Original Research Article

To Evaluate Factors Delaying Sputum Conversion in Smear Positive Pulmonary Tuberculosis Cases On Regimen For New Cases Under Revised National Tuberculosis Control Programme (RNTCP)

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Abstract: TB remains a leading health problem worldwide. About a third of world's population harbours the infection .Sputum smear microscopy for acid-fast bacilli (AFB) is currently the most important and widely available technique for the diagnosis of pulmonary TB in low and middle income countries. RNTCP detects those cases that are epidemiologically most important i.e. those that are most likely to transmit infection to their close contacts. It is also relatively inexpensive, can be accomplished under field conditions, can be done quickly, and is highly specific. Six month long "short-course" chemotherapy is currently the most effective treatment for most patients with tuberculosis, and direct observational therapy, short course (DOTS) helps many patients to complete the 6 month or more treatment regimen. The goal of tuberculosis treatment is to render patients non-infectious, break the chain of transmission and to decrease the pool of infection.
Keywords: TB- Tuberculosis, AFB-Acid Fast Bacilli, RNTCP-Revised National Tuberculosis Control Programme, DOTS-directly observed treatment Short course, SCR- sputum smear conversion rate.

INTRODUCTION

TB remains a leading health problem worldwide [1]. About a third of world's population harbours the infection; this large pool of infected people means that TB will continue to be a major problem in the foreseeable future. One untreated infectious tuberculosis patient is likely to infect 10-15 persons annually [2]. It is transmitted from person to person via droplets from the throat and lungs of people with the active respiratory TB disease. Globally in 2015, there were an estimated 10.4 million incidence cases of TB. It is estimated that about 40% of Indian population is infected with TB bacillus. Tuberculosis causes ill-health in millions of people each year and in 2015 was one of the top 10 causes of death worldwide, ranking above HIV/AIDS as one of the leading causes of death from an infectious disease.

Delay in tuberculosis case finding is a common problem worldwide. Several studies suggest that the delay from onset of first symptom of the disease to diagnosis of the same is unacceptably long. Patients become more contagious as the delay progresses, the longest delays are associated with the highest bacillary numbers on sputum smears. This is despite the fact that with a timely diagnosis and correct treatment, most people who develop TB disease can be cured. The risk for developing TB disease is also higher in persons with HIV, diabetes, other chronic debilitating disease leading to immune-compromise, poor living conditions, tobacco smokers etc.

Sputum smear microscopy for acid-fast bacilli (AFB) is currently the most important and widely available technique for the diagnosis of pulmonary TB in low and middle income countries [3]. RNTCP detects those cases that are epidemiologically most important i.e. those that are most likely to transmit infection to their close contacts. It is also relatively inexpensive, can be accomplished under field conditions, can be done quickly, and is highly specific [4].

Six month long "short-course" chemotherapy is currently the most effective treatment for most patients with tuberculosis, and direct observational therapy, short course (DOTS) helps many patients to complete the 6 month or more treatment regimen [5]. The goal of tuberculosis treatment is to render patients non-infectious, break the chain of transmission and to decrease the pool of infection [6]. As per the RNTCP guidelines, the treatment success of pulmonary TB cases is monitored by follow-up sputum microscopy at every 2 months of treatment. First follow-up sputum examination is performed at the time of completion of the intensive phase (end of 2 months of treatment), followed by final follow-up at the end of the treatment [7].

Conversion to a negative AFB sputum smear allows for assessment of the effectiveness of treatment and determines whether or not the treatment regimen can be switched to the continuation phase. If conversion is not achieved the patient is given an additional one month of intensive phase treatment [8]. When sputum smear positive patients are initiated on multidrug anti tuberculosis treatment, there is a multifold reduction in bacillary load expelled in sputum [9]. Patients, who respond, are likely to become smear and culture negative during the course of treatment. However, viable bacilli continue to be expelled for a period of time, during which they may continue to spread infection.

. According to the RNTCP norms, sputum smear conversion rate is expected to be not less than 90% and the treatment success rate to be more than 85%. Several factors have been identified which cause delayed smear conversion e.g. high initial sputum smear AFB grade, extensive lesions on chest X-Ray, uncontrolled hyperglycemia, old age, male gender, associated co-morbidities, multi drug resistant tuberculosis etc. Identification of factors related to persistent sputum positivity at the end of the intensive treatment phase may inform programs of patient groups that require more vigilant attention to ensure treatment adherence during the intensive phase. Further, understanding the relationship between the interim outcome of failure to convert to a negative AFB sputum smear and final treatment outcomes may provide an indicator of patients more likely to have poor outcomes.

Usually 80-90 % of the patients will under sputum smear conversion within 2-3 months of the treatment [10]. Some studies reported that the number of acid fast bacilli decreases rapidly after starting treatment and that 80-85 % of TB patients become non-infectious after 2 weeks [11-13]. Infection control measures are recommended for all sputum smear-positive patients to minimize the spread of infection. Measures are to be maintained until non infectiousness has been demonstrated. If potential factors associated with the persistent sputum positivity at the end of 2 month therapy are known, they may be helpful in stratifying patients according to risk of adverse outcome.

EXPERIMENTAL SECTION/MATERIAL AND METHODS:

This is an observational prospective study done in the department of Chest and Tuberculosis, Government Medical College, Amritsar. This study was conducted after approval from the institutions ethical committee before the start of study. The study included 200 patients over a period of 18 months. All patients diagnosed with sputum smear positive pulmonary tuberculosis which came to outpatient department or admitted in wards, were initiated on DOTS regimen for new cases registered under RNTCP (Revised National Tuberculosis Control Programme) in tuberculosis unit. Participants who meet the inclusion criteria were recruited after giving information regarding the study in their vernacular language and written informed consent was obtained.

Inclusion criteria:
1. Patients having sputum smear positive pulmonary tuberculosis.
2. Patients initiated on DOTS Regimen for new cases.

Exclusion criteria:
1. Sputum smear negative pulmonary tuberculosis patients.
2. Patients having extra-pulmonary tuberculosis.
3. Patients who are previously treated cases of pulmonary tuberculosis.
4. Drug resistant pulmonary tuberculosis patients.

The patients were explained about the purpose of the study. Those who satisfied the inclusion and exclusion criteria were interviewed and examined. Relevant investigations were performed to reach the diagnosis. Pre- structured performa was filled in all those cases which were included in the study.

The following details were recorded:
1. Detailed personal data was noted.
2. Symptoms: chief complaints were noted (fever, cough, expectoration, loss of weight, loss of appetite etc.) past & relevant personal history (chronic smoker/ history of alcohol intake/ history of any other addiction) was recorded.
3. Physical examination with systemic examination was done.
4. The HIV status and RBS levels of the patients were elicited from the patient's Revised National Tuberculosis

Control Programme treatment card. Chest X-Ray was done for radiological assessment.

Sputum microscopy: Each patient was given a sputum container with the laboratory serial number written on it. It was explained to the patient to rinse his/her mouth with plain water before collecting the sputum sample. Patients were instructed how to open and close the collection device produce good sputum (collecting real sputum, not saliva; deep inhalation and exhalation of breath followed by cough from as deep inside the chest as possible) avoid contamination of the exterior of the container (carefully spitting and closing the container); collect and safely deliver the sputum to the laboratory

The patients were given another labelled container for an early morning sputum sample. All the sputum samples were processed with Fluorescence staining method.

Table-1:Grading of sputum smears

Auramine O fluorescent staining grading (using 20 or 25x objective and 10x eye piece)	GRADING
>100 AFB/field after examination of 20 fields	3+
11-100 AFB/field after examination of 50 fields	2+
1-10 AFB/ field after examination of 100 fields	1+
1-3 AFB/100 fields	SCANTY
No AFB per 100 fields	NEGATIVE

These patients were administered anti-tuberculosis drugs under DOTS regimen according to category I, given intensive phase of intermittent supervised chemotherapy (Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol) for a period of 2 months. If at the end of this period, those who were still sputum positive by direct microscopy, the intensive phase of treatment was extended by 1 more month with same drugs. Those among them, who attained sputum conversion, were switched to a regime compromising Rifampicin and Isoniazid for a further period of 4 months. Dosage used were Isoniazid 600mg, Rifampicin 450mg, Pyrazinamide 1500mg, Ethambutol 1200mg. patients who weighed >60kg received additional Rifampicin of 150mg.

The bacteriological smear grading of the patients at the end of the Intensive Phase was assessed as done at times of initiation of treatment. Sputum conversion is the most suitable indicator to evaluate the treatment response [14]. The Smear Conversion Rate was calculated as per RNTCP guidelines. Sputum smear conversion is the change in the bacteriological status of sputum of patients from initial AFB positive to AFB negative after treatment. Smear Conversion Rate is proportion of number of sputum smear positive patients converted to sputum smear negative at the end of intensive phase out of total number of sputum smear positive patients initiated on treatment. Chi-square test was used for analysing categorical data. Statistical analysis to determine factors that prolong time to conversion was done by univariate analysis and stepwise regression analysis. P value of <0.05 was considered as significant. Any patient unable to complete the required follow up was excluded from data analysis.

$$\text{Sputum conversion rate} = \frac{\text{No. of sputum smear-positive converted to Sputum smear negative at the end of intensive phase}}{\text{Total no. sputum smear positive patients initiated On treatment}} \times 100$$

RESULTS AND DISCUSSION:

Present study was started on 200 sputum smear positive patients. All were started on DOTS Regimen for new cases. 4 patients died during the treatment and another 4 were excluded from the study due to loss to follow up. So further study was carried out on 192 patients. In the present study of smear positive pulmonary tuberculosis cases, 169 patients at the end of 2nd month were smearing negative. Conversion rate was calculated as 84.5%.

Table-2 shows that as the grade of sputum positivity increases, %age of sputum conversion decreases. Patients who were in group I (scanty) positive have 100% conversion at end of 2 months. Patients in group IV have lowest conversion rate i.e. 67.30%. Conversion rate in group II and III was 90.90% & 86.88% respectively.

Table-2: Distribution showing conversion rate in patients according to smear grading at start of treatment & at end of 2 month treatment

Grading of sputum smear	No. of SSP patients at the start of treatment	No. of patients smear negative at the end of 2 months	Sputum conversion rate (%age)
I (Scanty)	21	21	100
II (1+)	66	60	90.90
III (2+)	61	53	86.88
IV (3+)	52	35	67.30
Total	200	169	84.5

CONCLUSION:

The present study was carried out to evaluate factors delaying sputum smear positive pulmonary tuberculosis cases on regimen for new cases of 200 patients in the department of chest and TB, Government Medical College Amritsar. When sputum smear positive patients are initiated on multidrug anti -tuberculosis treatment, there is a multifold reduction in bacillary load expelled in sputum.[9] Patients, who respond, are likely to become smear and culture negative during the course of treatment. However, viable bacilli continue to be expelled for a period of time, during which they may continue to spread infection.

In the present study majority of patients in sputum smear grading positivity were in the group II (+1) 66 (33%) and minimum number were 21 in group I (scanty) (10.5%). Number of patients in group III (2+) was 61 (30.5%) and group IV (3+) were 52 (26.0%). The results of sputum smear positive conversion after 2 months in present study show that grade 1 has 100%, grade II is 90.90%, 86.88% of grade III and 67.30% of grade IV. In our study the overall sputum conversion rate at the end of intensive phase was 84.5%. Comparable with the present study the results of Bawri *et al.;* [15] also reported that out of 100 smear positive pulmonary tuberculosis cases, 84 (84%) patients were having their sputum smear converted at the end of 2nd month.

The present study reported significant association of initial sputum grade 3+ and low sputum conversion at the end of 2 months of follow-up sputum examination. This finding is significant as initial sputum smear grading can be used to identify patients with higher probability of not converting to sputum negative after 2 months of treatment. These results show as the grading increases, the sputum conversion rate decreases. Similarly T. Friedon *et al.;* [10] reported when sputum smear positive patients are initiated on DOTS therapy consisting of Rifampicin, Isoniazid, Pyrazinamide, Ethambutol, there is reduction in bacillary load along with symptomatic as well as radiographic improvement.

Tobacco consumption is an important risk factor for TB. In the present study 63% were smokers and 37% were non-smokers. Sputum smear conversion at the end of 2 months of non-smokers was 90. 9% and 83.1 % of smokers were sputum smear negative at the end of 2 months. In the present study smoking had a significant factor in delaying the sputum smear conversion of the smokers with TB. These results in the present study matched with the study conducted by K. Slama *et al.;* [16] who reported an association of smoking and delayed smear conversion.

In the present study 17% patients were having TB with diabetes. Sputum conversion at the end of 2 months 64.7% as compared to 93.0% in non-diabetics. The difference of findings in our study may be poor control of diabetes, might be the reason for these less number of sputum smear conversion. Another reason can be, treatment of TB in diabetes may pose problems as it has been reported that diabetic patients have some degree of impaired gastrointestinal (GI) drug absorption even in the absence of clinical gastro paresis [17]. Moreover the hyperglycemic state may additionally interfere with achieving adequate tissue levels of the medications, or with alveolar macrophage/CD4+ cell function [18].

In the present study, at the end of 2 months 93.2% with unilateral lesions in the X ray chest were sputum smear negative and only 70.5% patients with bilateral extensive lesions in the X-ray have got their sputum converted to negative at the end of 2 months. In the present study our results indicated that bilateral, extensive and cavitary lesions of radiological involvement are independent risk factors for delayed smear conversion, due to the high baseline bacillary burden of those patients.

The present study was supported by Khalid *et al.;* [19] that factors such as higher pre-treatment smear grading and bilateral radiographic involvement were associated with the delay of smear conversion. In concurrent with the present study Raunak Parikh *et al.;* [20] in an analysis of risk factors also indicated that patients who had a past history of tuberculosis disease, current cavitatory lesions on chest radiograph or a pre-treatment smear grade 3+had significantly delayed smear conversion.

In this study only 7 patients were HIV positive. Results of sputum smear conversion at the end of two months were HIV positive (100 %) and non HIV (87.7%) cases. In the shows the sputum smear conversion at the end of intensive phase of regimen for new cases.

The present study was carried out in the department of Chest and TB, Government Medical College Amritsar to evaluate factors delaying sputum conversion in smear positive pulmonary cases under Revised National Tuberculosis Control Programme. All the patients were put on DOTS regimen for new cases and finally concluded that

1. Majority of patients were males.
2. Majority of patients were those of 1+ sputum smear of grade II.
3. 21(10.5%) patients had sputum for AFB as scanty positive.
4. 61(30.5%) were patients with sputum for AFB 2+ grade III.
5. 52 (26%) patients were patients with sputum for AFB 3+ grade IV.
6. Sputum positivity after 2 months of treatment is high in 2nd -5th decade of age and low in <20 and >60 years age group.
7. Sputum smear conversion was high (90.8%) in females as compared to males (86.6%).
8. Sputum smear conversion was more 120(90.2%) in patients of rural residents. and 49(83.1%) in urban residents which was not significant statistically.
9. Patients who did not have sputum conversion after 2 months, 12(90.9%) cases were having h/o smoking while 11(83.1%) were non-smokers. This was statistically significant (p value= .021)
10. Patients having h/o drug addiction and who were sputum negative at the end of 2 months 75.9% and without h/o drug addiction were 90.2%.
11. Sputum smear negative after 2 months of TB -HIV and TB –NON HIV cases were 100% and 87.7%respectively.
12. Sputum smears conversion after end of 2 months treatment of patients with and without BCG scar mark were 86(85.1%) and 83(91.2%) respectively.
13. Sputum smear negative after 2 months of treatment of alcoholics and non-alcoholics patients were 69(89.6%) and 100 (87.0%) respectively.
14. 13 (29.5%) patients with bilateral extensive or cavitary lesions in the CXR did not have sputum smear conversion at the end of 2 months while other 10(6.8%) patients who did not show smear conversion have earlier unilateral involvement of CXR. This finding was statistically significant (p value 0.001)
15. Sputum smear conversion after end of 2 months treatment of patients of diabetics and non-diabetics were 22(64.7%) and 147(93%) respectively. This is statistically highly significant (p value is 0.000)

In the present study it was observed that increase in the sputum smear grading, diabetes mellitus and smoking and the presence of bilateral extensive involvement and cavitary disease seem to be significant factors associated with a delayed time to sputum smear conversion in patients with active pulmonary tuberculosis. Thus cure and conversion rates were linearly associated with initial smear grading. This finding can be used to identify patients with higher probability of not converting to sputum negative after 2 months of treatment. As observed viable tubercular bacilli continue to be expelled for up to two months, infection control measures should be maintained for such a time. Early diagnosis and intensified treatment and precautions against transmission should be specially considered for TB patients with these risk factors.

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