5%. In fact, most of the DR-TB cases were pulmonary which accounts for approximately 95%, and the majority of them were patients >15 years of age approximately 93% versus 6% among patients <15 years. Surprisingly, it was found that the resistance to isoniazid (H) was declining from 65.7% in 2014 to 55.8% in 2015 to 25.7% in 2016 to only 3.7% in 2017, which is contrary to the existing knowledge and literature that says almost all patients (>82%) with rifampicin resistant cases are resistant to isoniazid.[2,16] Aminoglycosides (Kanamycin, Capreomycin, and Amikacin) were found to be the third most common drug to which approximately 8.4% of subjects in 2017 were resistant compared to 5.6% in 2016 and 6.3% in 2015. Fluoroquinolones (ofloxacin, levofloxacin, and moxifloxacin) were the fourth common drug to which our patients were resistant accounting for 4.5% in 2017–7.5% in 2016–5.7% in 2015 which is again far from global data of 22%.[2] The authors believe that these variations in the resistance pattern are due to less number of rifampicin resistant cases subjected to first and/or second LPA. In fact, 4.37% (n = 148 out of 3382) of DR-TB cases were XDR-TB which is almost similar to another small single-center study 5.1%.[13] We also noticed that most of our patient complained of gastrointestinal

disturbances, arthralgia, peripheral neuropathy, skin rashes, and pyopneumothorax with fewer ototoxicity for which appropriate management and consultation with the concerned department was sought as needed. Moreover, conversion from MDR-TB to XDR-TB at our center remained significantly lower than our national and global conversion rate of 8.05% and 8.5%[2].

The proportion of notified patients initiated on treatment has increased from 74% in 2013 to 80% in 2017 which is appreciable and will help in achieving one important component of National Strategic Plan 2017–2025, indeed will help fill the gap between DR-TB detected and treatment initiated. Although an improvement in treatment success rate has been seen at DR-TB center, SSH from 40% in 2013 to 48% in 2017, it is still lower compared to international data. Importantly, conversion of MDR-TB to XDR-TB is lower, i.e., 7.7% at DR-TB center, SSH against 8.5% globally. Moreover, the treatment success rate for XDR-TB had significantly improved from 11% in 2015 to 34% in 2017 against 28% of national success rate.

Strength and Limitation of the Study

The current study showed a data of huge number of patients initiated on DR-TB regimen as per the PMDT Programme from January 2013 to June 2018 from a tertiary care center in India. Being a retrospective observational study cause-effect relation cannot be established. In addition, we also are not able to present the data on the side effect profile of patients initiated on treatment as well as the reason for stopping treatment in between (default) and addressing it.

CONCLUSION

The analysis shows 7.7% MDR patients converted into XDR; hence, there is a strong need to explore factors responsible for conversion. 7% of patients were of <15 years of age which indicates the need for separate Pediatric DR-TB ward, 18% of DR-TB patients were defaulters; hence, the reason for it should be sought and addressed. Treatment success rate has been seen improving from 40% in 2013 to 48% in 2017.

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