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Study Profile of Drug-Resistant Tuberculosis at A Northern India Hospital

Medical Science

KEYWORDS : Multi drug-resistant TB, Mycobacterium tuberculosis, Revised National Tuberculosis Control Programme(RNTCP),

Dr. Urvinderpal Singh	Professor and Head, Department of Pulmonary Medicine, Government Medical College, Patiala, India., * Corresponding author
Dr. Bharat Bhushan	Associate Professor, Department of Pulmonary Medicine, Government Medical College, Patiala, India.
Dr. Daksh Jhim	Junior Resident, Department of Pulmonary Medicine, Government Medical College, Patiala, India.
Dr. Kulbir Singh	Associate Professor, Department of Pulmonary Medicine, Government Medical College, Patiala, India
Dr. Deepak Goyal	Senior Resident, Department of Pulmonary Medicine, Government Medical College, Patiala, India.
Dr. Naresh Kumar	Senior Resident, Department of Pulmonary Medicine, Government Medical College, Patiala, India
Dr. Anand Kumar Bansal	Junior Resident, Department of Pulmonary Medicine, Government Medical College, Patiala, India.

ABSTRACT

Objectives: The present study was aimed to elucidate the various aspects of the (M)DR-TB, so as to further improve and strengthen the programme.

Materials and methods: Out of the registered 162 patients, 132 qualified for the study during the calendar year of 2012 and standardized treatment regimen (Category IV) was initiated according to RNTCP of India, based on WHO guidelines.

Results: The sputum smear conversion and culture conversion rates at 3 months and 6 months were found to be 89.39% and 90.15% respectively. Success rate was found to be 50.75% (cure rate and treatment completion rate combined) and a default rate of 27.27%, with ADRs noticed in majority of patients at different occasions.

Discussion and conclusions: Diagnosis of the co-morbidities and recognition of various addictions require timely interventions. Early detection of ADR(s) with appropriate management, responsible DOT provider services, effective monitoring and supervision are the corner stones for desired goal.

Introduction:

Tuberculosis (TB), known to mankind since ages, is a major health concern for India, [1] the world's second- most populous country after China. In 2012, out of the estimated global annual incidence of 8.6 million TB cases, 2.3 million were estimated to have occurred in India with annual mortality of 0.27 million countrymen. [2] The TB burden in India is still staggering. India's Revised National Tuberculosis Control Programme (RNTCP), based on the DOTS strategy endorsed by WHO, began as a pilot project in 1993 and was launched as a national programme in 1997, with the entire country covered under DOTS by 24th March 2006. [3] The emergence of resistance to drugs used for treatment of TB, and particularly multidrug-resistant TB (MDR-TB), has become a significant public health concern worldwide and is a major hindrance for effective TB control. [4]

Under the national programme with Programmatic Management of Drug Resistance Tuberculosis (PMDT) in India, MDR-TB is defined as a tubercular patient in whom *Mycobacterium tuberculosis* is resistant in vitro to Rifampicin(R) and isoniazid (H) with or without resistance to other antitubercular drugs, based on drug susceptibility (DST) results from an RNTCP-certified culture and DST laboratory. Notably, RNTCP under WHO guidelines has taken the programmatic decision that patients who have any 'R' alone resistance, should also be managed as if they are an MDR-TB case, even if they do not formally qualify as an MDR-TB case as per the above definition of multidrug-resistance TB. [5] (M)DR-TB is a man-made phenomenon. [4]

The number of MDR-TB cases among notified new pulmonary TB cases has been found to be 2.2% average; whereas amongst notified re-treatment pulmonary TB cases being 15% average. As per the calculations, the sum of these MDR-TB cases came out to be 64,000 patients in the year 2012[2] - a huge number indeed so as to drain nation's financial resources for their management ! Specific measures are being taken within the RNTCP to address the (M)DR-TB problem through appropriate management of patients and strategies to prevent its propagation and dissemination in the family/community. PMDT (erstwhile DOTS Plus), refers to programme based (M)DR-TB diagnosis, management and treatment. These guidelines also integrate the identification and treatment of more severe forms of drug resistance, such as extensively drug resistant TB (XDR-TB). [4]

AIM

Keeping in view the enormity and seriousness of the prevailing situation, the aim of the present study was to elucidate the various aspects of the (M)DR-TB, so as to take further steps to improve and strengthen the programme.

Materials and methods

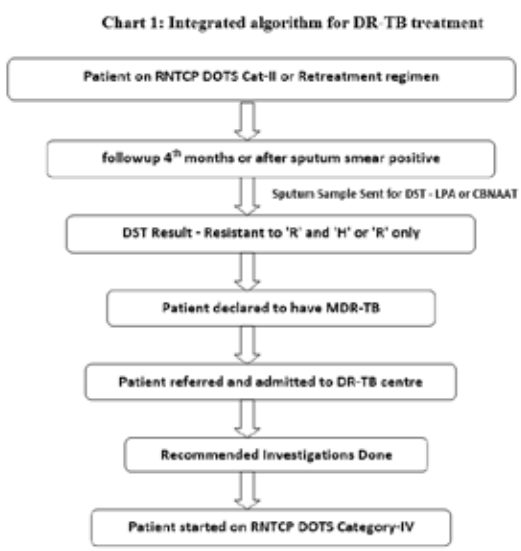
This study was conducted at Drug Resistance Tuberculosis Centre (DR-TB Centre), Department of Pulmonary Medicine, Government Medical College, Patiala, India.

CASE FINDING: The patients were selected during the period of 1st January to 31ST December of the year 2012. As per the RNTCP policy, the patients who remained posi-

tive during the follow up sputum smear after 4 months or more, who were on RNTCP DOTS Category II (retreatment regimen) were subjected to drug susceptibility test (DST). The sputum samples were subjected to DST for 'R' and 'H' by Line Probe Assay (LPA) i.e. molecular DST for Rifampicin and Isoniazid and Cartridge Based Nucleic Acid Amplification Test (CBNAAT)-i.e. the Gene-Xpert MTB/RIF assay for 'R'. Patients found to be resistance to R and H or R alone, belonging to 8-districts of Punjab i.e. Ludhiana, Patiala, Mohali, Sangrur, Fatehgarh Sahib, Roopnagar, Barnala and Mansa [4] were taken for the study.

INVESTIGATIONS: Pre-treatment evaluation of the diagnosed drug resistance tuberculosis cases, after admission, was carried out in the department, as per the specified guidelines. Patients were subjected to necessary investigations including: chest X-ray (PA view), hemoglobin, total and differential leukocyte count, platelet count, renal function tests, liver function tests, urine routine, HIV serology, thyroid stimulating hormone titers and urine pregnancy test for females (in reproductive age). [4] The integrated algorithm is given in chart-1.

Chart 1: Integrated algorithm for DR-TB treatment



ELIGIBILITY CRITERIA: Diagnosed cases of drug resistance tuberculosis, after the DST results were traced and enrolled into the study. However, patients under-18 years of age, pregnant women, patients having a concurrent major psychiatric illness or serious medical illnesses, patients having had >1month treatment with any second line anti-TB drugs, HIV seropositive cases and patients who died or defaulted within one month of starting the treatment were excluded from the study.

TREATMENT REGIMEN: The standardized treatment regimen (Category IV) consists of an intensive phase (IP) of 6-9 months with 6 drugs, namely kanamycin (Km), levofloxacin (Lfx), ethionamide (Eto), pyrazinamide (Z), ethambutol (E), and cycloserine (Cs) given daily (Km given for 6 days a week). This was followed by a continuation phase (CP) of 18 months with four drugs, namely Ofx, Eto, E and Cs. At the end of 6 months of treatment, if the fourth month culture remained positive, the IP was extended for a further 3 months. All patients enrolled to the study were treated with a daily supervised regimen. [4]

PATIENT MANAGEMENT AND DRUG LOGISTICS: As per the PMDT guidelines under RNTCP, each patient was registered in the DR-TB site register, allotted a PMDT number and supervised treatment was given for 7 days to look for any early adverse drug reaction(s)[ADRs] and drug intolerance. Thereafter, patients were discharged and drugs were given for 7 days- transit period. Patients were told to report to their respective district tuberculosis officer (DTO). The DTOs were informed by e-mails about their discharge and for further treatment. The DTO's responsibility is to arrange the drugs for each and every patient. The drug boxes of each patient were sent to the peripheral health institute. The designated DOT provider was responsible for administration and supervision of his/her treatment. [4]

FOLLOW UP: For follow up examination the required number of sputum specimens were collected and examined by smear and culture at least 30 days apart from the 3rd to 7th month of start of treatment (i.e. at the end of the months 3, 4, 5, 6 and 7) and at 3-monthly intervals from the 9th month onwards till the completion of treatment (i.e. at the end of the months 9, 12, 15, 18, 21 and 24). [4]

OUTCOME MEASURES: Outcome measures analyzed were: (i) time to sputum smear and culture conversion: defined as the duration from the initiation of treatment to the date of the first of the two consecutive negative smears or cultures, taken at least one month apart, irrespective of the subsequent results; (ii) smear and culture conversion rates at 3 and 6 months; (iii) treatment outcomes: such as cure, treatment completed, default, failure and death as per the RNTCP definitions.

RESULTS

A total of 162 patients with drug resistant tuberculosis were registered to DR-TB centre, Patiala, for initiating Category IV treatment during the calendar year 2012. Out of the registered patients during the said period, 132 qualified to be included in this study as per the set eligibility criteria.

TABLE 1
BASELINE CHARACTERISTICS OF 132 (M)DR - TB PATIENTS TREATED WITH THE STANDARDIZED TREATMENT REGIMEN UNDER RNTCP

Patients Characteristics		n*
Age, years	<30 30-45 >45	39 50 43
Sex	Male Female	100 32
Body wt. bands (kg)	16-25 26-45 46-70 >70	2 68 59 3
Area of residence	Rural Urban	62 70
Resistant to	R alone RH both	65 67

n* = no. of patients

The non-qualifying 30-exclusions included: 3-HIV seropositive patients, 13- less than 18 years' age, 4- defaulters within a month of start of treatment, 4- transferred out to other DR-TB centres, 3- taking second line anti-tubercular drugs already and 3- deaths within one month of start of treatment.

Amongst the qualifying 132 patients selected, 100 were males and 32 females. As per the area of residence declared by them 62(46.97%) were rural while 70 (53.03%) were urbanites. 67 patients (50.76%) were found to be of MDR-TB (resistance to both R and H) whereas 65 (49.24%) were dis-

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covered to be DRTB cases with resistance to R-alone. (Reference Table 1)

The sputum smear conversion and culture conversion rates (Table 2) at 3 months were found to be 89.39% (118/132) and at 6 months' interval, were 90.15% (119/132) for both smear and culture. At the end of treatment, 42 (31.81%) patients were declared cured and 25 (18.94%) completed the treatment. During the study, 18 (13.63%) patients died, 36 (27.27%) defaulted and 8 (6.06%) patients were declared XDR (Extremely Drug Resistant) with resistance to Kanamycin and Levofloxacin in addition to 'R' and 'H'. One (0.75%) patient failed the treatment and 2 (1.51%) were transferred out. The events of ADRs were seen in 72 (54.54%) patients. The summary of outcome is shown in Table 3.

TABLE 2
SMEAR AND CULTURE CONVERSION RATES AT 3 AND 6 MONTHS (n=132)

Month of treatment		Conversion Rate (%)	Died	Positive
Smear	3 months	118 (89.39)	5	9
	6 months	119 (90.15)	8	5
Culture	3 months	118 (89.39)	5	9
	6 months	119 (90.15)	8	5

TABLE 3
SUMMARY OF OUTCOME OF STANDARDIZED TREATMENT OF PATIENTS WITH (M)DR-TB (n=132)

Outcome	No.	%age
Cured	42	31.81
Rx completed	25	18.94
XDR	8	6.06
Died	18	13.63
Defaulted	36	27.27
Failed	1	0.75
Transferred out	2	1.51

XDR= extensively drug resistant

Discussion

Declared a 'global emergency' by world health organization in 1993, by an unprecedented step, tuberculosis burden still remains distressing. Multi drug resistance tuberculosis is a waking call and threat to global tuberculosis control [6], [7], [8] and is emerging as a major challenge to all. The rising number of (M)DR-TB cases, has multiple implications including its clinical management, social support and financial burden especially for developing nations- like India.

Present study results with 100 male patients versus 32 females with (M)DR-TB probably also depicts the 'male-dominant' character of our society. Being the 'bread-earner' for the family, the males are made to report earlier to the health facility than their female counterpart. The additional reasons for this gender disparity for disease reporting, may be attributed to more prevalence of smoking, alcohol abuse/ drug addictions amongst males as compared to their females. [9] Eighteen patients disclosed history of alcohol abuse (including 'local made' and 'Indian made foreign liquor'), drug addictions (opium and derivatives, cannabis and other synthetic substances etc.). Another essentially important and associated reason for the disparity being that because of the 'social-stigma' [9] attached to the disease, lesser females report for any medical advice and treatment and that also 'too late'.

89 patients from both sexes belong to the age group of 18-45 years whereas 43 patients were >45 years of age. This feature reflects and affirms the behavior of the disease itself, conforming to the fact from the earlier studies that TB primarily affects people in their youthful and productive age group with important socio-economic consequences. Literature unequivocally emphasizes that TB hinders socio-economic developments- with 75% of the cases being in economically active age group [10] and that two-third of the cases are males. [11]

Seventy patients being of urban residence and 62 from rural in the study, show some apparent difference in prevalence of the disease in urban vs. rural distribution. This dominance of disease occurrence amongst urbanites, in the present study, may be due to the migration of population from rural to urban areas in search of financial, educational and job/work opportunities, with changing demographic profile of the society, against the previous notional rural majority distribution in the region.

Co-morbid conditions including malnutrition, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, coronary artery disease were detected in 25/132 patients. Besides anti-tubercular chemotherapy, they received additional drug-administration for these diseases, and presented with more difficulties in management, because of the added ADRs and complications. Important ADRs noted were gastrointestinal, hepatitis, giddiness, arthralgia, skin reactions, swelling/pain at injection site, peripheral neuropathy, sleep disturbances, hearing impairments, hypothyroidism and anorexia etc. The literature also supports such findings of the ADRs with the second-line drugs.

At the end of 3 months, 118 patients' sputum smear was negative for AFB- 89.39% (118/132) and the same number of patients' sputum culture showed no growth of *Mycobacterium tuberculosis*. At 6 months, results for both sputum smear and culture negativity rose to 90.15% (119/132), whereas the rest of the patients remained positive, defaulted or died. Joseph et al showed results for both smear and culture conversion rates of 84 and 87 per cent at 3 and 6 months respectively [12] while Yew et al [13] showed the mean time for sputum smear and culture conversions of 1.7 and 2.1 months, respectively.

The present study showed a success rate of 50.75% amongst treated patients (which included a cure rate of 31.81% and treatment completion rate of 18.94%); which is higher than the national average of about 48 percent. [2] Some studies have shown a cure rate of above 60% with a high smear and culture conversion rates. The reports published from New Delhi [14] and Nepal [15] have shown a cure rate of 61 and 70 per cent respectively. Earlier, Joseph et al from India reported a cure rate of 66 percent [12]; Anderson et al, UK reported the treatment completion rate of 70.4 percent [16]; Yew et al in China reported cure rate of 81 percent [13] whereas study from Peru reported cure rate of 48 percent. [17]The comparative outcome of the present study with above mentioned studies is shown in table 4.

TABLE 4
COMPARISON OF OUTCOME OF PRESENT STUDY WITH OTHER STUDIES

Studies	No. of patients	Success rate	Died	Defaulted	Failed
Present study	132	67 (50.75%)	18 (13.63)	36 (27.27)	1 (0.75)
Joseph P. et al	38	25 (66%)	3 (7.89%)	5 (13.15)	5 (13.15)
Yew et al	63	51 (81%)	3 (4.7%)	-*	9 (14.3%)
Singla R. et al	126	76 (61%)	24 (19%)	22 (17%)	4 (3%)

Malla P. et al	175	123 (70%)	14 (8%)	29 (17%)	9 (5%)
Anderson LF et al	204	144(70.6%)	14 (6.9%)	14 (6.9%)	-*
Suarez PG et al	466	225 (48%)	57 (12%)	53 (11%)	-*

-*=no record available

The studies showing so high cure rate (vide supra) were done on group of patients at a single hospital or few centres with strict supervision and monitoring, with quick response time to take care of the defaulters or adverse drug reactions during the course of treatment. Whereas, in the present study, after initiation of category-IV treatment from the DR-TB centre at the hospital, rest of the treatment was continued at home; probably with more response time taken for intervention for any ADRs or drug intolerance or other complications during the course of therapy.

Present study showed the default rate of 27.27%, whereas Joseph et al showed the default rate of 13 percent [12], Anderson et al reported with 7.8% patients who lost to follow up [16] and Suarez et al of Peru reported it to be 11%.[17] The reasons assigned to the higher default rate (27.27%) in our study, as compared to the other mentioned comparative studies may be attributed to several associated reasons. These being- the often encountered ADRs to the second line drugs, co-morbidities, illiteracy and ignorance, malnutrition and tobacco/drug-addictions/alcohol abuse- which further add to the increased drug intolerance and associated complications, noticed late while on domiciliary treatment.Feeling of well-being among the patients after some months of taking treatment, social stigma and associated socio-economic factors, in addition to compromised supervision and monitoring at periphery are important contributory factors towards the default.

Another important finding from the study being that 8 (6.06%) patients became XDR-TB (Extensively Drug Resistance-TB) with resistance to Kanamycin and Levofloxacin in addition to 'R' and 'H'. Whether this was because of amplification of the initial resistance pattern or external re-infection could not be confirmed.

Conclusions

Though satisfactory success rate result findings of the present study are heartening, but high default rate remain unacceptable, especially while considering the performance of any programme for a country like India, with over 1.25 billion populace- as it wrecks nation's economic and human resources. Still important is to find out the reasons for default and to take corrective measures to improve the compliance of the patient towards the treatment of this 'monster disease'. Early diagnosis of the co-morbidities, recognition of tobacco/alcohol abuse and drug addictions, with regular and timely follow-up services, needs special attention. Undoubtedly, the corrective measures towards malnutrition, addictions, compromised-DOT provider services for drug administration and early detection of ADR(s)/drug intolerance followed by their appropriate management; regular counselling, education of the patients and concerned family members alongwith effective monitoring and supervisory services, will decisively contribute towards effective outcomes with desired goal by transforming the default rate towards success rate.

The vision is for a 'TB-free India' vis-à-vis 'TB-free Globe' until the disease ceases to be a public health problem. However, the gold quote remains, "It is better to prevent (M)DR-TB than to cure it."

Conflicts of interest: None.

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