FREQUENCY OF SECONDARY MULTI DRUG RESISTANCE PULMONARY TUBERCULOSIS IN CATEGORY-II FAILURE PATIENTS

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ABSTRACT

Objective: Multi-drug resistant tuberculosis (MDR TB), defined as resistance of Mycobacterium tuberculosis (MTB) to both isoniazid and rifampicin, is an emerging world health problem. This study was conducted to determine the frequency of secondary multi drug resistance tuberculosis in Category-II (Re-treatment regimen) failure patients.

Materials & Methods: This was cross-sectional descriptive study conducted at Department of Pulmonology, Lady Reading Hospital, Peshawar - Pakistan. Patients of either gender, on category-II pulmonary-TB treatment, with productive cough and fever (>99ºF) and positive Sputum AFB at the end of 5th month were included. Patients on quinolones, smear negative and those who have not used ATT in the past were excluded. Culture and drug sensitivity testing against rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin was done on sputum samples from these patients.

Results: Out of 159 patients, 69 (43.3%) were males and 90 (56.7%) females. Age of patients ranged from 9-70 years with a mean age of 28.87 years (±12.73SD). Mean duration of the Category-II treatment was 26.164 (±2.49 SD) weeks ranging from 20 to 32 weeks.

Among 159 sputum specimens, 122 (76.7 %) were culture positive and 37 (23.3 %) culture negative. 5 specimen grew Non-TB Mycobacteria. Among the MTB culture positive patients, 50 (42.7%) were males and 67(57.3%) females. Among culture negative patients, 17 (45.9%) were males and 20 (54.1%) females. 75(64.15%) patients were MDR among 117 samples. remaining 42(35.9%) didn't fulfill the MDR criteria.

Conclusion: there is high MDR-TB rate of 64.3% in our study. Risk factors were females, young age.

Key Words: MDR-TB, Category-II, sputum culture.

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INTRODUCTION

Tuberculosis is a major cause of morbidity and mortality throughout the world killing 2-3million people every year.[1] More than 90% of these deaths occur in the developing world that includes Pakistan.[2,3] Multi Drug resistant tuberculosis is defined as resistance of Mycobacterium tuberculosis (MTB) to both isoniazid and rifampicin. Primary drug resistance is said to occur in a patient who has never received anti tuberculosis therapy while secondary drug resistance refers to the development of resistance during or following chemotherapy in patients who had previously had drug-susceptible tuberculosis. It may threaten efforts to control TB by reducing the effectiveness of standard short course chemotherapy and by absorbing most of the resources of the natural TB control program.[4]

The prevalence of multi drug resistance tuberculosis (MDR-TB) is low in countries with high success rate. According to WHO estimate, more than 50 million people may be infected with drug resistance tuberculosis and its presence in some countries has reached epidemic levels. Inadequate previous treatment is also responsible for most of the drug resistance. In high burden countries previously treated cases is responsible for 4.4-26.9% resistance.[5]

The prevalence of MDR TB is increasing throughout the world both among new tuberculosis patients and as well as previously treated ones and previous treatment with TB is the strongest risk factor for MDR TB6. Despite the availability of effective chemotherapy, tuberculosis (TB) still remains a major health problem in most of the countries of the world.[7] Drug resistance is a threat to TB control programs worldwide. Patients infected with multiple-drug resistant strains are less likely to become cured, particularly if they are infected by HIV or suffer from another immune disease. The treatment is much more toxic and much more expensive (about 700 times) than the one of patients with sensitive organisms.[8]

In Pakistan the prevalence of MDR TB who has taken Anti tuberculosis treatments in the past accounts for 28%of all TB cases.[9] A definitive diagnosis of MDR TB requires that Mycobacterium tuberculosis be isolated on Culture and drug sensitivity completed. The duration of drug susceptibility testing has decreased from 4 to 6 weeks to 10 to 14 days with liquid media.[10] In high burden countries previously treated cases are responsible for 26.9% resistance.[11] In Pakistan the prevalence of MDR TB who has taken anti tuberculosis treatments in the past accounts for 28% of all TB cases[9]. The aim of this is to determine the frequency of MDR TB in our population.

The rationale behind doing this study is that more reliable estimates of the magnitude of MDR TB will be available locally that would be helpful for planning and expanding the programmatic management of drug resistance TB in a tertiary care hospital within the context of national TB control program.

OPERATIONAL DEFINITION:

CATEGORY II (RE-TREATMENT REGIMEN) TREATMENT:

INTENSIVE PHASE: First two months treatment with five drugs, Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, Streptomycin. Streptomycin is stopped at 3rd month while the remaining drugs are continued for one more month.

CONTINUATION PHASE: five months treatment with three drugs Isoniazid, Rifampicin and Ethambutol.

CATEGORY II (RE-TREATMENT REGIMEN) TREATMENT FAILURE: Patients on Category II treatment with cough and fever and positive sputum AFB and culture at the end of fifth month.

SECONDARY RESISTANCE: Resistance in patients who has taken ATT in the past, suggested by history, treatment registration card or TB control program record.

SECONDARY MDR T.B: Resistance of mycobacterium tuberculosis to at least Isoniazid and Rifampicin confirmed on pure culture and sensitivity, in patients who have already taken ATT in the past, suggested by history, treatment registration card or TB control program record.

MATERIALS AND METHODS

This was cross-sectional descriptive study conducted at Department of Pulmonology, Lady Reading Hospital, Peshawar - Pakistan. A total of 159 patients were included in the study through consecutive, non-probability sampling technique. Sample size was calculated through WHO sample size calculator using 28% prevalence of MDR TB, 95% confidence interval and 7% margin of error. Patients of either gender, on category-II pulmonary-TB treatment, with productive cough and fever (>99ºF) and positive Sputum AFB at the end of 5th month were included in the study. Patients on quinolones, sputum AFB negative and those patients who have not used ATT in the past were excluded.

Informed written consents were taken from all patients included in the study fulfilling the inclusion criteria and presented to pulmonology ward/OPDs of lady reading hospital Peshawar. All patients were admitted in pulmonology ward. Patients were interviewed to obtain bio data, history, physical examination and past treatment record. Sputum was sent for AFB microscopy to the hospital laboratory. Only patients with positive result were included in the study.

Sputum samples were collected in the early morning and in special sterilized container for culture and drug sensitivity testing. All samples were sent to Agha Khan University. Mycobacterial cultures were performed on both liquid as well as solid media. Susceptibility testing was performed using standard agar proportion method. Bias and confounders was controlled by strictly following exclusion criteria.

Statistical analyses were carried out with SPSS-15. Frequency and percentage were calculated for categorical variables like gender, presence of MDR

TB. Continues variable like age were described as Mean±SD. Results are presented as tables and charts.

RESULTS

In this study a total of 159 patients were included. There were 69 (43.3%) males and 90 (56.7%) were females (Table: 1). Age of patients ranged from 9-70 years with a mean age of 28.87 years and standard deviation of ±12.73. Mean age of male patients was 31(±12.70 SD) and that of the female patients was 27(±12.61 SD). (Table 2)

All patients included in the study were taking antituberculous therapy and the Mean duration of the Category II (Re-treatment regimen) treatment at presentation was 26.164 (±2.49 SD) weeks ranging from 20 to 32 weeks.

Out of 159 sputum specimens, 122 (76.7 %) were found to be culture positive and 37 (23.3 %) samples were culture negative. 5 among culture positive specimen grew Mycobacterium Other Than Tuberculosis. (Table-3)

Among the mycobacteria tuberculosis culture positive patients (n=117), 50 (42.7%) were males and 67(57.3%) were females. while among culture negative patients (n=37), 17 (45.9%) were males and 20 (54.1%) were females. (Table-4)

Among 117 tuberculosis cultures positive samples, 75(64.15%) were MDR (Multi Drug Resistant TB) while the other 42(35.9%) culture positive samples were not fulfilling the criteria for MDR i.e. Resistant to both Isoniazid and Rifampicin. Females made 60% (n=45) of MDR population as compared to male. (Table-5)

DISCUSSION

Tuberculosis (TB) is a chronic infectious disease caused by mycobacterium tuberculosis. Almost one third of the world population i.e. approximately two billions peoples are infected with Mycobacterium tuberculosis.[12] The incidence of tuberculosis in Pakistan reported in 2007 was 1.63 million.[13] Pakistan ranks 6th in the world with highest prevalence of

Table 1: Gender wise distribution of Patients (n=159)

Gender	Frequency	Percentage
Male	69	43.4
Female	90	56.6
Total	159	100.0

Table 2: Age-wise distribution of Patients (n=159)

Gender Of Patient	Number	Minimum	Maximum	Mean	Std. Deviation
Male	69	13	70	30.87	12.708
Female	90	9	70	27.33	12.613
Total	159	9	70	28.87	12.736

Table 3: Sputum acid fast Bacilli C/S Result

C/S Result	Frequency	Percent
Positive (MTB)	117	73.6
Negative	37	23.3
Mycobacteria other than tuberculosis	5	3.1
Total	**159**	**100.0**

Table 4: Sputum AFB C/S result and gender of Patient

Sputum AFB C/S result	Male (%)	Female (%)	Total (%)
Positive	50(42.7%)	67(57.3%)	117(100%)
Negative	17 (45.9%)	20 (54.1%)	37(100%)
Total	67(43.5)	87(56.5)	154(100)

Table 5: Drug resistance Pattern

Culture results	Frequency	Percent
Multi Drug Resistance	75	64.15%
Non MDR but Culture Positive	42	35.9%
Total	117	100%

tuberculosis.[14]

Multi-drug resistant tuberculosis (MDR TB), defined as simultaneous resistance of Mycobacterium tuberculosis to both isoniazid and rifampicin, is an emerging worldwide public health problem especially in the developing world. Drug-resistant TB is a purely man-made phenomenon as a result of sub-optimal chemotherapy.[15] Early detection and proper treatment of Mycobacterium tuberculosis are the most effective way of the controlling MDR TB.[16] Local knowledge of the drug susceptibility pattern of Drug Resistant clinical isolates is necessary to design an appropriate treatment regimen, thus preventing treatment failures.[17]

In our study we observed very high levels of resistance in patients already taking Category II (Re-treatment regimen) treatment. The frequency of multi-drug resistance (64.15%) among Mycobacterium tuberculosis. This is much higher than the figures reported by other studies. From Punjab, AFIP, reported MDR TB to be 30.7% in patients treated with category-II anti-tuberculosis regimen.[17] This figure is quite low then our reported proportion of MDR TB (64.15%). This difference is probably due to poor selection of patients, DOTS versus Non-DOTS regimen, health care availability. Similarly Khan J et al.[18] conducted study in Karachi in 1992 observed primary resistance to one or more anti-tuberculosis drugs in 17% and secondary resistance in 36% whereas Muzaffar A et al(Hyderabad) in his study showed primary resistance in 30% and secondary resistance in 70% cases.[19]

MDR TB is an emerging problem across the globe affecting both developing and developed countries. Tajikistan, in its first ever survey, found proportions of 16.5% MDR-TB among new TB cases and 61.6% MDR-TB among previously treated TB patients in Dushanbe city and Rudaki district.[20] China has reported the results of its first ever nation-wide drug resistance survey, with documented proportions of MDR-TB of 5.7% among new cases and 25.6% among those previously treated.[21]

This study also shows that in our population females were particularly at risk for MDR as compared to males. Our results are not in agreement with a previous study from Pakistan and Georgia reporting female gender as a significant risk factor of MDR-TB.[17,22,23] The association between females and MDR is likely to be related to poor access to health care in this group. There are considerable gender differences with regard to stigma related to TB and its social consequences which may result in different health seeking behaviors between males and females; however this area requires further study.[24]

Moreover our study showed that most of the MDR TB patients suffered were young and were in their reproductive stage of life. This higher MDR cases in the age group below 28 years of age is also in agreement with reported findings from other studies and needs to be taken into consideration when planning for MDR programs at a national level.[22, 25]

There was several limitation of this study first: this study included only those patients who were Category II (Re-treatment regimen) failure and cases with relapse, treatment after default and “others” were excluded. Second: the study only concentrated on the frequency of MDR TB and did not inquired about the causes of MDR TB. Third: drug sensitivity testing was performed only for first line ATT. All these limitations are potential area for further active research.

CONCLUSION

Our study reports an MDR rate of 64.3%. It also reports higher risk for MDR amongst women, relatively younger population in individuals with pervious history of tuberculosis. Resistance against Rifampicin and Isoniazid is a matter of great concern as we would be left with only the less effective drugs for treatment of TB.

To ensure optimal utilization of limited resources we strongly advocate that these at risk groups should be a particular focus of DOTS program. The optimal approach would be primary prevention through vaccination, continued surveillance and appropriate therapeutic decisions with monitoring of the patients to help reduce this alarmingly high rate of secondary MDR TB.

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