

ANALYSIS OF PATTERNS OF RESISTANCE TO FRONTLINE ANTITUBERCULAR DRUGS IN RNTCP CATEGORY I AND CATEGORY II FAILURE PATIENTS- A SINGLE CENTRE EXPERIENCE

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ABSTRACT

BACKGROUND

The aim of the study is to identify locoregional trends in the anti-TB drug resistance and to identify the incidence of MDR-TB in Category I and II treated TB patients.

MATERIALS AND METHODS

60 patients drawn from the TB Clinic of Coimbatore Medical College Hospital were included in this study. Sputum samples were cultured on Lowenstein-Jensen medium and tested for resistance to streptomycin, rifampicin, isoniazid and ethambutol. Results were computed and presented.

RESULTS

Patients who had failed category I regimen had far fewer drug-resistant bacteria than those who failed category II regimen. Standalone values of resistance to anti-TB drugs were comparatively higher than past studies of similar nature. Streptomycin experienced maximum resistance (33.3% of cases) and ethambutol (16.7% of cases) the least. The frequency of MDR-TB was 25%.

CONCLUSIONS

The findings of present study reveal an increasing frequency of overall anti-TB drug resistance and also of MDR-TB in study subjects. Further larger regional studies are needed to establish emerging trends of resistance.

KEYWORDS

Drug Resistant Tuberculosis, DOTS Failure, MDR-TB.

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BACKGROUND

The history of Tuberculosis (TB) is as old as that of mankind itself.¹ Over the years, antituberculosis drug therapy has evolved from TB sanatoria in cold peaks to modern combination chemotherapy. DOTS program by the WHO has met with major success and its implementation has been hailed as a major achievement of the WHO.

Natural mutation confers spontaneous and acquired resistance to anti-TB drugs with alarming frequency.² Combination chemotherapy has overcome this problem to some extent. However, noncompliance by patients and substandard combinations has led to the emergence of

Multidrug-Resistant TB (MDR-TB). This has threatened to eliminate the progress that has been made in the global control of TB. The present study is an attempt at identifying the locoregional trend in anti-TB drug resistance and frequency of MDR-TB.

MATERIALS AND METHODS

The present study has been designed as a cross-sectional study. It was conducted at Coimbatore Medical College Hospital (CMCH) from September 2012 through August 2013. The study group consisted of 60 patients (hereinafter called 'subjects') who presented to the TB clinic at CMCH and qualified for this study based on the inclusion and exclusion criteria as mentioned below in boxes 1 and 2, respectively. Subjects had been treated with anti-TB combination drug regimens under RNTCP (revised national tuberculosis control program) categories I or II. RNTCP categories have been described below in Table 4.³

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Inclusion Criteria

Patients with AFB positive sputum during ongoing treatment under RNTCP cat I or II for the duration of 4 months or more.

Exclusion Criteria

1. Patients with established or newly-detected diabetes mellitus.
2. Patients with HIV seropositivity at the time of enrolment into the study.
3. Patients with contaminated sputum samples.
4. Patients whose culture showed negative growth.

Two sputum samples were collected from each subject one of which was mandatorily an early morning specimen. Sputum AFB culture and sensitivity pattern detection testing was carried out at Intermediate Reference Laboratory (IRL), Chennai. A 1% Cetylpyridinium Chloride (CPC) transport medium was used for transportation of sputum sample from

Coimbatore to Chennai wherever the expected delay was more than 72 hours.

Cultures were put up using single step culture technique in Lowenstein-Jensen medium. All cultures were incubated for 6 weeks duration.

Resistance pattern was established for the following four drugs and drug combinations thereof: streptomycin, rifampicin, isoniazid and ethambutol.

RESULTS

It was observed that subjects who had received treatment under category I RNTCP protocol had a lower frequency of single and multi-drug resistance as compared with subjects who had received treatment under category II RNTCP protocol. The exact figures are tabulated below in Table 1.

RNTCP Category	Resistance to Rifampicin	Resistance to Isoniazid	Resistance to Streptomycin	Resistance to Ethambutol
Category I	1	1	1	0
Category II	18	18	19	10
Total	19 (31.6%)	19 (31.6%)	20 (33.3%)	10 (16.7%)

Table 1. Drug Resistance in Relation to RNTCP Category

Resistance to streptomycin was most common and to ethambutol was the least common in the present study population. The overall prevalence of resistance to individual drugs used in treatment as well as to various combinations of two or more drugs is highlighted in the adjoining Table 2.

Drug	Sensitive Cases	Resistant Cases	Percentage of Resistance
Streptomycin	40	20	33.3
Isoniazid	41	19	31.7
Rifampicin	41	19	31.7
Ethambutol	50	10	16.7

Table 2. Prevalence of Resistance to Individual Drugs in Subjects

Resistance to a combination of two or more drugs is more clinically and epidemiologically relevant. Table 3 shows the pattern of prevalence of resistance to combination drug regimes in this study group.

Notably, among the total group of 60 subjects who had failed treatment and were part of this study, 15 patients (25%) were MDR-TB positive. This compares with the 2010 WHO report on drug resistance in tuberculosis, which mentions a MDR-TB prevalence of 17.2% among treated patients in India.⁴

Number of Drugs	Drug Combination	Number of Patients		Total Number of Patients	Total Number of MDR Patients
		Male	Female		
Two drugs	HR	4	0	4	4
	SR	2	0	2	0
	SE	0	1	1	0
	SH	2	0	2	0
Three drugs	HRE	0	1	1	1
	HRS	1	2	3	3
Four drugs	HRES	6	1	7	7
Total					15

Legend: H - Isoniazid, R - Rifampicin, S - Streptomycin, E - Ethambutol.

Table 3. Prevalence of Resistance to Drug Combinations in Subjects

DISCUSSION AND LIMITED REVIEW OF LITERATURE

Mycobacterium tuberculosis was first identified by Robert Koch in 1882.⁵ Tuberculosis remains the most common infectious cause of death worldwide.⁶ Rifampicin, isoniazid,

ethambutol, pyrazinamide and streptomycin being the first line antituberculosis drugs form the backbone of TB treatment across the world.

Resistance to antitubercular drugs and drug combinations has been increasing steadily.⁴ Resistance to anti-TB drugs is a result of spontaneous mutations, which result either in overexpression of a target gene product (isoniazid, ethambutol), or in alteration of the drug target inside the bacterial cell (rifampicin, streptomycin), or in impaired uptake of the drug into the bacteria (pyrazinamide).² The rates of mutation range from 1 in 10⁶ to 1 in 10⁸ in various series.²

The World Health Organization (WHO) defines Multidrug-Resistant Tuberculosis (MDR-TB) as TB caused by strains of mycobacterium tuberculosis that are resistant to at least isoniazid and rifampicin.⁴ The patient who returns a positive sputum smear result at the end of 4th month of anti-TB treatment is a suspect for MDR-TB and warrants drug susceptibility testing.

The WHO further defines the extensively drug-resistant TB (XDR-TB) as resistance to at least rifampicin and isoniazid in addition to any fluoroquinolone and to at least one of the three following injectable drugs used in anti-TB treatment: capreomycin, kanamycin and amikacin.

India has a high proportion of MDR-TB cases and together with China accounts for approximately 50% of the total burden of MDR-TB cases in the world.⁴ As of 2008, the prevalence of MDR-TB in newly-detected tuberculosis patients in India was 2.3% while the prevalence of MDR-TB in treated tuberculosis patients was 17.2%. The total number of MDR-TB cases in India was estimated at 99,000 in 2008.⁴

The Revised National Tuberculosis Control Program (RNTCP) defines two broad categories for treatment of tuberculosis. These have been detailed in the adjoining Table 4.

Category I (Previously Categories I and III)	Category II (Previously Category II)
New cases <ul style="list-style-type: none"> • Sputum smear positive • Sputum smear negative • Extrapulmonary tuberculosis 	Previously treated <ul style="list-style-type: none"> • Smear positive relapse • Smear positive failure • Smear positive treatment after default • Smear negative pulmonary TB • Nonresponsive extrapulmonary TB

Table 4. Guideline Criteria for Division into RNTCP Treatment Categories

Comparisons can be drawn from similar past studies where resistance to individual drugs and their combinations thereof have been studied and quantified. Comparison of the findings of present study with a study by ME Kimerling et al is shown in the adjoining Table 5.⁷

Drug	Study by ME Kimerling et al.		Present Study	
	Number	%	Number	%
H	10	6.1	2	3.3
R	1	0.6	2	3.3
S	13	7.9	3	5
HS	61	37.2	2	3.3
HR	-	-	4	6.7
SE	-	-	1	1.7
RS	1	0.6	2	3.3
HRS	37	22.6	3	5
HRE	-	-	1	1.7
Sensitive to all Drugs	41	25.5	30	50

Table 5. Comparison of Percentage of Resistance to Anti-TB Drugs Between Present Study and Study by ME Kimerling et al.

It is noteworthy that there is gross difference in the resistance rates to particular drugs in the present study as compared with a similar previous study by ME Kimerling et al. This is likely explained by locoregional variations in mutation induced acquired resistance in the TB bacilli.

A similar study conducted by Bikram Singh Datta et al also obtained the resistance rates for combination chemotherapy in TB and their findings are compared with those of the present study in table 6.⁸

No. of Drugs	Name of Drugs	Study by Bikram Singh Datta et al.		Present Study	
		Number	Percentage	Number	Percentage
2 drugs	HR	7	13.4	4	6.7
3 drugs	HRE	5	9.6	1	1.7
	HRS	3	5.7	3	5
4 drugs	HRES	7	19.2	7	11.7

Table 6. Comparison of Percentage of Resistance to Anti-TB Drugs Between Present Study and Study by Bikram Singh Datta et al.

Again, the variation in rates of resistance to anti-TB drug regimens between present study and that of Bikram Singh Datta et al can be explained by locoregional variation in the rates of resistance conferring spontaneous mutations in tubercle bacilli.

CONCLUSIONS

TB is a mighty disease. Treatment for tuberculosis has been quite effective after the introduction of combination chemotherapy and DOTS protocol for drug administration and monitoring. Detection of new cases of TB also has improved by leaps and bounds.

Resistance to anti-TB drugs has been a major concern in the otherwise successful global fight against TB.

The present study has revealed resistance patterns, which show a higher percentage of MDR-TB than similar large surveys in the recent past. Perhaps speeding up the process of introduction of newer options to tackle MDR-TB would help curb this menace. Further studies in different regions of India are needed to identify emerging trends in X/MDR-TB.

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