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Study of Clinical Profile, Risk Factors, Pattern of Drug Resistance and Treatment Outcome in Previously Treated Patients of Pulmonary Tuberculosis

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Abstract:

Introduction: *Tuberculosis has been a scourge of mankind from times immemorial and still an important public health problem in India and other developing countries. An estimated 3.3% of new cases and 20% of previously treated cases have MDR-TB: these levels sadly have remained unchanged in recent years. In 2014 there were estimated 480,000 new cases of MDR-TB and approximately 190,000 deaths from MDR-TB worldwide.*

Materials and Method: *The sputum smear and culture for Mycobacterium Tuberculosis and drug sensitivity tests were performed in 67 patients who had received anti-TB treatment for more than 4 months as retreatment regimen. The sputum smear was positive for AFB in all the patients, the sputum culture was done by LJ method and the sensitivity to Streptomycin, INH, Rifampicin and Ethambutol was done. The clinical profile, pattern of drug resistance, probable risk factors for development of drug resistance and the treatment outcome was analyzed in the study group.*

Results: *65 patients of drug resistant PTB were included in the final analysis. 94%patients had moderately advanced to far advanced disease on chest radiograph.. Irregular anti-TB treatment was the contributory factor in the development of drug resistant PTB in two thirds of the patients. The resistance to Rifampicin, INH, Streptomycin and Ethambutol was seen in 89.23%, 81.54%, 60% and 46.15 % patients respectively. MDR – TB strains were isolated in 53(81.54%) patients. 24 patients(36.92%) had bacilli resistant to all the 4 first line drugs .The default rate was 27.59% and the cure rate was 59.05% in the study group. The mortality in the study group was 13.85%.*

Conclusions: *The high level of resistance seen to the first line drugs amongst previously treated patients of PTB is a subject of major concern and this study emphasizes the need for a concerted and integrated efforts by physicians to treat the patients with drug sensitive bacilli with all the seriousness it deserves to prevent emergence of resistant TB.*

Keywords *- **Pulmonary Tuberculosis, drug resistance, risk factors, treatment outcome.***

Introduction

World Health Organization declared Tuberculosis(TB) as a global emergency in 1993 because of the epidemic and the urgent need to improve the global TB control.[1] An estimated 3.3% of new cases and 20% of previously treated cases have MDR-TB: these levels sadly have remained unchanged in recent years. In 2014 there were estimated 480,000 new cases of MDR-TB, and approximately 190,000 deaths from MDR-TB worldwide.[2]

Effective therapy of tuberculosis was heralded by discovery of Streptomycin by Waksman in 1944. Soon it became clear that monotherapy with Streptomycin leads to development of resistance to the drug in vivo. MDR-TB has been described as the third epidemic complicating the epidemics of HIV and re-emergence of TB.[3,4] Despite it's global magnitude, the issue of MDR-TB has not been addressed by the nations with the seriousness it required. It is indeed a sad thing to note that TB is a leading cause of death from a curable infectious disease.[5] The study was undertaken in the Department of Pulmonary Medicine, Goa Medical College, Goa, India inorder to analyze the clinical profile, probable risk factors, pattern of drug resistance and treatment outcome in previously treated patients of PTB as there was no similar study in this part of the country.

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Materials and Method

The sputum smear and culture for Mycobacterium Tuberculosis and drug sensitivity tests were performed in 67 patients who had received anti-TB treatment for more than 4 months as retreatment regimen. All these patients had clinical, bacteriological and/or radiological deterioration. The sputum smear was positive for AFB in all the patients, the sputum culture was done by LJ method and the sensitivity to Streptomycin, INH, Rifampicin and Ethambutol was done.

The clinical profile, pattern of drug resistance, probable risk factors for development of drug resistance and the treatment outcome was analyzed in the study group. A detailed investigations included complete blood count, fasting and postprandial blood sugar, liver and renal functions, PA chest radiograph and HIV 1 &2 were done. Since the Line probe Assay (LPA) and CBNAAT tests were not available during the study period, patients were initiated on second line regimen containing Kanamycin, ethionamide, cycloserine, PAS, Ciprofloxacin and PZA for six months of intensive phase and followed by 18 months of continuation phase after omitting Inj. Kanamycin and PZA.

Patients were assessed every three months with a chest radiograph and sputum smear and culture by LJ method. The patient and the close relative was counseled and motivated at the beginning and during the course of the treatment.

STATISTICAL ANALYSIS

Statistical analysis was done with the help of Microsoft office 2007. Mean and percentages were used for the analysis of data.

Observations and Results

Sixty five patients were included in the final analysis in the present study. 58.5% patients were in the age group of 26-45 years; there were 45 males and 20 females with M:F ratio of 2.25:1.93.9% patients were from lower socioeconomic class, 29% were manual labourers and 10% were unemployed at the time of diagnosis. Cough, weight loss, dyspnea and fever were common presenting symptoms. 94% had moderately advanced to far advanced disease on chest radiograph. 36.9% were chronic alcoholic and 27.69% had features suggestive of COPD. (Table 1)

Table 1. The co-morbid condition probably contributing to the development of drug resistance

Co-morbid condition	Number	%
Alcoholism	24	36.92
COPD	18	27.69
Diabetes Mellitus	06	9.23
HIV Seropositivity	02	3.08

The financial constraints (58.46%), alcoholism (36.92%), poor motivation and ignorance and improper drug regimens were the causes of irregular treatment in the past.

53(81.54%) patients harboured bacilli resistant to INH and rifampicin i.e. MDR-TB strains. The pattern of drug resistance is shown in Table 2.

Table 2. The pattern of resistance to individual drugs

Drug	Number	%
Streptomycin	39	60
INH	55	84.92
Rifampicin	58	89.23
Ethambutol	30	46.15

Resistance to more than one drug was seen in 92.31 % cases in the study population, resistance to all the 4 drugs was observed in 36.92%patients (Table.3).

Table 3. Pattern of drug resistance

Resistance to	Number	%
One drug	5	7.69
Two drugs	20	30.77
Three drugs	16	24.62
Four drugs	24	36.92

Gastritis (43%), hepatitis (18.5%) and drug induced rash were the major side effects seen in the patients during the chemotherapy.

There were 9(13.85%) deaths during the study period. 6 patients died within one month of starting of treatment due to severe respiratory insufficiency leading to respiratory failure. The remaining 3 patients died due to acute MI, severe hepatitis and massive haemoptysis respectively. The treatment outcome is shown in Table 4.

Table 4. Treatment outcome

Treatment outcome	Number	%
Cured	35	59.05
Defaulted	16	27.59
Died	09	13.85
Treatment Failure	03	5.17
Relapse	02	3.45

The cure rate in the study group was 59.05% and 27.59% patients defaulted from the treatment despite all efforts to retrieve them by telephonic contacts and also despite regular counseling while they were on treatment.

Discussion

MDR-TB and XDR-TB strains have emerged as important cause of morbidity and mortality in TB patients. The treatment of drug resistant TB is almost 100 times as

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compared to the cost of treating a patient with drug sensitive bacilli, it is also associated with higher incidence of adverse drug reaction.6

Similar to the observations by Nevelli et al7 and Dongrey et al8 the present study noted that there is no difference in the clinical presentation of patients having drug resistant and drug sensitive PTB.

Maximum number of bacilli are present in cavitory lesions. In addition the concentration of the drug in necrotic material inside the cavities is poor. Secondly the number of drug resistant bacilli is directly proportional to the initial bacillary population.9 Hence the risk of developing drug resistant TB is higher in patients having moderately advanced and far advanced disease compared to those patients having minimal disease on chest x-ray. The present study had 55.5% patients moderately advanced to far advanced disease and 89% of them had cavitory disease similar to the findings by Panda et al.10

Irregular treatment is the main cause for development of drug resistance in the developing countries. Friedes et al11found that past history of treatment for TB was strongly associated with increased risk of drug resistance.MDR - TB was detected in 5.8% of new cases and in 20.1% among previously treated patients in a study by Lee et al12 in a Korean tertiary medical centre. History of non compliance to treatment was present in 54% patients with drug resistant TB in a study by Subhash et al13 and in the present study 65% patients had history of prior irregular anti-TB treatment.

Another important cause for development of drug resistant TB is alcoholism. This group is more likely to have poor adherence to treatment due to several reasons. Social problems, financial constraints, joblessness, stoppage of drugs due to adverse reactions like gastritis, hepatitis and lack of self discipline were observed in the alcoholics in our study. Other factors like low standard of living and indifference towards ill health is seen in this group.

When the patient has associated COPD the pill burden is increased, thus increasing the incidence of gastritis leading to interruption in treatment of both conditions. Secondly, there is drug interaction between Rifampicin and theophyllines used for treating COPD, thus leading to poor control of COPD. Thus the patients with associated COPD are likely to be irregular in drug collection as they may be too breathless to leave the house and attend a health care facility. This explains the probable the risk factor i.e. COPD seen in 18 (27.69%) patients in the study group.

A single time-point cross sectional survey carried out by TRC Chennai in a cohort of 3,357 smear positive cases in North Arcot district found the frequency of drug resistance in previously treated patients to be 67% to INH, 12% to Rifampicin and 11% to both INH and Rifampicin14. In a recently conducted study in Bengaluru , the multi-drug resistance in previously treated cases was found to be 12.8% (8.4-17.2%).15 High level of resistance to individual drugs was seen in study by Paramsivan et al 16 in North Arcot District where 81%, 69%, 56.2% and 69% to INH,Rifampicin,Streptomycin and to INH+ Rifa respectively. T.E.Tupasi et al17 noted that 23.4% patients had bacilli resistant to all the four first line drugs. Nagaraja C et al observed that the resistance to all the first line drugs was found in 65.2% patients in a study done at a tertiary care centre and included 224 cases of MDR-PTB patients.18 The present study shows a similar trend with 36.29% harbouring bacilli resistant to all the 4 drugs viz. S,H,R and E.

The treatment of drug resistant TB poses a challenge to the health care worker as the regimen comprises of high pill burden, the adverse drug reactions are seen with higher frequency and the regimen requires the patient to consume drugs daily for 24 to 27 months. Hence the cure and treatment completion rates are lower and high rates of default are observed. The cure rate and default rate was 64.7% and 28.5% respectively in the study done by Nagaraja C. et al.18 The cure rate and the default rates in the present study are on the similar lines i.e. 59.05% and 27.59% respectively.

In U.S.A as a whole nearly 90% of MDR is found among HIV seropositive tuberculosis patients with case fatality of around 70% in four to sixteen weeks time, while case fatality among non-HIV/MDR is as high as 25%.19 The present study had only 2 (3.08%) patients who were HIV positive and could be the reason for low mortality rate (13.85%) in the study group.The patients were strictly followed up and repeated counseling to ensure high compliance also is the reason for low mortality rate.

Conclusions

The high level of resistance seen to the first line drugs amongst previously treated patients of PTB is a subject of major concern and this study emphasizes the need for a concerted and integrated efforts by physicians to treat the patients with drug sensitive bacilli with all the seriousness it deserves to prevent emergence of resistant TB.

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