Comparing Outcomes in New Pulmonary Sputum Positive and Sputum Negative Cases Under RNTCP in Rural India

Abhijit Mukherjee 1, Rupak Singla 2 and Indranil Saha 3

(Received on 2.12.2008; Accepted on 18.6.2009)

Summary
Setting: The study was carried out at the Bagula TU, Nadia, West Bengal, India.
Objective: To find out the treatment outcomes of new smear negative cases, in low HIV prevalence population, and to compare the results with new smear positive cases in the same population.
Design: It was a retrospective record based study. All patients registered between January 1999 and June 2005 were divided into new smear positive and new smear negative groups and the difference in the outcomes analysed.
Results: Favourable outcome was less in new smear negative cases, compared to new smear positive (84% vs. 86%, p=0.002). Death and default were more in new smear negative cases, compared to new smear positive (death: 6.8% vs. 3.7%; default: 6.02% vs. 4.18%), (p < 0.05). Failure and transferred out were non- significantly higher in new smear positive group.
Conclusions: Smear negative patients had a worse treatment outcome compared to smear positive patients including lower favourable outcomes and higher deaths and defaults. The possible reasons need to be explored and corrective actions need to be taken accordingly. [Indian J Tuberc 2009; 56:144-150 ]

Key Words: Tuberculosis, Treatment outcome, RNTCP

INTRODUCTION

Under the RNTCP, new pulmonary tuberculosis patients are classified on the basis of the presence of acid fast bacilli in their smears. The demonstration of AFB in the smear of patients with tuberculosis depends on the presence of $10^4$ bacilli per ml of sputum. Smear negative patients, having a lesser bacterial load in their sputum, are also started on ATD depending on the presence of clinical and radiological evidence of tuberculosis.

During the initial years following the implementation of the Revised National Tuberculosis Control Programme (RNTCP), more stress was given to the areas of sputum positive case finding and cure of 85% of the detected cases. With the success achievement of the initial goals, the time has come to focus on another important sub-group of pulmonary tuberculosis patients, the sputum smear negatives.

Although studies on smear positive tuberculosis are abundant in the literature, there is very little work on smear negative cases in areas with low prevalence of HIV, the areas that are even now more common in India.

The present study was undertaken to find out the different treatment outcomes of new sputum smear negative cases, in a low HIV prevalence population and to compare the results with new sputum smear positive cases in the same population .

MATERIAL AND METHODS

It was a retrospective record based study, carried out at the Bagula Tuberculosis Unit (TU), Nadia, West Bengal. The TU caters to a population of approximately 0.5 million; where most of the people belong to the lower socio-economic status. The Bagula TU has five Designated Microscopy State Tuberculosis Demonstration and Training Centre.

State Tuberculosis Demonstration and Training Centre, Medical College, Kolkata.

1. Medical Officer, State Tuberculosis Demonstration and Training Centre, Medical College, Kolkata.
2. Head, Department of TB & Respiratory Diseases, RRS Institute of TB & Respiratory Diseases, New Delhi.
3. Assistant Professor, Department of Community Medicine, R.G. Kar Medical College & Hospital, Kolkata.

Correspondence: Dr. Abhijit Mukherjee, 34, S.N. Banerjee Road, New Barrackpore, Kolkata-700 131. e-mail: drabijit71@gmail.com.
Tel No. +91 9433187412,
Centres (DMC) manned by five trained laboratory technicians, supervised by a Senior Tuberculosis Laboratory Supervisor (STLS). A total of 2884 patients registered between January 1999 and June 2005 were evaluated for the study. 14 patients with incomplete records were excluded.

Diagnosis, classification and chemotherapy were done and the outcomes following treatment were noted as per the under mentioned RNTCP guidelines¹.

(a) **New**: A patient who has never had treatment for tuberculosis or has taken anti-tuberculosis drugs for less than one month.

(b) **Relapse**: A patient declared cured of TB by a physician, but who reports back to the health service and is found to be bacteriologically positive.

(c) **Failure**: Smear-positive patient who is smear-positive at five months or more after starting treatment. Failure also includes a patient who was initially smear negative but who becomes smear positive during treatment.

(d) **Treatment after default (TAD)**: A patient who received anti-tuberculosis treatment for one month or more from any source and who returns to treatment after having defaulted, i.e., not taken anti-TB drugs consecutively for two months or more.

(e) **Cured**: Initially smear-positive patient who has completed treatment and had negative sputum smear results, on at least two occasions, one of which was at completion of treatment.

(f) **Treatment Completed**: Sputum smear-positive case who has completed treatment, with negative smears at the end of the initial phase but none at the end of treatment.

Or: Sputum smear-negative TB patient who has received a full course of treatment and has not become smear-positive during or at the end of treatment.

(g) **Chronic**: A patient who remains smear-positive after completing a re-treatment regimen.

(h) **Died**: Patient who died during treatment, regardless of cause.

(i) **Default**: A patient who, at any time after registration, has not taken anti-TB drugs for two months or more consecutively.

(j) **Transferred Out**: A patient who has been transferred to another Tuberculosis Unit/District and his/her treatment results are not known.

(k) **Favourable Outcome**: Favourable outcome was defined as cured and treatment completed combined.

(l) **Unfavourable Outcome**: Died, default, failure and chronic cases together are taken together as unfavourable outcome.

Difference between two means and two proportions were tested by student t test and z test for proportion respectively.

**RESULTS**

At first, total patients were divided into two groups i.e. new sputum smear positive and new sputum smear negative. A total of 1458 new smear positive and 1412 new smear negative cases were registered. In both the cases proportion of male patients were more, compared to female. Proportion of males in new smear positive cases were significantly higher (72.8% vs. 67.0%; z=3.37, p < 0.01) than new smear negative cases. Mean age of new smear negative cases was significantly lower than new smear positive cases (39.6 ±17.0 yrs vs. 44.4 ± 18.5 yrs) (Table 1).

Favourable outcome was more in new smear positive cases, compared to new smear negative cases (88.06% vs. 84.13%), that too was statistically significant (p = 0.002). Out of unfavourable outcomes, death and default were more in new smear negative cases, compared to new smear positive (death: 6.8% vs. 3.7%; default: 6.02% vs. 4.18%) and in both the situations the difference was statistically significant (p < 0.05). However, failure and transferred out were non-
Figure: WHO guidelines for the diagnosis of smear negative tuberculosis.

Table 1. Demographic characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>New Smear positive</th>
<th>New Smear Negative</th>
<th>Statistical test value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>44.4± 18.5</td>
<td>39.6± 17.0</td>
<td>7.23*</td>
<td>0.000000 #</td>
</tr>
<tr>
<td>Total cases</td>
<td>1458</td>
<td>1412</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1062 (72.8)</td>
<td>946 (67.0)</td>
<td>3.37**</td>
<td>0.000745 #</td>
</tr>
<tr>
<td>Female</td>
<td>396 (27.2)</td>
<td>466 (33.0)</td>
<td>3.37**</td>
<td>0.000745 #</td>
</tr>
</tbody>
</table>

*student’s t test
** z test for proportion
# Statistically significant
significantly higher in new smear positive group (Table 2).

**DISCUSSION**

Sputum negative pulmonary tuberculosis constitutes about 50% of all new cases of pulmonary tuberculosis. Although the relative transmission rate of smear negative tuberculosis is lower than that of smear positive cases, it is still responsible for 17% of tuberculosis transmission.

In the RNTCP, the diagnosis of smear negative pulmonary tuberculosis rests upon clinical symptoms and the chest X-ray. The RNTCP recommends the screening of patients with symptoms of TB. The symptoms that are used for the screening of these patients are a productive cough for three weeks or more with or without haemoptysis, fever, chest pain, weight loss or night sweats who present on their own initiative at health facilities.

However, these symptoms, although seen in smear positive patients, are not classically present in smear negative PTB. So much so, that the presence of expectoration is considered a negative predictive factor for sputum negative tuberculosis and an alternative diagnosis, for example, bacterial pneumonia, chronic bronchitis or bronchiectasis, is considered. The chest X-ray also, has been conclusively proved to be of little value in the diagnosis of tuberculosis, especially in patients with sputum negative pulmonary tuberculosis.

Patients with sputum negative tuberculosis have a smaller mycobacterial burden and therefore their clinical and radiological manifestations are different from those with smear positive PTB.

The present study shows that the incidence of favourable outcome in cases of smear negative tuberculosis is only 84%, lower than that targeted by the WHO. Sputum positive tuberculosis on the other hand carries a favourable outcome of 88%.

It is generally believed that before the advent of the HIV epidemic smear negative pulmonary tuberculosis was associated with a good prognosis. Since then, there has been an increase in the adverse outcomes in areas with high incidence of HIV. The primary reason for this is an over diagnosis of smear negative pulmonary tuberculosis on the chest radiographs in the presence of other opportunistic HIV related infections. In the reporting unit, although the exact incidence of HIV infection is not known, it is likely to be low since the incidence of HIV in STD clinics in West Bengal is 0.88. The increased incidence of adverse outcome, therefore, is due to factors other than HIV.

**Table 2: Comparison of the outcomes of new smear positive and smear negative cases**

<table>
<thead>
<tr>
<th></th>
<th>New Smear positive</th>
<th>Percentage</th>
<th>New Smear Negative</th>
<th>Percentage</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favourable outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cured</td>
<td>1259</td>
<td>86.35</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment completed</td>
<td>25</td>
<td>1.71</td>
<td>1188</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1284</td>
<td>88.06</td>
<td>1188</td>
<td>84.13</td>
<td>0.002777 #</td>
</tr>
<tr>
<td><strong>Unfavourable Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>54</td>
<td>0.37</td>
<td>96</td>
<td>0.60</td>
<td>0.000272 #</td>
</tr>
<tr>
<td>Failure</td>
<td>36</td>
<td>02.47</td>
<td>21</td>
<td>01.49</td>
<td>0.079940</td>
</tr>
<tr>
<td>Default</td>
<td>61</td>
<td>04.18</td>
<td>85</td>
<td>06.02</td>
<td>0.031326 #</td>
</tr>
<tr>
<td>Transferred Out</td>
<td>23</td>
<td>01.58</td>
<td>22</td>
<td>01.56</td>
<td>0.913690</td>
</tr>
<tr>
<td>Total</td>
<td>174</td>
<td>11.93</td>
<td>224</td>
<td>15.86</td>
<td>0.002777 #</td>
</tr>
</tbody>
</table>

# statistically significant
The decreased incidence of favourable outcome in smear negative cases was seen to be due to the differences in the incidence of defaults and deaths among these groups.

In their study in Pakistan, Kamran Siddiqui et al found that 6.1% patients declared AFB smear negative from a tuberculosis programme laboratory were AFB smear positive when re-examined in a reference laboratory. Increased incidence of failure among smear negative pulmonary tuberculosis could be the result of improper categorization resulting in the prescription of inappropriate drugs. However, further studies to identify causes of failure must be undertaken.

Default is significantly higher in patients with sputum negative PTB. Several socio-economic, demographic, drug and occupational factors, that have been found to be associated with an increased incidence of default from anti-tubercular therapy, are likely to be present equally in both the groups since they belong to the same population. During the initial years of the implementation of the RNTCP, more stress was given to the identification and cure of sputum positive patients. This lack of attention of the tuberculosis programme workers towards the sputum negative group resulted in more defaults. This study includes patients since 1999, when the DOTS programme was initially started in the area.

The present study observed that smear negative patients had significantly higher deaths. Patients with sputum negative PTB, seen in this study, have a significantly lower mean age than the other group and hence a decreased physiological chance of death. The other important reasons for the increased incidence of death in smear negative PTB can be i) prevalence of HIV, ii) delay in the diagnosis of patients in this group and iii) inaccurate diagnosis under operational conditions.

In areas with low incidence of HIV, delay in diagnosis is an important cause of increased incidence of death in patients with smear negative pulmonary tuberculosis. This delay from the appearance of symptoms to the time of diagnosis of the disease can be divided into two intervals. Patient delay defined as the time interval from the appearance of the major pulmonary symptoms of the disease until the first visit to the medical facility and health service delay defined as the time interval from the first consultation until the date of diagnosis. Studies have shown that the mean time interval in the delay in seeking medical attention that is the patient delay is higher in patients with smear negative pulmonary tuberculosis. This suggests that these patients seem to stay at home until they notice an alarming symptom or are grossly incapacitated by the disease.

Radiological facilities under programme conditions are available at the higher centres of treatment, which in most cases are located far from the patients’ residence. Distance from the nearby health care facility has been shown to be linked to the increase in the delay in seeking medical treatment. In the study population access to radiological facilities and often economic constraints of radiological investigations result in the delay in diagnosis of smear negative tuberculosis.

This delay in the diagnosis causes patients to be more seriously ill at the time of presentation. In the current study approximately 25% of patients were seriously ill at the time of diagnosis. Analysis of all deaths in the smear negative group shows that about 35% of patients who died during therapy were seriously ill at the time of presentation.

Diagnosis of smear negative tuberculosis should take at least 15 days under programme conditions, which should be the optimum health service delay. However, in their study in Ethiopia, Demissie M. et al found that 85% of patients were diagnosed in less than 15 days which indicates that the correct diagnostic procedure for the diagnosis of these cases is not being followed. This will result in several false positive cases and an over-diagnosis of smear negative pulmonary tuberculosis.

Bacterial pneumonias are the commonest cause of misdiagnosis on the radiographs and may occur in 14.0 to 41.2 % of cases. Other lung diseases mimicking tuberculosis are interstitial pneumonitis, carcinoma, lymphoma, chronic
obstructive pulmonary diseases, Interstitial lung diseases, occupational lung diseases like silicosis, etc.

The use of clear cut radiological criteria can help in better detection of pulmonary tuberculosis. In their study in Kenya, van Cleeff MR et al\(^8\) has shown that the introduction of a four point scoring system, improved the diagnosis of smear negative cases by reducing over-diagnosis up to 67%, while only 8% fewer culture positive cases would start immediate treatment. In the absence of clear cut radiological criteria under the RNTCP, difficulties in the interpretation of chest radiographs are common.

The training given to the medical students in the undergraduate programmes or the medical officers under the RNTCP is not adequate in the interpretation of radiological reports, especially in the detection of smear negative tuberculosis. Moreover, although the interpretation of the chest radiograph is more difficult than a sputum smear result, quality control is hardly practised.

Follow-up of sputum smear negative patients, at the end of the intensive phase, under the RNTCP is by sputum microscopy. Radiological follow-up at the end of intensive phase will give an opportunity for the re-assessment of the diagnosis, and plan the use of ancillary investigations like sputum culture in patients without significant radiological improvement at the end of the intensive phase.

The limitations of our paper are that we have not done HIV, X-ray, diabetes status, and duration of symptoms analysis as it is not available under programme conditions. A more detailed study incorporating all these would be helpful.

**To conclude, sputum negative tuberculosis constitutes almost half the cases of pulmonary tuberculosis. We believe that delayed presentation, delay in the diagnosis and improper diagnosis under field conditions in smear negative cases are responsible for the decreased incidence of favourable outcome in low HIV areas. We recommend a more intense training of medical students during their undergraduate courses and health service doctors involved in the RNTCP, formulation of clear cut radiological guidelines for the detection of pulmonary tuberculosis, and the establishment of quality control in the interpretation of chest X rays in the diagnosis of smear negative tuberculosis. We also recommend the routine use of chest radiographs along with sputum smear examination at the end of the intensive phase for follow up of smear negative cases.**

**REFERENCES**


