Research Article

Study of mycobacterium culture and sensitivity pattern of various anti-tubercular drugs in suspected multidrug resistant tuberculosis patients

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Abstract

Resistance to the first line drugs is the most difficult part of treating tuberculosis. Different studies have found upto 3% previously treated patient and Upto 17% patients who have taken Antitubercular treatment previously as being multidrug resistant MDR TB(Multi drug resistant tuberculosis) is defined as resistance to isoniazid and rifampicin. More and more patients are attending chest OPDs with pulmonary. tuberculosis and not responding to primary line of antituberculosis drugs. We undertook a study in our institution to find the drug susceptibility pattern in 50 patients who were suspected to be MDR (resistant to INH + Rifampicin) and found only 2% of such patients to be sensitive to both INH and RFM (i.e. 98% were MDR-TB patient),no patient was sensitive to all the first line drugs,21patients(42%)were sensitive to only one first line drug and 4% patients sensitive to only one drug cycloserine. Our study endeavoured to find the sensitivity and resistance patterns of the mycobacterium to the various antituberculous drugs. This study will be useful in identifying and choosing which drugs are more effective in management of MDR Tuberculosis. **Abbreviation**: MDR: Multi Drug resistant Short Running Head: Drug Sensitivity pattern in M.D.R Tuberculosis

Keywords: MDR TB, Mycobacterium culture, Drug Resistance, Sensitivity Pattern

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INTRODUCTION

Transmission of tuberculosis occurs by air borne spread of infection droplets and droplet nuclei containing the tubercle bacilli. The source of infection is a person with sputum smear positive pulmonary tuberculosis. Transmission often occurs indoor where droplets and droplet nuclei can stay in the air for a longer time. With the advent of various Anti-Tubercular drugs, Anti-Tubercular treatment has become more and more effective. Short course chemotherapy and DOTs/RNTCP have made it possible to achieve the goals of cure rate of 85% among newly detected infectious cases and maintain detection rate of at least 70% of all such cases in the population. The emerging trend of resistance to various first line Anti-Tubercular Drugs is disturbing. Multi Drug Resistant Tuberculosis is a laboratory diagnosis and should not be a clinical impression of treating doctor. Resistance to Isoniazid and Rifampicin is called Multi Drug Resistance. Resistant to one drug is called monoresistance; resistance to two or more drugs is called polyresistance. Another type of resistance called Extensive. Drug Resistance is resistance to INH, rifampicin, at least one injectible amino glycoside and a fluroquinolone. About 3 % previously untreated patients and up to 17% previously treated patients have multidrug resistant tuberculosis. The diagnosis and appropriate treatment of multidrug resistant tuberculosis patients is very important not only because they will spread the multidrug resistant strain of tuberculosis to other patients but also because MDR tuberculosis leads to severe

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morbidity and has high mortality rate since it is difficult to treat. Our study attempts to find drug resistant cases and to see the sensitivity pattern of mycobacteria in our area to the various antitubercular drugs.

MATERIAL AND METHODOLOGY

SUBJECT: Patient above 15 years of age who have taken Anti- Tubercular drug at least one time.

INCLUSION CRITERIA

1. Patients above the age of 15 yrs.
2. Taken Anti- Tubercular Drug at least 1 time and still Sputum positive after 5 months.
3. Initially Sputum negative but positive after 5 months.

EXCLUSION CRITERIA

1. Severely ill patients / end stage diseases.
2. Patients >60yrs and <15yrs of age.

STUDY PROCEDURE

1. 50 patients of suspected drug resistant tuberculosis were studied on the basis of the above inclusion and exclusion criteria.
2. Informed consent was taken.
3. Appropriate information, including symptoms about the patients was collected.
4. Detailed history regarding their treatment, checking of old X-rays and Sputum reports.
5. Family history of TB.
6. History of TB in Contacts.
7. Sputum collection in a sterile container.
8. Culture on LJ Medium/BACTEC METHOD and sensitivity testing to

The following antitubercular drugs was carried out:Isoniazid, Rifampicin, Pyrazinamide, ethambutol, Streptomycin, Kanamycin, Ofloxacin, Cyloserine, Ethionamide, Paraaminosalicylic acid (PAS).

RESULTS

Table 1: Sex distribution

Sex	Number of Patients	Percentage
Male	29	58%
Female	21	42%
Total	**50**	**100%**

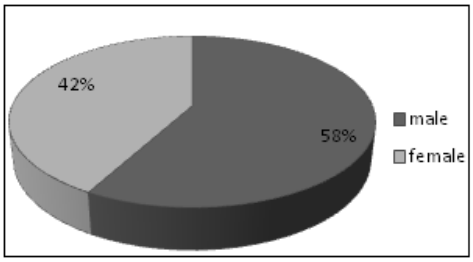

Figure 1: Pie Chart- Sex Distribution

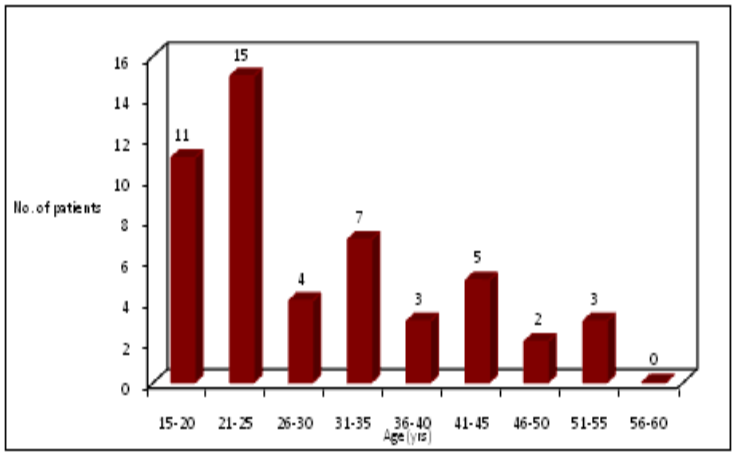

Figure 2: Age Distribution Bar Diagram

Table 2: Resistance and Sensitivity to Antitubercular Drugs

Drug	Resistance	Sensitivity
Streptomycin	30	20
Isoniazid	47	3
Rifampicin	49	1
Etnambutamol	31	19
Pyrizinamide	30	20
Paraaminosalicylic	11	39
Ethionamide	11	39
Cycloserine	20	30
Kanamycin	7	43
Ofloxacin	27	23

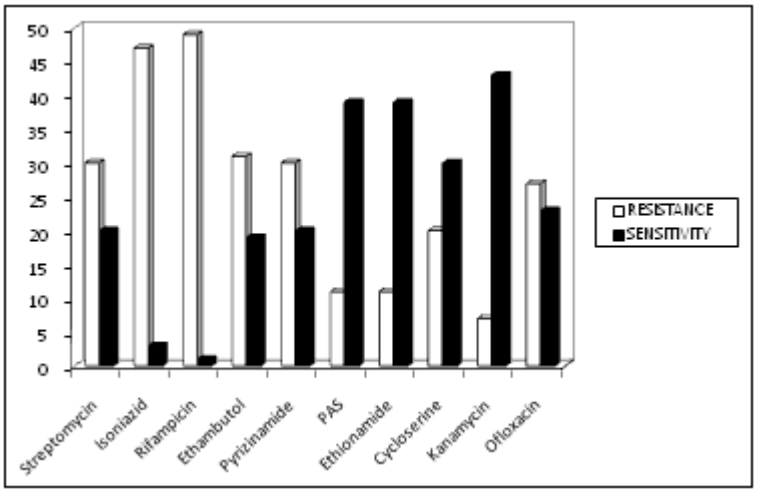

Figure 3: Resistance and Sensitivity Pattern Bar Diagram

DISCUSSION

The study was done to know the sensitivity pattern of various Antitubercular. Drugs in Aurangabad (TB U -2) in suspected Multidrug Resistant. Tuberculosis patients by performing sputum culture of mycobacterium Tuberculosis. It comprised of 50 patients of pulmonary tuberculosis, who previously had taken tuberculosis treatment and remain sputum positive at the end of five

months, who show radiological deterioration after 8 months or those who have become sputum positive after being sputum negative initially. Multidrug-resistant tuberculosis (MDR TB) is resistance to both isoniazid and rifampicin with or without resistance to other drugs. Globally, about 3% of all newly diagnosed patients have MDR-TB. The proportion is higher in patients who have previously received antituberculosis treatment reflecting the failure of programmes designed to ensure complete cure of patients with tuberculosis. While host genetic factors may probably contribute, incomplete and inadequate treatment is the most important factor leading to the development of MDR-TB. The definitive diagnosis of MDR-TB is difficult in resource poor low income countries because of non-availability of reliable laboratory facilities and efficiently run tuberculosis control programmes based on Directly Observed Treatment Short courses (DOTS). For newly diagnosed patients, the frequency of resistance to at least one antituberculosis drug ranged from 1.7 per cent in Uruguay to 36.9 percent in Estonia (media, 10.7%). The median prevalence of MDR-TB among new cases of tuberculosis was only 1.0% but the prevalence was much higher in Estonia (14.1%), Henan province in china (10.8%), Latvia (9%), the Russian oblasts of Ivanovo (9%) and Tomsk (6.5%), Iran (5%) and Zhejiang Province in china (4.5%). In our study of 50 patients who were suspected Multidrug Drug Resistant Tuberculosis

1. Sex Ratio Male: Female 58%: 42% Males are more commonly affected as compared to female. (58% - 42%)
2. Age Group Most commonly seen in 21 – 25 age group (30%) 2nd Most commonly seen in 15 – 20 age group (22%) 3nd Most commonly seen in 31 – 35 age group (14%)
3. Resistance Pattern to single drug It revealed a resistance in 47 patients to isoniazid (94%), 49 patients to rifampicin (98%), 30 patients to streptomycin (60%), 31 patients to ethambutol (62%), 30 patients to pyrazinamide (60%). Resistance was seen in 27 patients (47%) to ofloxacin.
4. Sensitivity Pattern to single second line drug Second line drugs mainly injectible (Kanamycin) has highest sensitivity in 43 patients (86%), followed by Para amino salicylic acid in 39 patients (78%), Ethionamide in 39 patients (78%) followed by cycloserine in 30 patients (60%) Only 3 patients of suspected multidrug resistance were sensitive to isoniazid (6%) and 1 patient (2%) sensitive to rifampicin.
5. Sensitivity to first line drugs (H R Z E S) in this study of suspected multidrug resistance No patient was sensitive to all the first line drugs 2 patients were sensitive to four first line drugs 6 patients were sensitive to three first line drugs 8 patients were sensitive to two first line drugs 21 patients were sensitive to only one first line drug.
6. Sensitivity to isoniazid and rifampicin 3 patients were sensitive to isoniazid (6%) 1 patient was sensitive to rifampicin (2%) 1 patient of the above was sensitive to both isoniazid and rifampicin
7. Sensitivity to only single or two drugs 2 patients (4%) were sensitive to single drug – cycloserin 2 patients were sensitive only to two drugs out of whom – One patient sensitive to (ofloxacin + cycloserine) and the other was sensitive to (pyrinazamide + para amino salicylic acid)

In India, prevalence of primary MDR-TB in newly diagnosed cases has been observed to be 3.4 percent or less. Data meticulously collected at the Tuberculosis research center (TRC), Chennai over the last three decades suggest that rifampicin resistance started appearing in the early 1990s and MDR-TB levels in newly diagnosed patients has been one percent or less[1, 8.] Mutations occurring in MTB confer resistance to anti tuberculosis drugs. Mutations in rpoB (rifampicin) Kat/G and the ribosomal binding site of inhA (isoniazide) ,gyrA and gryB (ofloxacin) and r/A and rrs (streptomycin) causes resistance to the drugs. In a recent study from India[2]. Patients with HLA-DRB 1*13 and DRB 1*14 were found to have two fold increased risk of developing MDR-TB. Park *et al*[3] found that susceptibility to MDR-TB in Korean patients was strongly associated with HLADRB1*08032-DQB1*0601 haplocytes. The exact role of these factors is not known. It is likely that these loci or the alleles linked with them play a permissive role in conferring increasing susceptibility to the development of MDR-TB.

Factors related to previous antituberculosis treatment

Incomplete and inadequate treatment: Review of published literature strongly suggest that the most powerful predictor of the presence of MDR-TB is a history of treatment of tuberculosis. TB patients in India get treated not only through the Revised National Tuberculosis Control Programme (RNTCP), but also receive treatment from private medical practitioners. Irregular, incomplete, inadequate treatment is the commonest means of acquiring the drug resistant organism. Use of a single drug to treat TB is another cause of MDR TB in the Indian setting. This could have occurred because of ignorance, use of penicillin/streptomycin combination, use of rifampicin for other diseases, and economic constrains. Futhermore, there is a problem of using unreliable combinations with

an appreciable failure rate such as thiacetazone/isoniazid as initial treatment. Another common error in prescription practice is the "addition syndrome", if another drug is added to the existing regimen when the patients appears to deteriorate clinically and if resistance had developed to the drugs in use, adding another drug effectively amounts to monotherapy with the drug. Unreliable drugs with poor bioavailability from unregulated companies may pose a risk (e.g. rifampicin, isoniazid, pyrazinamide combination). The important problem in our country is the bizarre regimen for inadequate periods given by alternate medicine practitioners. OTC availability of antitubercular drugs adds to this. Inadequate treatment compliance: treatment compliance is significantly affected due to change over from fully supervised sanatorium treatment to unsupervised domiciliary treatment. Non compliance is because too many drugs including antacid, multivitamin, heamatinics, etc. are given to the patients. Thus, the physician finds it difficult to identify noncompliance in patients. Considering the changing epidemiological scenario DOTS is presently being advocated by the WHO to be the only effective way to control tuberculosis[4,5,6]. However, DOTS has not been adopted universally and the control programme in several parts of the world is chaotic[7]. In my study of 50 patients of suspected multidrug resistance, resistance to isoniazid and rifampicin alone was seen in 47 and 49 patients respectively. Resistance to all first line drugs was seen in 13 patients. A study to find the trend of drugs resistant Mycobacterium in a tertiary Tuberculosis centre concluded that a significant increase in the isoniazid and streptomycin resistance in the last few years would present a serious challenge to effective management of tuberculosis. To conclude, first line antitubercular drug should be reserved for the treatment of tuberculosis and second line drug especially quinolones should be reserved for management of M.D.R T.B patients.

CONCLUSION

Our study of 50 patients highlights the increasing trends of resistance to various first line anti tuberculosis drugs, and sensitivity pattern of second line drugs. Only one patient (2%) was sensitive to both isoniazid and rifampicin, 98% were resistant to isoniazid and rifampicin, no patient was sensitive to all the first line drugs; and 4% patients were sensitive to a single drug only i.e. cycloserine. This raises the issue of presence of Extreme Drug Resistance and the difficulty in managing such patients in clinical settings in India. There is an urgent need for a proper nationwide survey to evaluate the true picture of resistance and stronger implementation of RNTCP guidelines.

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