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Original Article

Factors Responsible for Relapse Among the Cured Tuberculosis Patients and Frequency of Drug Resistance Among Them

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Abstract

Background: Tuberculosis (TB) is considered as one of the major disease responsible for the morbidity and mortality. Pakistan is ranked 5th in terms of disease burden of TB which is very alarming for the worldwide. Patients who are diagnosed with TB gets registered with TB control program for the treatment. Major factors responsible for the rise in TB patients includes delayed or missed diagnosis. We planned to examine and investigate the predictors of relapse TB in patients who had successfully completed the TB treatment amid a unit of sputum smear-positive pulmonary tuberculosis (PTB) patients. Prevalence of drug resistance among these patients was also determined.
Objective: To identify the factors associated with relapse among cured patients under DOTS program and determine the frequency of drug resistance among the relapsed cases of cured TB patients.
Study type settings & duration: This cross sectional, descriptive study was conducted in collaboration with Pakistan Health Research Council (PHRC) TB research center and Institute of Chest Medicine, King Edward Medical University, Mayo Hospital Lahore and PHRC CRC NIH Islamabad from April 2017 to October 2018
Methodology: Two hundred cases of TB were selected for the research purpose who had relapse of TB, and were previously declared as cured for the TB. The cases were subjected to Ziehel Neelsen (ZN) smear microscopy and later on LJ culture. Two sputum specimens from each subject was collected for ZN smear microscopy, GeneXpert and culture for Mycobacterium Tuberculosis (MTB) detection on Lowenstein-Jensen media. Those found positive on culture were then tested for drug susceptibility for first and second line drugs by standard drug proportion method on LJ medium. A semi-structured questionnaire was used to collect the information. Data was analyzed by using the SPSS.
Results: A total of 200 patients of relapse were included in the study and a total of 84 (42%) cured patients were found with relapse. The major factors for the relapse were addiction history 35 (42%), non-adherence to previous treatment 50 (59.5%), co-morbidity with diabetes 22 (26.2%) and hypertension 20 (24.8%). With respect to the frequency of drug resistance Isoniazid and Rifampicin resistance was very high in proportions of 44% and 37% respectively. The Multi-Drug Resistance (MDR) status was found to be positive among 30 (36%) cases of relapse.
Conclusion: TB is a menace that needs to be eradicated. From the study it is fairly concluded that critical factors including addiction, non-adherence, diabetes and hypertension were responsible for relapse of TB. We recommend more studies with larger sample sizes for further evaluation at a larger prospective. Such studies would definitely provide key solutions for TB control agencies in the future.
Key words: Relapse, ziehel neelsen (ZN) smear microscopy, GeneXpert, multi-drug resistance, lowenstein-jensen media.

Introduction

Like other infectious diseases TB is an infectious disease affecting human beings worldwide. As of WHO in 2005 there were more than 8 million cases in the whole world.[1] The South-East Asia Region is a major hub for Tb infections and more than 4 million cases are found in this region.[2] There is high occurrence of TB in Pakistan and, out of the 22 countries with high burden of TB, Pakistan stands 8th on the list. In a study in 2007 approximately 0.3 million cases of TB were reported in Pakistan and prevalence is calculated to be around 181 per 100,000 people.[3,4]

Retreatment TB is carried out after a person previously treated for TB has possibly not completed the treatment or the bacilli is reactivated or the case has again acquired the infection from outside.[5,6] Various studies have been conducted to check the relapse of TB and varying rates with 0% to 14% in one study [7] and 18% in another has been reported.[8] Various extrinsic elements like non-

adherence, and cigarette smoking have been found to be responsible and associated with recurrence occurring after complete treatment and also after default.[8]

A reinfection of TB with the new strain or its relapse with the same strain can account for an episode of retreatment TB. DNA fingerprinting techniques for Mycobacterium tuberculosis can be performed to differentiate between a a relapse of TB or its reinfection.[8,9] It is impossible to clinically distinguish whether it is reactivation or reinfection which lead to retreatment TB in a patient. True treatment failure, exogenous reinfection and endogenous reactivation are the things that are considered to be main factor behind retreatment. The 2004 and 2007 studies performed in United states and Canada revealed some areas where new TB cases were quite low and also relapse was minimal.[10,11] This is contrary to the findings of another study [12] in Houston, USA where the cause of recurrence of TB was a new strain of Mycobacterium TB that caused reinfection.[2]

Another study in high TB prevalent site in South Africa,[13] showed relatively different association of relapse and reinfection. A study on mine workers of South Africa[10] reported that the most common cause of recurrent TB was relapse while in HIV infected patients the highest cause was exogenous reinfection with new M. TB strain. However, former research in South Africa[14] reported that mostly recurrent TB was the consequence of exogenous reinfection and the evidence was provided by using DNA fingerprinting.

Retreatment pulmonary TB exclusively due to non-adherence to treatment with anti-TB drugs has been widely studied, chiefly in high burden TB countries. The common factors accountable for default or failure of TB treatment have been classified as age, gender, marital status (personal)[15,16] alcohol use, income, employment (behavioral and socio-economic),[17,18] health system, co-morbidities, and community.[19]

This study was executed to understand the factors for relapse and subsequently plan new strategies for the control of relapse. The steps taken will help eventually in controlling TB in masses in Pakistan.

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Authors Contribution

AAS conceptualized the project and did the drafting, revision & writing of manuscript. SS did the data collection, Literature search was done by AI. NJ performed the statistical analysis.

Methodology

A total of 200 cases of pulmonary tuberculosis patients were selected randomly from the outpatient department of PHRC TB research center Lahore from April 2017 to October 2018 with unknown Acid Fast Bacilli smear microscopy results but having a history of previously successful Ant TB treatment. Standard questionnaire was designed to interview the cases, after the confirmation of AFB in their sputum on microscopy and culture. The participants were asked about their medical history, household, demographic, & social characteristics. Information was also gathered regarding the BCG vaccination, weight, height, clinical symptoms of TB and co-morbid conditions, if any.

International definitions were used for the outcomes of treatment. Relapse was a case who was again positive for TB after successful treatment with DOTS program and declared cured based on microbiological reports (two sputum samples positive for AFB by direct smear, one smear and one culture positive from separate samples, or two cultures positive).

Selected patients were asked to submit their sputum samples for Sputum smear microscopy. The smears were stained with ZN method using 1% Carbol Fuchsin, 25% sulphuric acid and 0.3% methylene blue. A minimum of 100 oil fields was observed to declare negative smear. Smear was considered positive if it contained at least 3 AFB in observed 100 oil fields for this study. The results were reported according to the WHO/International Union of against Tuberculosis and Lung Diseases (IUATLD) criteria where no AFB per 100 high power field is reported as negative, 1-9 AFB per 100 high power field is reported as actual count per 100 high power field, 10-99 per 100 high power fields is reported as 1+, 1-10 AFB per high power field in at least 50 fields is reported as 2+ and more than 10AFB per high power field in at least 20 fields is reported as 3+.

Petroff's culture procedure was used to culture the sputum samples of the patients. Cultures grown on LJ medium with PH 6.8 were applied to standard drugs including rifampicin (40.0 µg/ml), isoniazid (0.2 µg/ml), streptomycin (4.0 µg/ml), ethambutol (2.0 µg/ml) and, pyrazinamide (100.0 µg/ml).The second line drugs were also used in their respective concentration. The standard proportion method was adopted for the concentrations of the drugs used for culture.

Results

Total 200 tuberculosis patients with confirm relapse of TB were included in the study from Pakistan health research council TB research center Lahore from April 2017 to October 2018. Out of these 200 cases of relapse a total of 84(42.00%) cases were cured tuberculosis patients and they had confirmed relapse of TB.

Most 65 (77.2%) of the study participants were married and 33 (39.3%) illiterate .The demographic characteristics of study subjects are presented in Table-1.

Table 1: Demographic characteristics of cured TB patients.

Character	*Description*	*N*	*%*
Gender	Male	48	57.1
	Female	36	42.8
Marital status	Married	65	77.3
	Unmarried	19	22.6
History of contact	Yes	53	63.0
	No	31	37.0
BCG scar	Yes	79	94.0
	No	3	3.6
Educational status of patients	Illiterate	33	39.2
	Primary	11	13.0
	Middle	11	13.0
	Intermediate	22	26.2
	Graduate	7	8.3

Table 2: Duration of treatment taken during first episode of TB.

Duration of Treatment (Months)	*Cases*	
	N	*%*
6	2	2.4
8	15	17.8
9	6	7.1
12	4	4.7
Many years back	7	8.3

At completion of first episode of treatment 84 (42.0%) had negative sputum smear microscopy and were cleared to be cured for the Tuberculosis but came back with relapse.

Irregular treatment completion during the first episode of TB was found to be one of the factor responsible for the relapse. Total 15 (17.8%) cases had completed 08 months while 6 (7.1%) of the cases were on ATT for 9 months. The details are given in Table-2.

Among Co-morbidities diabetes was found to be a prominent factor where 22 (26.2%) of the diabetic patients had relapse of TB. Hypertension was also found to be associated with relapse as 20 (24.8%) hypertensive patients had relapse. The details are given in Table-3.

Table 3: Co-morbidity status among cured TB patients.

Co-morbidity	*Cases*	*%*
Diabetes	22	26.2
Hepatitis B	10	11.9
Hepatitis C	1	1.2
Hypertension	20	23.8
Heart patient	1	1.2
Kidney disorder	5	5.9
Joint problem	3	3.5
Diabetes + hypertension	7	8.3
Diabetes + kidney disorder	2	2.4
Hypertension + hep B	2	2.4

Drug & tobacco addiction was another found to be associated with the relapse. A total of 35 (41.6%) addicts are found to have a relapse of TB after successful completion of ATT. The details are given in Table-4.

Table 4: Addiction status in relapsed cured TB patients.

	N (%)
Addicts	35 (41.6)
Smokers (Tobacco)	35 (41.6)
Alcohol	7 (20)
Drug	3 (8.5)
Heroine	1 (2.8)
Chars	2 (5.7)

Another important finding of the study intervention was that a total of 72 (86%) had symptoms of TB after ATT but they didn't continue the treatment and came back with relapse.

Our results also showed that 53 (63%) cases had positive history of contact with TB patients, This is the major contributing factor associated with relapse among cured TB patients. Ventilation is another factor associated with relapse. We found out that 15 (18%) cases had no ventilation in their houses. Among these 15 (18%) cases 9 (60%) had positive history of contact with TB patients, and it can be reported that no ventilation and positive history of contact were responsible for majority of the relapse.

We also calculated the frequency of drug resistance among the cases of relapse. Among the LJ culture it was found that 31 (37%) cases of relapse were diagnosed with MDR TB (rifampicin resistance).

All the cases were also subjected to drug sensitivity testing. Our study found out that a very high frequency of drug resistance cases emerged

as cases of relapse. The details of First line drug sensitivity are given in Table-5.

Table 5: First line drug sensitivity results.

First line Drugs	*Sensitive*	*Resistant*
	N (%)	*N (%)*
Rifampicin	53 (63)	31 (37)
Isoniazid	47 (56)	37 (44)
Streptomycin	53 (63)	31 (37)
Ethambutol	73 (87)	11 (13)

Discussion

Endogenous reactivation occurs because of incomplete bacteriological cure, which is typically caused by irregular and uneven medication intake. Extrinsic factors(inappropriate and unsuitable choice of medications, use of regimens with low bactericidal potency, underdoing of the medications, inadequate duration of treatment, overlooking the presence of pre-existing resistance to drugs) could also result in endogenous reactivation.[19,20] Incomplete treatment during first episode of TB was found to be the biggest factor responsible for relapse cases of TB and in our study the ratio was found to be 59.5% which was quite high as compared to an investigated ratio of 1.3%.[21]

Living in overcrowded families was claimed to be a risk factor for relapse TB in a study conducted by Gustafson et al. People living in overcrowded families were reported to be at higher risk of being captured and recaptured by this deadly disease. The risk of TB relapse also increases by 5% due to addition of each adult in the household.[22] In a study by Soomro et al. in 2009, all (100) study participants were living in overcrowded households.[22] In our study, we also found significant ratio of 33 (39%) cured TB patients living in overcrowded families.

Addiction is accounted as an important cause of relapse TB observed during different studies.[22] Our study also found that 42% addicts had relapse of TB and this figure somehow corresponds with the reported ratio of 60% in another study.[22] Santa has shown that cigarette smoking was the reason of an increased likelihood of re-infection.[15] In our study also a great (42%) proportion of smokers were found with relapse in cured TB patients.

In a study, it was reported that intensity of exposure among household contacts and extent of activities that they shared was associated with an increased risk of TB infection.[22] Positive contact history (close friend or a family member) with TB patients was also one of the main finding of our study reported by 63% of cured patients . A period of less than a year was reported in a study by Caminero et al. for the recurrence of TB.[23] While 25.5 months period was noted as the median time interval between the cure of TB and its subsequent diagnosis in a study by van Rie et al.[24] Our study also reported a similar median time interval of 27 months.

Information on drug sensitivity patterns amid relapse TB patients was also reported by the study. There was quite high proportion of resistance seen for primary TB drugs and this reveal a serious lack of attention to this aspect of the TB care process. The proportion of drug resistance to primary TB drugs varied from 16% for Rifampicin to 29% for Isoniazid stated in one study which is quite low from the 37% for rifampicin and 44% for isoniazid noted in our study.[25]

The findings of this study underlines the fact that resistance to any TB drug is significantly more probable in patients with retreatment pulmonary TB. The significance of this study is supported by the potential of the increasing emergence of MDR which is an important and unfortunately serious outcome of retreatment TB.

Hence from the study it can be determined that the relapse is a major factor behind the failure of TB programs. We need to carefully look at the co-morbidities associated with TB patients and monitor and modify the treatment regimens. Furthermore development of drug resistance among the cured cases needs to be controlled through surveillance mechanisms in order to eradicate the TB menace.

Conflict of interest: None declared.

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