Original Article

Study of prevalence and outcome of standardized treatment on category I pulmonary tuberculosis cases in North India: A single center experience

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ABSTRACT

Background and Objective: The emergence of resistance to drugs used to treat tuberculosis (TB), and particularly multidrug-resistant TB, has become a significant public health problem globally. In spite newer modalities for diagnosis and treatment of TB, unfortunately, millions of people are still suffering and dying from the disease. The present study was aimed to study the prevalence of initial drug resistance and the treatment outcome at the end of 6 months in TB patients attending a dedicated TB outpatient department (OPD) in North India. **Materials and Methods:** A cross-sectional, observational study was carried out on 100 patients of newly diagnosed pulmonary TB with or without glandular involvement attending TB OPD of a tertiary care hospital over a period of 6 months. **Results:** Culture positivity was encountered in 82% of the cases, while 14% were smear positive though culture negative. Out of all culture positive patients, 56.1% were susceptible to all antitubercular drugs, while 43.9% were resistant to one or other antitubercular drugs (isoniazid, rifampicin, streptomycin or ethambutol). Of the 46 drug-susceptible cases, 93.48% got cured, while 2.2% defaulted and 2.2% had treatment failure. About 86.1% of the 36 initial drug resistant were cured with 2RHZE/4RH, while 5.6% (n = 2) defaulted treatment and 8.3% were treatment failures. **Conclusion:** Treatment outcomes of this small group of drug-resistant pulmonary TB patients treated with the standardized regimen was encouraging in this setting. Close attention needs to be paid to ensure early identification of drug-resistant cases; good laboratory methodology and quality control measures; regular supply of quality antitubercular drugs; adherence to the prescribed regimen; effective patient education and counseling; and to the timely recognition and treatment of adverse drug reactions for better treatment outcome.

Key words: Category I TB patients, drug-resistant tuberculosis, multidrug-resistant-tuberculosis, standardized regimen, treatment outcome

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Access this article online	
Quick Response Code:	Website: www.caijournal.com
	DOI: 10.4103/2225-6482.166073

How to cite this article: Moitra S, Sen S, Mukherjee S, Das P, Sinha S, Bose M. Study of prevalence and outcome of standardized treatment on category I pulmonary tuberculosis cases in North India: A single center experience. Community Acquir Infect 2015;2:83-92.

INTRODUCTION

Tuberculosis (TB) is contagious and airborne. It ranks as the second leading cause of death from a single infectious agent, after the human immunodeficiency virus (HIV). According to World Health Organization (WHO), 9 million people fell ill with TB in 2013, including 1.1 million cases among people living with HIV. In 2013, 1.5 million people died from TB, including 360,000 among people who were HIV-positive. 510,000 women died from TB in 2013, including 180,000 among women who were HIV-positive.[1] Of the overall TB deaths among HIV-positive people, 50% were among women. TB is one of the top killers of women of reproductive age. An estimated 550,000 children became ill with TB and 80,000 children who were HIV-negative died of TB in 2013. The TB mortality rate has decreased 45% since 1990.[1] It remains a major public health problem in India. About 40% of the population in India is estimated to be infected with TB bacillus. Every year approximately 1.8 million people develop TB and nearly 400,000 die from it. The annual incidence of smear-positive TB is estimated to be 75/100,000 populations (based on the annual risk of tuberculosis infection study done for the four zones of the country from 2000 to 2003). India accounts for one-fifth of the global incidence of TB and tops the list of 22 high TB burden countries. TB kills more adults in India than any other infectious disease.[2]

In India, every day:

- More than 5000 develop TB disease.
- More than 1000 people die of TB (i.e., 1 death every 1.5 min).

Tuberculosis is a barrier to socioeconomic development. It is estimated that the annual cost to society and the country due to TB amounts to nearly US$ 3 billion in indirect costs and US$ 300 million in direct costs. The greatest burden of TB incidence and mortality in India is in adults aged 15-60 years, which include the most productive members of society.[2] TB affects more men than women, but still kills more women than all causes of maternal mortality put together. Every year due to TB (as per estimates made in 1997):

- More than 170 million workdays are lost.
- Nearly 300,000 school children drop out from the schools.
- More than 100,000 women are rejected by their families.

The resurgence of TB worldwide has been accompanied by an increase in the incidence of multidrug-resistant-TB (MDR-TB) on all continents. While significant advances have been made in the rapid and accurate diagnosis of *Mycobacterium tuberculosis*, the molecular biology methods used in the research laboratory to elucidate the mechanisms of drug resistance cannot be transferred to the centers delivering patient care. The emergence of resistance to drugs used to treat TB, and particularly MDR-TB, has become a significant public health problem in a number of countries and an obstacle to effective TB control.[3] In India, the available information from the several drug resistance surveillance studies conducted in the past suggest that the rate of MDR-TB is relatively low in India.

Multidrug-resistant tuberculosis

Globally in 2013, an estimated 480,000 people developed MDR-TB, and there were an estimated 210,000 deaths from MDR-TB. The number of people diagnosed with MDR-TB tripled between 2009 and 2013 and reached 136,000 worldwide. Extensively drug-resistant-TB (XDR-TB) has been reported by 100 countries in 2013. On average, an estimated 9% of people with MDR-TB have XDR-TB.[1]

Drug-resistant TB has frequently been encountered in India, and its presence has been known virtually from the time anti-TB drugs were introduced for the treatment of TB. There have been a number of reports on drug resistance in India in the past, but most studies used nonstandardized methodologies and biased or small samples, usually from tertiary level care facilities.[4]

The prevalence of MDR-TB, defined as resistance to isoniazid (INH) and rifampicin (R-cin) with or without resistance to other drugs, is found to be at a low level in most of the regions. Data from studies conducted by Tuberculosis Research Centre (TRC) (Tiruvallur district and the Chennai corporation area) and NTI, have found MDR-TB levels of <1-3% in new cases and around 12% in re-treatment cases.[5,6] A retrospective analysis of various randomized clinical trials conducted by the TRC with various R-cin containing regimens in the initial intensive phase (IP), and with and without R-cin in the continuation phase (CP), revealed an overall emergence of resistance to R-cin in only 2% of patients, despite a high level (18%) of initial resistance to INH, either alone or in combination with other anti-TB drugs.[7] With a rapid increase in coverage of the revised national tuberculosis control program (RNTCP) and the high cure rate observed in most regions, a similar trend of low emergence of resistance is expected across the country.

Recent RNTCP guidelines have introduced new standards for registering, monitoring, and reporting outcomes of MDR-TB cases. This uniform information management system allows systematic, consistent data collection and analysis, which facilitates appropriate supervision and monitoring and will play an important role in shaping future policies and recommendations [Tables 1 and 2].[4]

The new treatment outcome definitions make a clear distinction between two types of patients:

- Patients treated for drug-susceptible TB.
- Patients treated for drug-resistant TB using second-line treatment.

The two groups are mutually exclusive. Any patient found to have drug-resistant TB and placed on second-line treatment is

Table 1: Categories and treatment regimens according to RNTCP guidelines[4]

Category of treatment	Type of patient	Regimen*
Category I	New sputum smear-positive Seriously ill** new sputum smear-negative Seriously ill** new extra-pulmonary	$2H_3R_3Z_3E_3+4H_3R_3$
Category II	Sputum smear-positive relapse Sputum smear-positive failure Sputum smear-positive treatment after default Others***	$2H_3R_3Z_3E_3S_3+1H_3R_3Z_3E_3+5H_3R_3E_3$
Category III	New sputum smear-negative, not seriously ill New extra-pulmonary, not seriously ill	$2H_3R_3Z_3+4H_3R_3$

*The number before the letters refers to the number of months of treatment. The subscript after the letters refers to the number of doses per week, **Seriously ill also includes, any patient, pulmonary or extra-pulmonary who is HIV positive and declares his serostatus to the categorizing/treating medical officer. For the purpose of categorization, HIV testing should not be done, ***In rare and exceptional cases, patients who are sputum smear-negative or who have extrapulmonary disease can have relapse or failure, RNTCP: Revised National Tuberculosis Control Program, HIV: Human immunodeficiency virus

Table 2: Treatment outcome categories as per RNTCP guidelines[4]

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear-or culture-negative in the last month of treatment and on at least one previous occasion
Treatment completed	A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment
Died	A TB patient who dies for any reason before starting or during the course of treatment
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for which the treatment outcome is unknown to the reporting unit
Treatment success	The sum of cured and treatment completed

RNTCP: Revised National Tuberculosis Control Program, TB: Tuberculosis

removed from the drug-susceptible TB outcome cohort which means that management of the standard TB register and of the second-line TB treatment register needs to be coordinated to ensure proper accounting of the outcomes of treatment.

All bacteriologically confirmed and clinically diagnosed TB cases should be assigned an outcome except those with rifampicin-resistant-TB or MDR-TB, who are placed on a second-line drug regimen.

India is the country with the highest burden of TB with WHO statistics for 2013 giving an estimated incidence figure of 2.1 million cases of TB for India out of a global incidence of 9 million.[1] The estimated TB prevalence figure for 2013 is given as 2.6 million. The prevalence of MDR-TB has though been believed to be at a low level in most regions of the country. Various studies have found MDR-TB levels of about 3% in new cases and around 12-17% in retreatment cases. However, even if there are such a small percentage of cases, it still translates in India into large absolute numbers. The present study was aimed to study the prevalence of initial drug resistance in TB patients attending the hospital outpatient department (OPD), and the treatment outcome in these patients at the end of 6 months.

MATERIALS AND METHODS

A total of randomly selected 100 patients of newly diagnosed pulmonary TB with or without glandular involvement attending TB OPD of a tertiary care hospital over a period of 6 months were included in the study. Ethics permission was obtained and written informed consent was sought before recruiting patients for this observational study.

Inclusion criteria

- Subjects irrespective of age or sex presenting with symptoms such as cough, low-grade fever, hemoptysis, chest pain, weight loss, loss of appetite or anorexia, and glandular swelling for at least 3 weeks.
- A detailed history of previous anti-tubercular treatment (ATT) was taken and only those patients who had never had treatment for TB (new case or category I) were included.
- Symptomatic with or without lymphoglandular swellings whose smear was acid-fast *bacilli* (AFB) positive were included.
- Symptomatic having minimal, moderate or far advanced radiological lesions suggestive of pulmonary TB were included.
- Those who understood the purpose of the study and were ready to provide information regarding their health status and those who signed an informed consent document.

Exclusion criteria

- Pregnant women.
- Patients having a concurrent major psychiatric illness or serious medical illnesses,

- Patients having <1 month treatment with any second-line anti-TB drugs, and HIV positive cases.
- Those unable to comprehend for other reasons were excluded from the study.

All cases were subjected to hemogram, urine-routine/microscopy, hepatic and renal function tests, blood sugar and Mantoux test. Screening for HIV infection was done using enzyme-linked immune sorbent assay in all the patients after consent. Fine needle aspiration cytology (FNAC) of glandular lesions and other radiological investigations were done in relevant cases. All patients underwent X-ray chest posteroanterior (PA)-view examination. Chest radiographs were classified according to the American Thoracic Society Classification.

All patients were directed to collect the early morning sputum specimen in a sterilized wide-mouthed bottle with a tightly fitting cork stopper for 3 consecutive days. All sputum samples were transported to the microbiology lab as soon as possible after collection. The sputum was first concentrated by Petroff's method. The sputum was sent for smear for AFB using Ziehl-Neelsen staining technique and positive smears were graded as per RNTCP guidelines.[4]

Culture for isolation of *M. tuberculosis* was done on Lowenstein-Jensen medium. Cultures were examined for growth after incubation at 37°C for 4 days (for rapidly growing mycobacteria and contaminants) and every week thereafter up to 8 weeks. The colonies of *M. tuberculosis* were defined as rough, crumbly, waxy, nonpigmented (buff colored). Negative cultures were defined as no growth after 8 weeks.

Drug susceptibility testing of patient's sputum samples was done using proportion method. Only one culture-positive sputum sample from each patient was selected for drug susceptibility testing to INH (0.2 μg/mL), R-cin (1 μg/mL), ethambutol (EMB) (5 μg/mL), and streptomycin (SM) (2 μg/mL). The numbers of colony forming units growing on the medium containing the drug were compared with the number on the control plate. The proportion of resistant cells in the total viable population of the original inoculums were then calculated and expressed as a percentage. Significant proportion of growth above which the isolate was labeled resistant was set at 1% as per the recommendations.

Results of the sputum conversion, at 2 months and 6 months, clinical and radiological improvements were analyzed in drug sensitive as well as in drug-resistant cases separately. The treatment outcomes were reported as per RNTCP guidelines [Table 2].

Individualized treatment regimens were used as per the needs of individual cases according to their previous history of ATT and their initial drug sensitivity test (DST) patterns. The intensive phase (IP) consisted of at least five main drugs: Any aminoglycoside, any fluoroquinolone, any thioamide, and any two/more of the following: Pyrazinamide and ethambutol (EMB), para-aminosalicylic acid (PAS) or cycloserine. Any other first line ATT was included as per treatment history of individual patients. In addition, INH was prescribed in most cases. The continuation phase (CP) consisted of at least three of the most active and best tolerated drugs to which either the *Bacilli* were sensitive (DST), or the patient was responding in the form of negative smears and/or culture. These included any one of the fluoroquinolones (ciprofloxacin, ofloxacin or levofloxacin), anyone thioamide, and anyone/two or more of the following: Pyrazinamide and EMB, PAS or cycloserine in this order of preference. The IP, with duration of 3-6 months (extended to 9 months if necessary) was given till at least three consecutive smears and last available culture reported negative. If the culture results were positive, IP was extended till negative smears were obtained, up to a maximum of 9 months. In rare cases, where the patient remained sputum positive by the culture at 9 months and when the patient was tolerating injectable drugs, injectables were continued till sputum conversion. Some patients required regimen changes during their IP due to the failure of response to the initial regimen. The drugs in CP were given for at least 18 months after culture conversion.

In case of intolerance to any drug during treatment, the offending drug was replaced by an appropriate substitute, thus meriting a deviation from the initially prescribed regimen (as per DST pattern).

Data analysis was done at the end of the study. Descriptive statistics has been analyzed. Where possible, demographic, and categorical data were analyzed with parametric or nonparametric tests whichever found applicable. Data are represented as frequency and percent. Mean was calculated to represent the nominal variables. All statistical analysis for various outcome measures were performed using various statistical software packages like Statistical Package for the Social Sciences (Windows version 17.0; SPSS Inc., Chicago [IL], USA), GraphPad Prism (GraphPad Software Inc., USA), Microsoft Excel and Medcalc version 5 (MedCalc Software bvba, Belgium). The data of the defaulting patients were censored at the last follow-up visit.

RESULTS

The present study assessed the treatment outcomes of the newly diagnosed sputum positive/FNAC positive TB, with no prior history of anti-tubercular chemotherapy treatment (category I) presenting 1st time at a dedicated TB center in North India [Figure 1].

Demographic profile

The mean age of the presenting patients was found to be 30.51 ± 17 years with age distribution ranging from 11 to 76 years. Males represented 60% of the study population, while females represented 40%, thus having male to female ratio as

3:2. 83% of the total selected category 1 patients had cough as a symptom on presentation, followed by 76% who had weight loss and 70% who had fever as their primary symptoms [Figure 2]. Duration of symptoms, however, varied from 15 to 30 days.

About 89% of the study subjects were tested Mantoux positive (reactors) with induration more than 10 mm, while 8% were Mantoux negative (nonreactors) with indurations <10 mm. About 3% were borderline reactors with indurations of 10 mm.

Radiological examination

According to the American Thoracic Society classification for pulmonary lesions in TB, 43% had a minimal lesion, 54% had moderately advanced lesions, and 3% had far advanced lesions [Figure 3].

A total of 53% of the study subjects had evidence of consolidation with 35% having unilateral and 18% having bilateral consolidation. 46% had cavitary lesions on chest X-ray-PA with 37% having unilateral and 9% having bilateral cavities. Of the 2 patients of other category, one had sputum positive military Koch's and other had associated tubercular mediastinal lymphadenopathy.

Clinical examinations of the category 1 patients before the initiation of the treatment revealed that all the specimens were direct smear positive from AFB, with 44% having 1+, 37% having 2+, and 19% of the patients having 3+ sputum positivity. Culture positivity was encountered in 82% of the cases, while 14% were smear positive though culture negative.

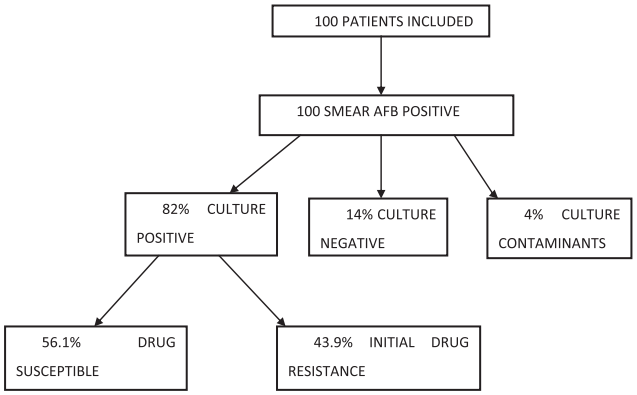

Figure 1: Study profile of included category 1 patients

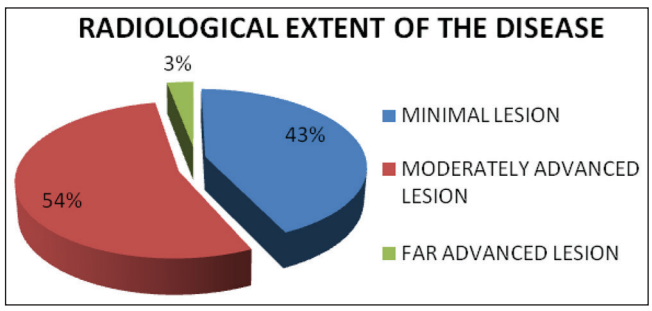

Figure 3: Radiological presentation for pulmonary lesions (according to the American Thoracic Society classification)

Drug susceptibility profile

Drug susceptibility pattern in initial culture positive cases revealed that out of total number of smear-positive category 1 patients, 82% were culture positive. Out of them, 56.1% were susceptible to all antitubercular drugs, while 43.9% were resistant to one or other antitubercular drugs (INH, R-cin, SM or EMB).

Among 82 patients tested culture positive, resistance to INH alone was found in 13.4% cases, R-cin alone in 2.4%, while resistance to both SM alone and EMB alone was 3.7%. Drug resistance to INH and others (SM/EMB) was 7.3%. However, there was no resistance to R-cin and other groups. The total number of multi-drug resistance cases that is, resistance to INH, R-cin and/or others (SM/EMB) was 13.4%. There were a total of 7.3% cases, which were resistant to more than one drug, other than the combination of INH and R-cin. Among these, 1.2% was resistant to INH + SM, 3.7% to INH + EMB, and 2.4% resistant to all three drugs that is, INH, SM, and EMB together [Figure 4].

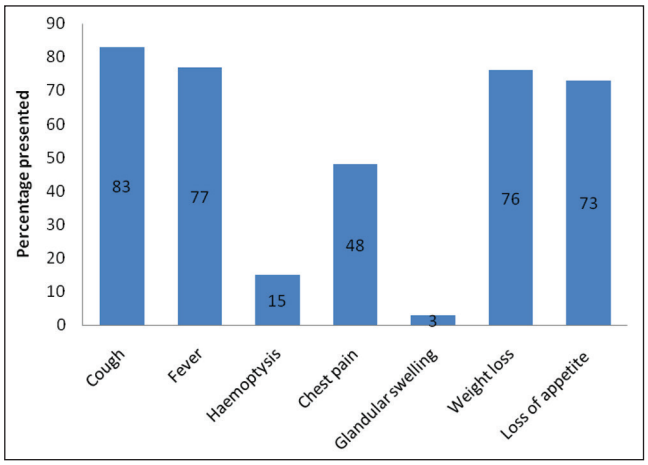

Figure 2: Clinical signs and symptoms on presentation

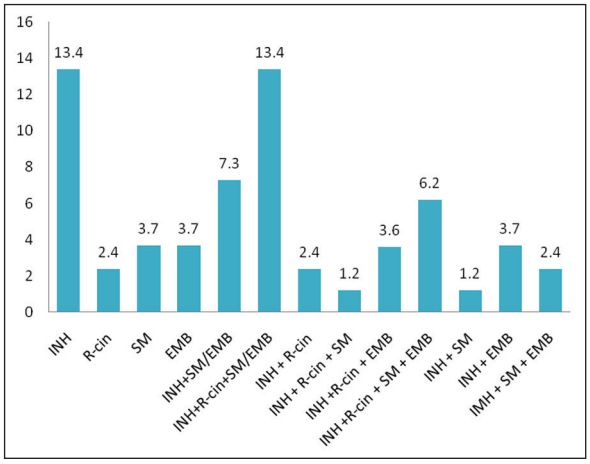

Figure 4: Antitubercular drug susceptibility among study participants

Treatment outcomes

Of the 46 drug-susceptible cases, 93.48% got cured, while 2.2% defaulted and 2.2% had treatment failure. 86.1% of the 36 initial drug resistant were cured with 2RHZE/4RH, while 5.6% (n = 2) defaulted treatment and 8.3% were treatment failures [Table 3]. In those 4 patients who were initially smear positive, but, whose cultures had got contaminated, 75% got cured, while 21% defaulted. Thus on overall, 91% patients got cured 2RHZE/4RH, 5% defaulted treatment, 4% did not respond to the regimen (treatment failure), and 1% relapsed after 2 months of treatment completion.

Treatment outcome measures from individual regimen analysis suggested that 90.9% (n = 10) patients with initial drug resistance to INH alone got cured while one patient defaulted treatment. Of the two R-cin only resistant cases, all got cured. Two out of three SM only resistant cases got cured while one defaulted. In the EMB alone resistant group, all three cases got cured.

In case of treatment outcome of drug-resistant cases to more than one drug (other than combination of INH and R-cin), all cases got cured with the treatment (2RHZE/4RH) in the INH + SM (n = 1) and INH + SM + EMB (n = 2) group. Of the three cases of INH + EMB, 66.7% (n = 2) got cured, while 33.3% (n = 1) treatment failed. Thus of the six cases of INH and others (EMB/SM) group, 5 (83.3%) got cured, while 1 (16.7%) treatment failed [Table 4].

A total of 100% cure rate was seen following treatment (2RHZE/4RH) in INH + R-cin (n = 2) resistant cases and INH + R-cin + SM (n = 1) resistant cases. In the INH + R-cin + EMB resistant groups 66.7% (n = 2) got cured, while 33.3% (n = 1) treatment failed. While of the five cases in the INH + R-cin + SM + EMB resistant group, 80% (n = 4) got cured, while 20% (n = 1) failed treatment. Thus in the MDR group, 9 (81.8%) of the 11 cases got cured with treatment, while 2 (18.2%) had treatment failure.

Overall outcome

Among the 46 initial drug sensitive cases, 98% showed clinical improvement, 96% showed radiological improvement, and 96% became both smear negative and culture negative at the end of 2 months. At the end of 6 months, the corresponding figures were 98%, respectively, for all four parameters with 1 patient defaulting during the treatment.

Among the 36 initial drug-resistant cases, 92% showed clinical improvements, 98% improvements, 88% showed radiological improvement, 89% became smear negative, and 92% became culture negative at the end of 2 months. At the end of 6 months, the corresponding figures were 91%, 88%, 91%, and 91%, respectively, for all four

Table 3: Treatment outcome measures for various drug resistant TB cases

Treatment outcome categories	Drug susceptible cases (%)	Drug resistant cases (%)	Contaminated cases (%)	Smear positive/culture negative (%)
Cured	43 (93.48)	31 (86.11)	3 (75)	12 (85.71)
Treatment completed	43 (93.48)	31 (86.11)	3 (75)	12 (85.71)
Treatment failed	1 (2.17)	3 (8.33)	0	0
Died	0	0	0	0
Lost to follow-up	2 (4.35)	2 (5.56)	1 (25)	2 (14.28)
Not evaluated	0	0	0	0
Treatment success	43 (93.48)	31 (86.11)	3 (75)	12 (85.71)
Total	46	36	4	14

TB: Tuberculosis

Table 4: Treatment outcome measures among drug resistant cases

Drug resistant cases	Cured	Treatment completed	Treatment failed	Died	Lost to follow-up	Not evaluated	Treatment success
INH	10	10	0	0	1	0	10
R-cin	2	2	0	0	0	0	2
SM	2	2	0	0	1	0	2
EMB	3	3	0	0	0	0	3
INH+EMB/SM	5	5	0	0	1	0	5
R-cin+EMB/SM	0	0	0	0	0	0	0
INH+R-cin+EMB+SM	9	9	0	0	2	0	9
INH+R-cin	2	2	0	0	0	0	2
INH+R-cin+SM	1	1	0	0	0	0	1
INH+R-cin+EMB	2	2	0	0	1	0	2
INH+R-cin+ SM+EMB	4	4	0	0	1	0	4
INH+SM	1	1	0	0	0	0	1
INH+EMB	2	2	0	0	1	0	2
INH+SM+EMB	2	2	0	0	0	0	2

INH: Isoniazid, EMB: Ethambutol, SM: Streptomycin, R-cin: Rifampicin

parameters with 2 patients defaulting during the treatment [Table 5].

A total of 25 patients completed 2 months follow-up out of which 1 patient relapsed at 2 months. 16 patients completed 4 months with no relapse.

Adverse drug reactions profile

Tuberculosis patients frequently suffer from adverse drug reactions (ADRs). These unwanted effects influence patient adherence to prescribed medicine. In some cases, drug side effects are also life-threatening, which often necessitate the suspension of treatment or the use of ancillary medication. Out of 100 cases observed, 68 cases reported with various ADRs such as nausea, vomiting, joint pain, body ache, etc. A total of 10% ADRs were reported with nausea and vomiting, 9% ADRs were reported with joint pain and body ache, and so on [Table 6].

DISCUSSION

Anti-TB drug resistance is a major public health problem, threatening progress in TB care and control worldwide. Drug resistance arises due to improper use of antibiotics in chemotherapy of drug-susceptible TB patients which is a result of a number of factors including, administration of improper treatment regimens, and failure to ensure that patients complete the whole course of treatment. Essentially, drug resistance arises in areas with weak TB control programs. A patient who develops active disease with a drug-resistant TB strain can transmit this form of TB to other individuals.[8]

Tuberculosis is a treatable and curable disease. Active, drug-sensitive TB disease is treated with a standard 6 months course of four antimicrobial drugs that are provided with information, supervision, and support to the patient by a health worker. Without such supervision and support, treatment adherence can be very difficult, and the disease can spread. The vast majority of TB cases can be cured when medicines are provided and taken appropriately. Between 2000 and 2011, an estimated 37 million lives were saved through TB diagnosis and treatment.[9]

The Indian Government's RNTCP was started in 1997. It was then expanded across India until the entire nation was covered by March 2006. The program uses the WHO recommended directly observed treatment short course (DOTS) strategy and reaches over a billion people in 632 districts/reporting units. The initial objectives of the RNTCP in India were to achieve and maintain a TB treatment success rate of at least 85% among new sputum positive (NSP) patients and simultaneously achieve and maintain detection of at least 70% of the estimated NSP people in the community.[10]

In 2010, the RNTCP made a major policy decision that it would change focus and adopt the concept of universal access to quality diagnosis and TB treatment for all TB patients in India. This involves extending the reach of RNTCP services to all people diagnosed with TB, as well as improving the quality of existing services. The major aim is to achieve the following targets by the end of 2015 are as follows: Early detection and treatment of at least 90% of estimated TB cases in the community, including HIV-associated TB; initial screening of all previously treated (retreatment) smear-positive TB patients for drug-resistant TB and successful treatment of at least 90% of all new TB patients, and at least 85% of all previously treated TB patients.

Five priority actions — from prevention to cure — are needed to address the MDR-TB epidemic. These are as follows: Prevent MDR-TB; scale up rapid testing and detection of all MDR-TB cases; ensure prompt access to appropriate MDR-TB care; implement appropriate TB infection control measures to minimize the risk of disease transmission; and increase political commitment with financing.[1]

In India, TB care is provided by both public and nonpublic sector health facilities. Patients from the public sector are usually managed within program settings as specified by the RNTCP and this includes collecting the information below on the provision of TB patient care.[11]

Standard anti-tubercular drugs have been used for decades, and resistance to the medicines is widespread. Disease

Table 5: Overall outcome (clinical, radiological, and microbiological) in study patients

Outcome categories	Drug sensitive cases(n = 46)				Drug resistant cases (n = 36)				Smear positive/culture negative and smear positive/culture contaminated cases (n = 18)			
	At 2 months		At 6 months		At 2 months		At 6 months		At 2 months		At 6 months	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Clinical improvement	45	1	44	1	33	3	313	3	18	0	16	0
Radiological improvement	44	2	44	1	29	7	304	4	18	0	16	0
Microbiological improvement												
Smear	1	45	1	44	4	32	3	31	0	18	0	16
Culture	1	45	1	44	3	33	3	31	0	18	0	16

Table 6: Overall ADR in study patients

ADR	Frequency (%)
Nausea	10 (10)
Vomiting	10 (10)
Joint pain	9 (9)
Body ache	9 (9)
Dizziness	8 (8)
Weakness	7 (7)
Epigastric burning/discomfort	6 (6)
Rashes	4 (4)
Constipation	3 (3)
Jaundice/hepatitis	2 (2)

ADR: Adverse drug reaction

strains that are resistant to a single anti-TB drug have been documented in every country surveyed. Drug resistant TB has frequently been encountered in India and its presence has been known virtually from the time anti-TB drugs were introduced for the treatment of TB. MDR-TB is a form of TB caused by bacteria that do not respond to, at least, isoniazid (INH) and rifampicin (R-cin), the two most powerful, first-line (or standard) anti-TB drugs. There had started to be some criticism of this approach and in particular the lack of second-line drugs and appropriate regimes for people who had failed their first treatment and who were the people most likely to already have drug-resistant TB. The only people able to receive second-line drugs were those who were taking part in some pilot DOTS-Plus MDR-TB programs, which had been initiated in 2007 in Gujarat and Maharashtra. Although these services had been extended to further states, by September 2010 only 2985 MDR-TB patients had been started on treatment.[11]

Before 2010 all patients receiving treatment through the RNTCP were placed in one of three categories according to such criteria as to whether they had received treatment before, whether they were seriously ill and whether they were sputum positive. However, all categories received different combinations of the four main first-line anti-TB drugs, with the addition of SM and a slightly longer course of treatment for those who had received TB treatment before.

In early 2010, the RNTCP acknowledged that and launched new guidelines referred to as the DOTS-Plus guidelines for the management and treatment of patients with drug-resistant TB. DOTS-Plus traditionally refers to DOTS programs that add components for MDR-TB diagnosis, management, and treatment. The new guidelines emphasized that there was to be full integration of DOTS and DOTS-Plus activities under the RNTCP.[12]

As the treatment of MDR-TB is more complex than drug-sensitive TB, and as access to laboratory facilities is needed for diagnosis, the actual provision of the MDR-TB services was to be carried out in designated DOTS-Plus sites. The stated aim was to treat 30,000 MDR-TB cases annually by 2012-2013.

Traditionally the view in India had been that MDR-TB is not easily transmissible and that most drug-resistant TB arises from the failure of people to take their drugs properly, rather than from them becoming infected with an MDR-TB strain. Therefore, a high-quality DOTS program and supervising people taking their drugs should prevent the emergence of resistance.

However, the DOTS-Plus guidelines acknowledge that ongoing transmission of drug-resistant strains is also a significant source of new drug-resistant cases, and that timely identification of MDR-TB cases and their treatment with appropriate regimens are essential to stop transmission, quite apart from the humanitarian aspects of providing appropriate treatment for people with drug-resistant TB. However, despite this the DOTS-Plus guidelines emphasize that the basic DOTS program without the MDR components must continue to be the priority for TB control in India. In addition, the guidelines say that in every DOTS implementing unit of the country, DOTS should be prioritized above DOTS-Plus.

The primary cause of MDR-TB is inappropriate treatment. Inappropriate or incorrect use of anti-TB drugs, or use of poor quality medicines, can all cause drug resistance. Disease caused by resistant bacteria fails to respond to conventional first-line treatment. MDR-TB is treatable and curable by using second-line drugs. However, second-line treatment options are limited and recommended medicines are not always available. The extensive chemotherapy required (up to 2 years of treatment) is more costly and can produce severe ADRs in patients.[9]

In some cases, more severe drug resistance can develop. XDR-TB is a form of MDR-TB that responds to even fewer available medicines, including the most effective second-line anti-TB drugs. About 480,000 people developed MDR-TB in the world in 2013. More than half of these cases were in India, China, and the Russian Federation. It is estimated that about 9.0% of MDR-TB cases had XDR-TB.

The RNTCP has tried to involve nonpublic health providers in promoting TB care, but it is believed that many patients continue to seek treatment elsewhere and currently go unreported. While national data for India is not available a number of studies and surveys of TB prevalence including self-reporting of TB prevalence have suggested that up to 46% of patients may not be currently reported. There are many reasons why people in India may seek care outside the RNTCP. These include poor knowledge about TB and services available through the national program, convenience of these services, a desire for confidentiality, and personalized care.[13]

All the 100 patients underwent X-ray chest (PA view) examination and extent of the radiological lesion was

classified as minimal, moderately advanced, and far advanced, as per American Thoracic Society Classification. A standard 6-foot PA chest radiograph was obtained for all patients. The cavitary disease was defined as the presence of a gas-containing lucent space at least 1 cm in diameter within the lung parenchyma surrounded by an infiltrate or fibrotic wall >1 mm thick. According to the American Thoracic Society classification for pulmonary lesions in TB, 43% had minimal lesion, 54% had moderately advanced lesions, and 3% had far advanced lesions. 53% of the study subjects had evidence of consolidation with 35% having unilateral and 18% having bilateral consolidation. 46% had cavitary lesions on chest X-ray-PA with 37% having unilateral and 9% having bilateral cavities. Of the 2 patients of other category, one had sputum positive military Koch's and other had associated tubercular mediastinal lymphadenopathy. A limitation of our study was the presence of cavitary disease was made using standard PA chest radiographs. Small cavitary lesions may have been found in some of the noncavitary patients if computed tomography of the chest had been used.

Clinical examinations of the category 1 patients before the initiation of the treatment revealed that all the specimens were direct smear positive from AFB, with 44% having 1+, 37% having 2+, and 19% of the patients having 3+ sputum positivity. Culture positivity was encountered in 82% of the cases, while 14% were smear positive though culture negative.

Drug susceptibility pattern in initial culture positive cases revealed that out of total number of smear positive category 1 patients, 82% were culture positive. Out of them 56.1% were susceptible to all anti-tubercular drugs, while 43.9% were resistant to one or other antitubercular drugs (INH, R-cin, SM or EMB). The total number of multi-drug resistance cases that is, resistance to INH, R-cin, and/or others (SM/EMB) was 13.4%. There were a total of 7.3% cases, which were resistant to more than one drug, other than combination of INH and R-cin. Of the 46 drug susceptible cases, 93.48% got cured, while 2.2% defaulted and 2.2% had treatment failure. High cure rates were seen in the first east African study[14] with a failure rate of 0.02% and 0.04% in the second east African study. Similarly Jain *et al*.[15] reported 94% success rate in drug sensitive cases.

Treatment outcome in the present study to individual initial drug resistant cases to INH, showed a 90.9% cure rate with 9.1% defaulting treatment. Of the two R-cin resistant cases, 100% cure rate was observed, while in patients with streptomycin (SM) resistance alone 66.7% got cured and 33.3% defaulted. Of the EMB alone initial resistance, 100% cure rate was observed. These results suggest that 6 months short course chemotherapy using 2RHZE/4RH gives good cure rates in patients with initial resistance to INH, R-cin, SM, and EMB single suggesting that the other potent antimycobacterial agents were effective in these mono drug resistant cases.

Treatment outcome in drug resistant cases to more than one drug (other than the combination of INH and R-cin) in the present study, in patients initially resistant to both INH and SM was 100% cured, while INH and EMB resistant showed 66.7% cure rate. 100% cure rate was observed in 2 patients with initial resistance to INH, SM, and EMB. Treatment outcome in MDR cases showed 81.8% getting cured with 18.2% having treatment failure.

Among the 46 initial drug sensitive cases, 98% showed clinical improvement, 96% showed radiological improvement, and 96% became both smear negative and culture negative at the end of 2 months. At the end of 6 months, the corresponding figures were 98%, respectively, for all four parameters with 1 patient defaulting during the treatment. Among the 36 initial drug resistant cases, 92% showed clinical improvements, 98% improvements, 88% showed radiological improvement, 89% became smear negative and 92% became culture negative at the end of 2 months. At the end of 6 months, the corresponding figures were 91%, 88%, 91% and 91%, respectively, for all four parameters with 2 patients defaulting during the treatment. Sputum smear and culture conversion are important indicators for the effectiveness of treatment and the infectivity of the patient. Though smear conversion can be taken as an indicator, culture conversion which reflects viability of tubercle *bacilli* is more sensitive and is considered necessary to monitor progress in MDR-TB patients.

Patients with TB require retreatment if they fail or default from initial treatment or if they relapse following initial treatment success. In our study, 25 patients completed 2 months follow-up out of which 1 patient relapsed at 2 months. 16 patients completed 4 months with no relapse.

Responsibility for successful treatment is assigned to the health care providers. It is important for clinicians to evaluate a patient's response to treatment to determine the efficacy of the treatment and to identify any adverse reactions. The frequency, severity, and the nature of anti-TB therapy induced ADRs have been always a concern. Studies have shown that multidrug regimens can cause undesirable ADRs such as arthralgia, neurological disorders, gastrointestinal disorders, hepatotoxicity, and allergic reactions. ADRs increase patient discomfort and cause substantial additional costs because of excess outpatient visits, laboratory tests, and even in serious instances hospitalization. ADRs may lead to prolonging of treatment, drug resistance, and treatment failure. These unwanted effects influence patient adherence to prescribed medicine. In some cases, drug side effects are also life-threatening which often necessitate the suspension of treatment or the use of ancillary medication. At the same time, alternative drugs may cause severe complications with few effects. It may also increase morbidity and mortality of disease. Of 100 cases observed, 68 cases reported with various ADRs such as nausea, vomiting, joint pain, body ache,

etc. 10% ADRs were reported with nausea and vomiting, 9% ADRs were reported with joint pain and body ache, and so on. High incidence of ADRs observed in the study highlights the need for adequate clinical back up for managing ADRs while decentralizing treatment for MDR-TB. Though severe adverse reactions were frequent, treatment could be continued in most cases with modification of the treatment regimen. Other studies have reported major adverse reaction ranging from 19% to 72%.[16-18]

Our study has several limitations. First, we studied only patients with documented smear positive new case who were ATT naive. We have excluded those patients or new cases, who were on ATT <1 month though they fits into new case (category I) definitions. Second, it was a cross-sectional observational study with a small sample size. It was a single center experience. Hence, the results cannot be a representative of national data.

Adherence to treatment was attained by strong health education to the patient and their family members prior to start treatment and at different periodic intervals, decentralized DOTS supplemented with rigorous supervision by experienced health care staff, intense monitoring, prompt identification and management of ADRs, and involvement of community and family in providing DOTS.

CONCLUSION

Tuberculosis continues to be a global public health problem, with an estimated 9.4 million incident cases of TB and 1.8 million deaths in 2008. Drug resistance and obstacles to successful DOTS impede disease control. Among patients being retreated for TB because of initial treatment failure, default from initial treatment, or relapse following initial treatment, drug resistance is common and retreatment outcomes inferior. Nearly 20 years after the WHO declaration of TB as a global public health emergency, major progress has been made toward 2015 global targets set within the context of the Millennium Development Goals. Two years ahead of the deadline, the global TB report 2013 and accompanying supplement countdown to 2015 assess progress toward the 2015 targets and the top priority actions needed to achieve and/or move beyond them. Globally by 2012, the TB mortality rate had been reduced by 45% since 1990. The target to reduce deaths by 50% by 2015 is thus within reach.[19] Short course chemotherapy is thus seen to be highly efficacious with high cue rates and low relapse rates in both the drug susceptible as well as in initial drug-resistant cases to individual and multi-drug resistant cases.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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