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Original Research

A Hospital Based Prospective Observational Study to Evaluate the Various Factors Associated with Drug Resistance Tuberculosis among Presumptive Drug Resistant Tuberculosis Patients

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***ABSTRACT*:**
Background: The universal drug sensitivity testing (UDST) approach can lead to major changes in pattern of detection of resistance among TB patient. The resistance that develops in a patient who has received prior chemotherapy is defined as acquired drug resistance. This change needs to be assessed and addressed earliest so that any deficiency or weakness if found can be assessed and changes in strategy can be done within time frame. The aim of this study evaluated the various factors associated with drug resistance tuberculosis among presumptive drug resistant tuberculosis patients. **Material & Methods:** A hospital based prospective observational study done on 100 cases done in the Department of Respiratory Medicine, SP Medical College, Bikaner. Sputum for acid fast bacilli, smear microscopy, culture and drug susceptibility tests were performed at Department of Microbiology, SP Medical College, Bikaner. Drug susceptibility testing of the samples was performed by the radiorespirometric Buddemeyer technique (a manual modification of the Bactec 460 technique). The value of the mean Difference in growth indices (ΔGI) in the triplicate drug containing vials was compared to that for 1:100 control for the same day. If ΔGI was less in the drug containing vials than the 1:100 control, the bacteria were considered susceptible; if more, they were considered resistant. **Results:** Our study observed that out of 100 cases, 85 (85%) cases had drug sensitive of TB & 15 (15%) cases had drug resistant of TB. Male preponderance were occurred in drug sensitive (66%) and drug resistant TB (11%). Among 15 drug resistant TB cases, 12 cases were resides in rural areas and 3 cases were reside in urban areas. Sputum positivity status of DR-TB patients, mostly DR-TB cases (40%) had 3+ followed by 2+ in 26.66% cases, 1+ in 13.33% cases, negative in 13.33% cases and only 6.66% cases had scanty in agar plate (table 2). The mostly DR-TB occurred in previously treated case (80%) and 20% cases had newly diagnosed cases of TB. **Conclusion:** We can easily conclude from the present study that well administered and dedicated first line treatment for susceptible cases is the need of hour to prevent development of resistance in such cases.
Keywords: TB, Drug sensitive, Drug resistant, Sputum positive

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INTRODUCTION:

Tuberculosis (TB) in humans has been described since ancient times. Its causative agent, *Mycobacterium tuberculosis* (MTB), is widely disseminated. The WHO estimates that approximately one-third of the global community is infected with *M. tuberculosis*.[1] According to the RNTCP status report-2012, India had 2 million reported TB cases, which was responsible for one-fifth of the global burden.[2]

India is the second largest populated country in the world, accounts for a quarter of the global TB burden. Every year around 2 million people develop TB in India and 300,000 die due to the TB. It is also one of the most serious public health challenges in India[3-5]

Isoniazid (INH), ethambutol, rifampicin, pyrazinamide, and streptomycin are important components of first-line anti-tubercular regimens. A combination of isoniazid (INH) and rifampicin (RIF) form the cornerstone of short course chemotherapy for TB. Drug resistance can be primary or acquired. Primary drug resistance is defined as drug resistance in a patient who has not received any past antitubercular treatment. The resistance that develops in a patient who has received prior chemotherapy is defined as acquired drug resistance. Strains of *M. tuberculosis* that are resistant to both isoniazid and rifampicin, with or without resistance to other drugs, have been termed multidrug resistant strains (MDRs). This is an emerging problem and has great importance to public health worldwide. Several reports have indicated that drug resistance is increasing among pulmonary TB patients in India.[6-8] However, various Indian studies have shown that the rate of MDR-TB is very low (0—6%).[9]

Levels and trends of drug resistance vary by location.[10] Additionally, drug resistance serves as an epidemiological indicator, which allows investigators to assess the extent of resistant bacterial transmission in the community.[8] Therefore, drug resistance surveillance (DRS) is considered a useful tool to assess the drug susceptibility profile among newly diagnosed and previously treated patients, as well as to determine the effective functioning of TB control programs.[10] Early identification of drug-resistant strains, particularly MDR strains, is crucial in order to permit the timely administration of appropriate drug regimens and minimize transmission of these strains.

Programmatic management of drug resistant tuberculosis (PMDT) was introduced under RNTCP in 2007 to treat DR-TB by first DOTS-PLUS guidelines. According to the recommendations of World health organisation (WHO) 2011, PMDT guidelines revised in 2012. First national drug resistance survey (2014-2016) was an eye opener for planners, suggested that drug resistance to anti tubercular drugs in new cases is not much less than previously treated patients. Looking into the threatening situation RNTCP now offers CBNAAT for all notified new TB cases, to detect drug resistance at earliest and further test for drug resistance as per requirement. This universal drug sensitivity testing (UDST) approach can lead to major changes in pattern of detection of resistance among TB patient. This change needs to be assessed and addressed earliest so that any deficiency or weakness if found can be assessed and changes in strategy can be done within time frame. The aim of this study evaluated the various factors associated with drug resistance tuberculosis among presumptive drug resistant tuberculosis patients.

MATERIAL & METHODS:

A hospital based prospective observational study done on 100 cases done in the Department of Respiratory Medicine, SP Medical College, Bikaner.

INCLUSION CRITERIA

1. All notified new TB patients.
2. TB patients found positive on any follow-up sputum smear examination during treatment with first line drugs including treatment failures.
3. Previously treated TB patients.
4. Close contacts of multidrug resistant tuberculosis patients who found sputum smear positive for pulmonary tuberculosis disease.
5. Paediatric TB non-responders.
6. TB with HIV.

EXCLUSION CRITERIA

1. DR Treatment failure & default
2. Patients Still on DR treatment.
3. Patient with CBNAAT-MTB not detected reports.
4. Patients sensitive to Isoniazid and Rifampicin both.

STUDY POPULATION

After applying inclusion and exclusion criteria on study universe, study population were selected.

Group- A (Drug Native Cases)

All new cases of tuberculosis

Group B (Drug exposed cases)

All previously treated cases of tuberculosis

1. Treatment failure cases
2. Treatment after loss to follow up cases
3. Recurrent tuberculosis cases

PROCEDURE:

Detailed history was taken from each and every patient. Patients were carefully inquired about their symptoms such as fever, cough, expectoration, chest pain, breathlessness, loss of appetite and loss of weight. Past history of anti tubercular drug intake was taken. Routine hematological investigations were requested for each patient including complete blood count, random blood sugar, liver function tests, kidney function tests, Elisa for HIV I & II and urine for routine-microscopy. A standard X-ray chest PA view was ordered for every patient. Sputum for acid fast bacilli, smear microscopy, culture and drug susceptibility tests were performed at Department of Microbiology, SP Medical College, Bikaner.

Sputum for AFB fluorescent microscopy

Sputum / tissue / fluids specimens were aseptically collected from individual reported in outdoor/indoor patients at our centre who were suspected to have pulmonary tuberculosis disease on the basis of their presenting symptoms. The slides were air dried and examined on the day of staining under fluorescent microscope (Olympus) at x200 magnification. The bacteria fluoresced as reddish golden yellow rods on dark background. Artifacts tended to appear hazy yellow or grey green and lacked the reddish tinge and were poorly delineated. Although the organisms tended to appear larger than expected due to fluorescent glow, they retained their slightly curved rod like structure. The characteristic features of M. tubercle bacilli were conformed under oil immersion lens using x400 magnification.

DRUG SUSCEPTIBILITY TESTING by Cartridge-based nucleic acid amplification test (CBNAAT) and Line Probe Assay (LPA) and Culture-

All sputa/extrapulmonary samples were first homogenized and concentrated by Petroff's method (modified). Two sputum samples of 1 ml were collected in a falcon tubes and one is analysed by CBNAAT on Xpert® MTB/RIF manufactured by Cepheid, endorsed by WHO (2010). Another sample is transferred to microbiology lab for LPA. The sample for CBNAAT was diluted with three times the reagent, incubated at room temperature and loaded into the cartridge for automated analysis with results in 100 minutes. Detection of mycobacteria by fully integrated and automated amplification and detection using real-time Polymerase chain reaction and rifampicin resistance as it targets the rpoB gene of mycobacteria was carried-out in the same setting. Line probe assays are drug susceptibility tests that use PCR and reverse hybridization methods for the rapid detection of mutations associated with drug resistance. Line probe assays are designed to identify M. tuberculosis complex and simultaneously detect mutations associated with drug resistance. In paients where CBNAAT results in mycobacterium tuberculosis detected and rifampicin sensitive than another sample is sent for 1st line LPA Which detects isoniazid (H) and rifampin(R) resistance. If CBNAAT results in mycobacterium tuberculosis detected and rifampicin resistant than another sample put for 2nd line LPA to detect drug resistance to fluoroquinolones (FQ) and Second line injectables (SLI).[11] Drug susceptibility testing of drug resistant cases repeat samples sent for Lowenstein-Jensen slopes as well as in Dubos broth carried out by 'proportion method' and cultured on Lowenstein-Jensen slopes as well as in Dubos broth. Culture-negative or contaminated samples were excluded from the analysis. Biochemical tests for niacin and catalase production were performed to confirm the identity of *Mycobacterium tuberculosis*. Drug susceptibility testing of the samples was performed by the radiorespirometric Buddemeyer technique (a manual modification of the Bactec 460 technique).[12,13]

Briefly, samples were inoculated into Dubos broth containing 14C Palmitic acid (Board of Radiation and Isotope Technology, India). Vials were set up in triplicate each containing 0.5 × 106/ml of Acid Fast Bacilli (AFBs) in absence (positive control) as well as presence of drugs (µgs/ml): Isoniazid (H – 0.1), Rifampicin (R – 2), Pyrazinamide (Z – 100) and Ethambutol (E – 2.5).

Negative controls consisted of medium without acid fast bacilli (AFBs) as well as with heat killed AFBs. A 1:100 dilution of the positive control was also maintained. Readings were obtained daily until the eighth day in counts per minute (cpm) on a Wallac 1409 DSA liquid scintillation counter. Growth indices (GI) were calculated for the drug containing vials and the 1:100 positive control.

Difference in growth indices (ΔGI), identical to that applied in the Bactec 460 method, calculated over consecutive days was used to determine susceptibility. The value of the mean ΔGI in the triplicate drug containing vials was compared to that for 1:100 control for the same day. If ΔGI was less in the drug containing vials than the 1:100 control, the bacteria were considered susceptible; if more, they were considered resistant.[14,15]

Grading of smears The table below depicts information on grading and the number of fields to be examined in different situations:-

200-250x magnification: 1 length = 30 fields = 300 HPF	400x magnification: 1 length = 40 fields = 400 HPF	Grading	Result
No AFB per 1 length	No AFB per 1 length	0	Negative
1-29 AFB per 1 length	1-19 AFB per 1 length	Scanty	Positive
30-299 AFB per 1 length	20-199 AFB per 1 length	1+	Positive
10-100 AFB per 1 field on average	5-50 AFB per 1 field on average	2+	Positive
More than 100 AFB per 1 field on average	More than 50 AFB per 1 field on average	3+	Positive

STATISTICAL ANALYSIS:
Logistic regression analysis was used to assess the association between drug resistance and independent factors. A significance level of $P < 0.05$ was considered statistically significant.

RESULTS:
Our study observed that out of 100 cases, 85 (85%) cases had drug sensitive of TB & 15 (15%) cases had drug resistant of TB. Male preponderance were occurred in drug sensitive (66%) and drug resistant TB (11%). Among 15 drug resistant TB cases, 12 cases were resides in rural areas and 3 cases were reside in urban areas. In drug resistant TB cases smoking habits present in 7 cases and 8 cases had absent of smoking habits**.** HIV negative in 14 cases and only one case with HIV positive in drug resistant TB cases (table 1)**.**
Sputum positivity status of DR-TB patients, mostly DR-TB cases (40%) had 3+ followed by 2+ in 26.66% cases, 1+ in 13.33% cases, negative in 13.33% cases and only 6.66% cases had scanty in agar plate (table 2).
Our study showed that the mostly DR-TB occurred in previously treated case (80%) and 20% cases had newly diagnosed cases of TB (table 3).

Table-1: Association of DR-TB with age

Demographic profile	Drug Sensitive TB N=85 (%)	Drug Resistant TB N=15 (%)	Total N=100 (%)	P-value*
Age Groups (yrs)				
11-20	12 (12%)	2 (2%)	14 (14%)	0.489
21-30	19 (19%)	6 (6%)	25 (25%)	
31-40	12 (12%)	2 (2%)	14 (14%)	
41-50	19 (19%)	2 (2%)	21 (21%)	
51-60	12 (12%)	1 (1%)	13 (13%)	
> 60	11 (11%)	2 (2%)	13 (13%)	
Gender				
Male	66 (66%)	11 (11%)	77 (77%)	**0.778**
Female	19 (19%)	4 (4%)	23 (23%)	
Area of residence				
Rural	52 (52%)	12 (12%)	64 (64%)	**0.140**
Urban	33 (33%)	3 (3%)	36 (36%)	
Smoking status				
Yes	24 (24%)	7 (7%)	31 (31%)	**0.072**
No	61 (61%)	8 (8%)	69 (69%)	
HIV status				
Reactive	0 (0%)	1 (1%)	1 (1%)	**0.326**
Negative	85 (85%)	14 (14%)	99 (99%)	

Table-2: Association of DR-TB with sputum positivity status

Sputum Positivity Status	Drug Sensitive TB n (%)	Drug Resistant TB n (%)	Total n (%)	P-value*
Scanty	4 (4%)	1 (1%)	5 (5%)	0.337
1+	20 (20%)	2 (2%)	22 (22%)	
2+	33 (33%)	4 (4%)	37 (37%)	
3+	22 (22%)	6 (6%)	28 (28%)	
Negative	5 (5%)	2 (2%)	7 (7%)	
Not Done	1 (1%)	0(0%)	1 (1%)	
Total	**85 (85%)**	**15 (15%)**	**100 (100%)**	

Table-3: Association of DR-TB with type of case

Type of Case	Drug Sensitive TB n (%)	Drug Resistant TB n (%)	Total n (%)	P-value*
New	47 (47%)	3 (3%)	50 (50%)	<0.001
Previously Treated	38 (38%)	12 (12%)	50 (50%)	
Total	**85 (85%)**	**15 (15%)**	**100 (100%)**	

*Chi square test

Our study showed that the mostly DR-TB occurred in previously treated case (80%) and 20% cases had newly diagnosed cases of TB.

DISCUSSION:

The emergence of drug-resistant strains of MTB is an increasing problem in both the developed world and developing countries. Strains of *M. tuberculosis* that are resistant to both isoniazid and rifampicin, with or without resistance to other drugs, have been termed multidrug resistant strains (MDRs). This is an emerging problem and has great importance to public health worldwide. Several reports have indicated that drug resistance is increasing among pulmonary TB patients in India.[6-8] However, various Indian studies have shown that the rate of MDR-TB is very low (0-6%).[9]

Therefore, drug resistance surveillance (DRS) is considered a useful tool to assess the drug susceptibility profile among newly diagnosed and previously treated patients, as well as to determine the effective functioning of TB control programs.[10] Early identification of drug-resistant strains, particularly MDR strains, is crucial in order to permit the timely administration of appropriate drug regimens and minimize transmission of these strains.

Our study observed that out of 100 cases, 85 (85%) cases had drug sensitive of TB & 15 (15%) cases had drug resistant of TB. Male preponderance were occurred in drug sensitive (66%) and drug resistant TB (11%). Among 15 drug resistant TB cases, 12 cases were resides in rural areas and 3 cases were reside in urban areas.

A study done by Berhanu Seyoum et al (2014)[16] found that the mean age of the patients was 28.8±11.9 (range: 18 to 75 years) and 270 (75.6%) were in the age group of 18–34 years.

The prevalence of MDR-TB is lower than 2.2% among new cases and 16% among retreatment cases; however, this translates into nearly 89,000 estimated MDR-TB cases among all TB cases notified in 2013.[17] India is one of the nations in the world which has the highest burden of MDR-TB. India has 22% (64,000) global MDR-TB cases which are highest in the world according to the WHO 2012 TB report. As per the WHO Global TB Report 2013, India accounts for 64,000 MDR-TB cases out of which 300,000 cases notified as pulmonary TB cases. In 2013, an estimated 480,000 new cases of MDR-TB were reported among which an estimated 190,000 people died of MDR-TB (“Global TB Control 2015, WHO”) worldwide.[17,18]

Sputum positivity status of DR-TB patients, mostly DR-TB cases (40%) had 3+ followed by 2+ in 26.66% cases, 1+ in 13.33% cases, negative in 13.33% cases and only 6.66% cases had scanty in agar plate. The treatment is given in two phases, the intensive phase (IP) and the continuation phase (CP). The total duration of treatment for regimen for MDR-TB is 24–27 months, depending on the IP duration. If the 4th or 5th month culture result remains positive, the treatment is extended by 1 month. Extension of IP beyond 1 month will be decided on the results of sputum culture of 5th or 6th and 6th or 7th months.

Our study showed that the 50% previous treated cases & 50% in new cases of tuberculosis. In drug resistant tuberculosis, Rifampicin resistant (MDR) were occurred in 9% of cases in previous treated tuberculosis & 2.50% cases of newly diagnosed tuberculosis by CBNAAT test. The transmission of DR-TB strains is increasing and playing an important role in emergence of MDR-TB. However, from the available data, it is not feasible to comment on the trend of MDR among new TB cases. The proportion of previously treated cases with MDR-TB varied from 8% to 67%; although, these studies have been conducted in different locations, which indicate an increasing trend of MDR among previously treated cases over the period.[19,20]

In India, it is difficult to determine the exact magnitude of the problem of DR-TB as the majority of the laboratories providing services for microscopic diagnosis of TB, and there are only a limited number of laboratories capable of conducting quality assured the first-line and second-line drug susceptibility testing (DST) in India.[21]

CONCLUSION:

We can easily conclude from the present study that well administered and dedicated first line treatment for susceptible cases is the need of hour to prevent development of resistance in such cases. Rapid diagnostic tests for resistance (such as Line Probe Assay) are also needed to be employed routinely by all national reference laboratories and intermediate reference laboratories to minimize the diagnostic time period and to minimize the transmission of resistant strains.

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