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Original Research Article

Prevalence of primary INH and Rifampicin resistance among treatment Naïve tuberculosis cases in tertiary care teaching hospital in Puducherry: A prospective cross-sectional study

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ABSTRACT

Background: India contributes to approximately one-third of total global tuberculosis (TB) and one-fourth of all Multi-Drug Resistant TB (MDR-TB) burden respectively. The First National drug resistance survey (2014-16) showed MDRTB rates of 6.19% overall and 2.14% in newly diagnosed TB cases. With the above problem of primary drug resistance among newly diagnosed tuberculosis cases, the present study was planned to find the prevalence of Isoniazid (INH) and Rifampicin resistance in the treatment naïve new tuberculosis cases.
Materials and Methods: Study design: Prospective, cross-sectional.
Subjects: Treatment naive newly diagnosed pulmonary tuberculosis cases.
Sample Size: 125.
Procedure: After informed written consent, Sputum samples were collected and subjected to culture in MGIT 960 and positive cultures were recorded and subjected to drug sensitivity testing for INH (0.1 μg/ml) and Rifampicin (1 μg/ml) and a parallel non-drug MGIT was run as a control.
Results: Most cases were males and belonged to the 20-59 years age group. Isoniazid (INH) resistance was found in 7 out of 125 samples, none had resistance to rifampicin. None of the categorical variables or grading of smear were having any statistically significant correlation with INH resistance.
Conclusions: INH resistance was found to be low (5.6%) with negligible MDR in the current study. Regular and large studies are needed to quantify and tackle the problem of primary MDR TB.

1. Introduction

The Global TB Report 2017 published by World Health Organization (WHO) estimates that India contributes 27% (2.79 million) and 25% (147 000) of the global burden of TB and multi-drug resistant TB (MDR-TB), respectively.[1,2] The First National Drug Resistance Survey (2014-16) of India showed among all TB patients tested, the MDR-TB rate was 6.19% with 2.84% among new and 11.60% among previously treated TB patients.[3]

One of the promising method, well evaluated and accepted in varying settings is the fluorimetry based liquid culture detection system, Mycobacterial Growth Indicator Tube (MGIT 960) (Becton and Dickinson, USA).[4] Currently, MGIT 960 is considered the gold standard in the liquid culture system and was introduced for diagnosis and DST of *M. tuberculosis* under the National Tuberculosis

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Elimination Program.[4,5] With the above problem of primary drug resistance among newly diagnosed tuberculosis cases the present study was planned to find the prevalence of INH and Rifampicin resistance in the treatment naïve new tuberculosis cases. We also tried to find a correlation between sputum grading, sociodemographic factors, and resistance patterns.

2. Materials and Methods

2.1. Study design

It was a cross-sectional study done between November 2016 to March 2018, undertaken in a tertiary care medical college located in the union territory of India. Ethical clearance from the Institute Ethics Committee (Human Studies) was obtained. All Adult patients attending Pulmonary medicine OPD who were diagnosed with new sputum smear-positive tuberculosis and have not received ATT drugs for more than 2 weeks were included in the study after taking informed written consent.

Research question: What is the prevalence of INH and Rifampicin resistance in treatment naïve new tuberculosis cases?

Sample size: The sample size of 125 was calculated by open epi software from openepi.com taking hypothesized frequency of outcome factor (MDR) in the population (new smear-positive patients) as 3% +/- 3, with confidence limit as 3% at the confidence interval of 95% and power of 80%.

2.2. Inclusion criteria

1. Treatment naive new tuberculosis cases (those cases who have received anti-tuberculosis drugs for less than 2 weeks).

2.3. Exclusion criteria

1. Subjects who were previously treated for pulmonary or extrapulmonary tuberculosis for more than 2 weeks
2. Subjects not willing to participate in the study.

2.4. Specimen collection and processing

Suspected cases of tuberculosis were given a wide-mouth bottle for collection of sputum. Two sputum specimens were collected (spot & early morning). Sputum was subjected to ZN and/or fluorescent stains (as per RNTCP/NTEP guidelines) and studied under light & Fluorescent microscopy respectively. Results were recorded and documented as per RNTCP guidelines. Patients with positive results were screened as per inclusion and exclusion criteria. Those patients with positive smears were asked to participate in the study and details of the study explained both verbal and documents. After taking informed consent willing patients were asked to give 2 more samples in a sterile sputum collection bottle in Falcon tube for MGIT culture and DST. Samples were taken to Intermediate Reference Laboratory, Government hospital for chest diseases, Gorimedu, Pondicherry as soon as possible but not later than 72 hours. Sputum samples were processed as per instructions by MGIT manufacturer FIND Diagnostics. The culture was done in MGIT 960 and positive cultures were recorded and subjected to drug sensitivity testing for INH (0.1 μg/ml) and Rifampicin (1 μg/ml) and a parallel non-drug MGIT was run as a control. Data were recorded and analysed.

2.5. Culture and drug susceptibility in liquid media (BACTEC MGIT 960)

The samples were processed as per the guideline For BACTEC^{TM} MGIT 960^{TM} TB system given by the manufacturer FIND diagnostics.[6]

2.6. NaOH-NALC procedure

The equal volume of sputum sample and NaOH-NALC-Sodium citrate solution was added and vortexed lightly around 15-30 seconds. NALC-NaOH solution was added to the mixture and allowed for 15-20 minutes (25 minutes max). Vortex was done lightly in every 5-10 minutes. Phosphate buffer (pH 6.8) was added up to the top ring and mixed well and centrifuged at 3000 rpm for 15-20 minutes and allowed the tubes to stand for 5 minutes to settle down. The supernatant was discarded carefully into the container containing a mycobactericidal disinfectant. Phosphate buffer (pH 6.8) 1-2 ml was added and resuspended the sediment with the help of a pipette or vortex mixer. Polymyxin B, Amphotericin B, Nalidixic acid, Trimethoprim, and Azlocillin (PANTA) was reconstituted according to the manufacturer's description and then used in MGIT tubes.

2.7. Inoculation into MGIT medium

7 ml MGIT tubes were aseptically added with 0.8 ml of MGIT growth supplement and PANTA and then 0.5 ml of a well-mixed processed/concentrated specimen and mixed by inverting the tube several times. The tubes and caps were wiped with a Mycobactericidal disinfectant and inoculated tubes were kept at room temperature for 30 minutes.

Inoculated MGIT (7 ml) tubes were then entered in the BACTEC MGIT 960 instruments after scanning. Tubes were incubated at 37°C. MGIT tubes were kept incubated until the instrument flagged them positive. Once a MGIT tube is flagged positive, the tubes were manually observed, and smear was made and stained with Auramine Rhodamine for AFB to rule out any contamination. After a maximum of 6 weeks, the instrument flags the tube negative if there is no growth. The second Sample was also subjected to the Line Probe Assay for cross-checking the resistance pattern, the sample was processed as per the manufacturer's guideline

by Hain's MTBDR plus for LPA.[7,8]

2.8. Statistical analysis

Outcome variables: Resistance to INH and Rifampicin.

Distribution of data on categorical variables related to gender, age, weight, sputum grade, sputum smear results, symptoms like cough, fever, haemoptysis, loss of appetite and loss of weight, presence and absence of HIV seropositivity, co- morbidities, smoking history, history of ATT, household contact and resistance to INH and Rifampicin etc. were expressed in frequency and percentage.

The distribution of the variables was revealed via the Kolmogorov-Smirnov test. The correlation of Resistance and various variables like age, sex, symptoms, socioeconomic status (based on Modified Kuppusamy Scale 2019),[9] smoking, diabetes, and household contact history were analyzed by one-way Anova with Bonferroni correction using IBM-SPSS program (SPSS version 19.0; SPSS Inc, Chicago, IL) All statistical analysis was carried out at 5% level of significance and p-value <0.05 was considered as significant.

3. Results

A total of 125 newly diagnosed microbiologically confirmed cases of pulmonary tuberculosis were recruited in the study. Most of the patients were male (n=105, 84%) and 84 cases (67%) were between age of 20 to 50 years with a mean age of 43.44 (SD ±14.14) years. The mean weight was 44.08(SD±8) kg and most patients (n=100, 80%) were in 40-59 kgs weight range. General characteristics of the cases are given in the Table 1. Based on the Modified Kuppuswamy socioeconomic scale updated for January 2018, Sixty-seven (53.6%) cases belonged to the lower socioeconomic group, whereas 40(32%) belonged to the upper lower group. A total of 107 cases out of 125 (85.6%) belonged to lower and upper lower socioeconomic groups.

Table 1: General characteristics of the cases

Characteristic	N (%)
Male	105 (84)
Female	20 (16)
Smokers	25 (20)
Non-Smoker	100 (80)
HIV Seropositive	0 (0)
Household Contact	4 (3.2)
Diabetes	18 (14.4)
Asthma	7 (5.6)
CKD	3 (2.4)
Hypertension	4 (3.2)
Previous history of ATT intake	0 (0)
Socioeconomic status(category)	
Lower(V)	67 (53.6)
Upper Lower (IV)	40 (32)
Lower Middle (III)	14 (11.2)
Upper Middle (II)	4 (3.2)
Upper (I)	0 (0)

3.1. Presenting complaints

One hundred and eleven out of one hundred twenty-five (90.4%) patients presented with cough as chief complaint followed by Fever in 92(73.6%), loss of appetite in 79(63.2%), and loss of weight in 42 (33.6%) cases. In Twenty-eight (22.4%) patients the presenting complaint was haemoptysis. Among comorbidities, Diabetes mellitus was most common(n=18,14%) followed by asthma (n=7, 5.6%). None of the cases had a previous history of anti-tubercular drug intake. All cases were HIV-Sero-negative.

3.2. Sputum smear grade of first and second samples

Fifty-five patients provided grade 2 samples whereas in 56 patients the first sample of sputum was grade 3. Thirteen samples were grade 1and one was smear negative. The second sample results showed one smear-negative, 15 were grade 1, 55 were grade 2 and 56 were grade 3 samples.

3.3. MGIT results and resistance pattern

All 125 (100%) samples showed growth of mycobacterium tuberculosis and on sensitivity 7 (5.6%) showed resistance to INH, and none of the samples showed resistance to Rifampicin. These results were similar when confirmed by Line Probe Assay(LPA).

None of the categorical variables showed a statically significant correlation with the INH resistance status. All INH resistance cases were male (7/105) and all 20 females were sensitive to INH, but the association was not statically significant (p=0.596). There was no statically significant association found between the sputum grades and the presence of INH resistance (p=.348).(Table 2)

4. Discussion

In this prospective cross-sectional study, a total of 125 treatment naïve new smear positive pulmonary tuberculosis cases were included.

A male predominance of pulmonary tuberculosis with Male to Female ratio of 5.25:1 was noted in our study which probably reflects the study population distribution as a whole. Similar male gender predominance has also been noticed in other studies.[28,30,32–35] This gender difference may be due to the high prevalence of tuberculosis in the male population due to their exposure to external environment for their occupation and other related work. The mean age of Pulmonary tuberculosis patients was 43.44 years (SD ±14.14). Most of the patients were between 21 to 50 years of age, with nearly 67% of the patients (84/125

Table 2: Correlation of resistance with categorical variables

S. No.	Categorical Variables	Result	INH Resistance n (%)		p value
			Absent n (%)	Present n (%)	
1	Sex	Male	98(83.1)	7(100.0)	0.596
		Female	20(16.9)	0(0.0)	
2	Rifampicin Resistance	Absent	118 (100)	7(85.7)	0.056
		Present	0(0)	0(0)	
3	Cough	Absent	12(10.2)	0(0)	1.00
		Present	87(73.7%)	5(71.4)	
4	Fever	Absent	31(26.3)	2(28.6)	1.000
		Present	87(73.7)	5(71.4)	
5	Haemoptysis	Absent	90(76.3)	7(100)	0.343
		Present	28(23.7)	0(0)	
6	Weight Loss	Absent	79(66.9)	4(57.1)	0.687
		Present	39(33.1)	3(42.9)	
7	Loss of Appetite	Absent	41(35.3)	3(42.9)	0.700
		Present	75(64.7)	4(57.1)	
8	Household Contact	Absent	114(96.6)	7(100)	1.000
		Present	4(3.4)	0(0)	
9	Jaundice	Absent	116(98.3)	7(100)	1.000
		Present	2(1.7)	0(0)	
10	Asthma	Absent	111(94.1)	7(100)	1.000
		Present	7(5.9)	0(0)	
11	DM	Absent	100(85.5)	6(85.7)	1.000
		Present	17(14.5)	1(14.3)	
12	Smoking	Absent	93(78.8)	7(100)	0.343
		Present	25(21.2)	0(0)	
13	Socioeconomic Status	Lower	64(54.2)	3(42.9)	0.687
		Upper Lower	36(30.5)	4(57.1)	
		Lower Middle	14 (100))	0(0)	
		Upper Middle	4(100)	0(0)	

Table 3: Global studies on primary initial drug resistance

Study	Any Drug	H%	S%	R%	E%	H+R%
Cohn et al. review of 63 surveys (1985-1994) [10]	-	0 – 16.9	0.1 – 23.5	0 – 3.0	0 – 4.2	0 – 10.8
WHO-IUATLD 1994 –1997 surveillance [11]	9.9 (2.0-40.6)	7.3 (1.5-31.7)	6.5 (0.3-8.0)	1.8 (0-16.8)	1.0 (0-9.9)	1.4 (0-14.4)
WHO-IUATLD 1996 –1999 surveillance [12]	10.7 (1.7-36 .9)	6.2 (0-28.1)	5.2 (0.3-32.4)	1.2 (0-15.8)	0.6 (0-11.1)	1 (0.0-14.1)
WHO-IUATLD 1999-2002 surveillance [13]	10.2 (0-57.1)	5.7 (0-42.6)	6.3 (0.51.5)	1.4 (0-15.6)	0.8 (0-24.8)	1.1 (0-14.2)
Walls G et al 2015 [14]	12.7	3	-	3	-	8.1

patients) between 20 and 50 years of age. This finding in the present study is consistent with other studies. [28,30,32–35]

As this age group of the population constitutes an economically productive section of society, the presence of disease in this segment has far-reaching socio-economic implications. Pressure to continue working in spite of poor health could lead to decreased compliance toward regular medication thereby increasing the threat of developing drug resistance. A national drug resistance survey found 58% males in the age group of 25-55 years and females more common in the younger age group (72% in 15-45 years). [3] In the present study the most common co-morbidity found was Diabetes (18,14.4%), followed by seven (5.6%) cases of asthma, three cases of chronic kidney disease and four cases were hypertensive. Similar results have been found in previous studies also. In the study done by Myneedu et al most common comorbid condition found was diabetes (2%). [28] Agwan et al. found diabetes in 21 out of 110 (19.1%), Hypertension in 18(16.4%) and steroid use in 30(27.3%) cases. [26] In our study, all 125 cases were Sero-negative for HIV1 & 2. This is similar to the study done by Agwan et al, as they excluded HIV seropositive patients. This is in contrast to other studies. A study done in New Delhi by Myneedu et al., showed the prevalence of HIV

Table 4: Indian studies for initial/primary drug resistance

Study	Total prevalence	H%	S%	R%	H+R%
ICMR (1968)[15]	20.4	14.7	12.5	-	-
ICMR (1969)[16]	22	15.5	13.8	-	-
Krishnasamy KV et al (1976)	-	10.6	9.5	-	-
Trivedi et al (1988)[17]	20	13.4	7.9	-	-
Chandrasekharan et al (1990)[18]	21.2	17.4	5.7	3	1.3
Chandrasekharan et al (1992)[29]					
Rural	34.9	32.8	5.1	4.4	3.4
Urban	20.5	17.3	4.1	2.9	1.4
Paramsivan et al (2004)[30]					
North Arcot(1985-89)	25.0	13	4	2	1.6
Pondicherry(1985-91)	13.9	6	4	0.9	0.7
Gupta et al (1993)[19]	19.5	10.1	7.6	3	0.7
Jain et al (1992)[20]	-	18.5	-	0.6	0.4
Jena et al (1996)[21]	7.9	2.9	4.9	1	0.4
Parmasivan et al (2002)[22] Tamil Nadu	18.8	15.4	6.8	4.4	3.4
R. Prasad et al (2001)[23]	27.4	15.6	11.7	3.9	5.0
Sofia et al (2004)[24] Bangalore city	27.7	13.7	22.5	2.6	2.2
Pereira M et al(2004)[25] Pune	20	10	-	0	10
Mahadeo et al(2005)[31]					
Mayurbhanj	5.3	2.5	3.9	0.7	0.7
Hoogli	16.7	10.3	13.7	3.0	3.0
Vivek Agwan et al(2015)[26]	29.0	5	-	17.3	7.2
Harshita Gupta et al (2013)[27]	21.3	18.3	10.1	4.7	4.7
V.P. Myneedu et al (2015)[28]	23.2	7.1	5.6	0.9	4.0
1st National Drug resistance survey (2014-16)[3]	22.54	11.06 Mono Res 3.85	2.2	0.0	2.84
Present Study	5.6	5.6	-	0.0	0.0

as 0.09%.[28] Several other studies reported MDR TB in 4.5-27% of patients co-infected with HIV.[14,25,36,37] In the present study twenty-five (20%) cases were smokers, similar findings are also found in several studies. Harshita Gupta et al. in their study from Lucknow reported 64.4% smokers.[27] In a study done in New Delhi by Myneedu et al., found 49 out of 453 cases (10.8%) smokers.[28] Household contact to TB and MDR TB is a well-documented risk factor for developing Initial MDR TB.[38] In our study, only four patients had household contact as tuberculosis. All were sensitive to both INH and Rifampicin. Gupta et al., in their study from Lucknow reported 23.3% of cases with a history of household contact of tuberculosis patients. They also found higher primary MDR and other combinations of drug resistance rates (4.7%).[27]

4.1. Socioeconomic status

Fifty-five percent of cases (69/125) were laborers by occupation, students, housewives, office job and driver cases were 16, 13,20 & 7 in number respectively. Based on the Modified Kuppuswamy Socioeconomic scale[9] updated for January 2019, Sixty-seven cases belonged to the lower socioeconomic group, whereas 40 belonged to the upper lower group. A total of 107 cases out of 125 (85.6%) belonged to lower and upper lower socioeconomic groups. Fourteen cases were from lower middle and 4 cases were from the upper-middle-income group. These findings are similar to various studies done in past in India.[27,28,35] Gupta et al., in their study reported 78.6% cases belonged to upper-lower and 18.8% to the lower-middle socioeconomic group.[27]

All 125 (100%) samples showed growth of mycobacterium tuberculosis and on sensitivity 7 (5.6%) showed resistance to INH, and none of the samples showed resistance to Rifampicin. This outcome is lower in contrast with national drug resistance survey of 2.2% of primary MDR.[3] Treatment naïve MDR rates as reported by various Indian studies, over the years ranges from 0.6% to 24% as detailed in the Table 4. Much higher rates were found in studies from Lucknow and Mumbai, with treatment naïve MDR-TB to be 13.2% and 24% respectively.[35,39] These studies might have a potential bias in the patient selection, as the retreatment cases could not be fully excluded leading to high MDR rate. Estimates of drug resistance in new cases carried out at the National Institute

for Research in Tuberculosis (NIRT), Chennai showed that primary resistance to INH was 14.7%, 12.5% to SM and 7.7% to both INH and SM. Recent studies in 2013 from Lucknow by Gupta et al.[27] and in 2015 from New Delhi[28] by Myneedu et al., have reported MDR rates of 4.7% and 4.0%, mono-resistance to INH 18.3% and 7.1% respectively. In our study, mono-resistance to rifampicin was found to be zero; which is similar to the recently concluded first National Drug resistance survey (2014-16) of India.[3] This survey showed INH mono-resistance of 3.85% and any INH resistance of 11.06%, negligible Rifampicin resistance and MDRTB rate of 2.84% among new TB patients. The survey also found pyrazinamide resistance rates of 6.95%. Globally several studies[10,12,13] reported initial drug resistance ranges from 0-10.8 (Cohn et al.,).[10] WHO-IUATLD surveillance between the years 1994- 97, 96-99 and 1999-2002 have reported primary INH, resistance in 7.3 %, 6.2%, and 5.7% respectively. They also reported MDR in 1.1, 1.4, and 1.1 percent. A summary of various International and Indian studies are given in Tables 3 and 4 respectively.

5. Limitations

The limitation of the study was less number of cases. A large number of patients were from other states and did not give consent for the study due to logistic problems. Further none of our patients had HIV seropositivity which denied opportunity to study the impact of HIV on primary drug resistance. Similarly, very few patients had a history of household contact with tuberculosis patients and none of them had resistance, we could not study the impact of the same on primary drug resistance.

6. Conclusion

Primary drug resistance in treatment naïve cases of tuberculosis is not rare. Mono-resistance to Isoniazid is common (5.6%). Mono-resistance to Rifampicin is negligible. Primary MDR is also very less but present. The proper history of ATT exposure is of utmost importance to rule out primary drug resistance.

Newer diagnostic techniques like CB-NAAT should be offered upfront to a newly diagnosed tuberculosis case to rule out primary drug resistance and proper treatment. A regular survey of drug resistance is very important for the knowledge of the problem and preparation for the same.

7. Conflict of Interest

None of the authors had any conflict of interest.

8. Source of Funding

None.

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