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Sputum smear positivity at two months in previously untreated pulmonary tuberculosis patients

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ABSTRACT

Background and Objectives: In pulmonary tuberculosis, bacteriological status at two months affects subsequent treatment and prognosis. The effect on treatment outcome and risk factors for sputum conversion at two months treatment in previously untreated pulmonary tuberculosis (PTB) patients was studied in the following report.

Methods: A 1:1 case-control study was performed from June 2006 to February 2008 on patients in the Revised National Tuberculosis Control Program in a tertiary level institute in Delhi, India. Patients with previously untreated PTB with sputum smear positive at 2 months of treatment (cases) were compared with those who achieved conversion (controls).

Results: In 74 cases and 74 controls, independent risk factors for sputum smear positive at two months were: illness for >2 months, presence of cavity or extensive disease on chest X-ray, and interruption in intensive phase of treatment. Patients with smear positive at 2 or 3 months of treatment were more likely to fail or default from treatment. Aforesaid factors were also associated with sputum culture positive status at 2 months in univariate analysis. Patients who interrupted treatment ≥ 3 times in the first two months were more likely to be culture positive at two months and had a higher rate of default and failure.

Conclusions: Illness for more than 2 months, presence of cavity or extensive disease on chest X-ray, and interruption in intensive phase of treatment are independent risk factors for sputum smear positivity at two months, which in turn is associated with poor treatment outcomes. Patients with these factors merit special attention under the national program.

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Introduction

In the Revised National Tuberculosis Control Program (RNTCP) of India [Central Tuberculosis Division 2005], new sputum

smear-positive patients with pulmonary tuberculosis (PTB) are treated with a regimen consisting of an initial intensive phase (IP) of 2 months of thrice-weekly isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) followed by

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4 months of thrice-weekly H and R (2[HRZE]₃/4[HR]₃) under the Directly Observed Treatment Short Course Strategy (DOTS). At the end of 2, 4 and 6 months of treatment, two direct sputum smears for acid-fast bacilli (AFB) are performed. In patients who remain smear positive at two months, the intensive phase is extended for one more month after which they are put on continuation phase irrespective of the smear status [1].

The bacteriological status at 2 months is an important milestone in the management of PTB patients. It influences subsequent treatment to be given to the patient [1–3]. Persistent sputum smear positivity at 2 months presages poor outcome, higher rates of treatment failure, and relapse [1,4,5]. Further, patients who harbor multi drug-resistant strains may be more likely to be positive at two months of treatment under DOTS [6].

In intermittent therapy, missing the dose on its due date can challenge the efficacy of the regimen since the increased gap may not be sufficient to sustain the lag period [7]. This interruption in treatment may ultimately lead to failure of a given anti-tuberculosis (ATT) regimen [6,8]. The effect of missing single or multiple ATT doses in the first two months on bacteriological status at two months of treatment was not previously known.

The primary aim of the present study is to study clinical, radiological and bacteriological factors that may be associated with sputum smear positivity at the end of two months of treatment under RNTCP. The influence of interruption of treatment on sputum positivity at two months and on treatment outcome was also analyzed.

Materials and methods

A 1:1, case-control study was performed from June 2006 to February 2008 on patients enrolled in the RNTCP in Lala Ram Sarup Institute of Tuberculosis and Respiratory Diseases, a tertiary level national TB institute in South Delhi, India. The study was reviewed and approved by the ethics and research committee of the Institute. The study group consisted of new sputum AFB smear-positive PTB patients started on treatment under RNTCP. The patients were enrolled in the study at the end of the initial two months of treatment.

The 'cases' were comprised of patients whose sputum direct smear was positive for AFB after 2 months of treatment. Sputum was examined and graded per RNTCP guidelines as: scanty, 1+, 2+, 3+ or negative [1]. The 'controls' were comprised of patients whose sputum direct smear was negative after two months of treatment. The control group was matched by age and sex. As far as possible, the controls were selected from the same DOTS center and within a month of the date of registration of the cases. The cases and controls were followed-up until treatment completion, and treatment outcome was recorded. Informed consent was obtained and a standardized Performa was filled out.

The data regarding the duration of illness prior to starting treatment; tobacco smoking, alcohol intake, socioeconomic status [9], associated diabetes mellitus (DM), body mass index (BMI), human immune-deficiency virus (HIV) status and radiological extent of disease at enrollment were collected.

If any dose of ATT was missed in the intensive phase, it was counted as 'treatment interrupted'. In RNTCP, these doses are subsequently given and the total number of doses in the regimen is completed. The patients were advised to provide two sputa (spot and early morning), which were stained by Ziehl Nelson method for AFB and also cultured for *Mycobacterium tuberculosis* on Lowenstein-Jensen medium. Positive cultures were subjected to drug susceptibility testing (DST) by using the absolute concentration method. The minimum inhibitory concentration (MIC) of the drugs used was as follows: SM 16 µg/ml, INH 0.4 µg/ml, RMP 128 µg/ml and EMB 8 µg/ml.

The data for radiological extent of disease was collected in the categories mentioned by NTA [10], but for data analysis, the category 'far advanced' was compared with the aggregation of 'less advanced' and 'minimal' category, termed as 'less advanced' in this study. Similarly, data for initial sputum grade was collected as per RNTCP definitions [1], but, for analysis, sputum grade 3+ was compared with the aggregate of '2+, 1+ and scanty' termed as 'non-3+'.

Data was analyzed in SPSS version 12.0 (SPSS Inc., Chicago, IL). For parametric data – t test for independent samples and Analysis of Variance; for nominal data – Pearson's chi square test or fisher's exact test was used. For hypothesis testing, a probability of 0.05 was considered significant. Those variables which were significant on univariate analysis were tested for independent association using binary logistic regression.

Results

In the study period, data from 74 cases and 74 controls was obtained. Table 1 shows the clinical, bacteriological and radiological profile of cases and controls. On univariate analysis (Table 1), it was found that patients who were smear positive at two months did not differ significantly with respect to age, sex, associated DM or HIV, smoking and alcohol use from those who were smear negative at two months. The patients who were smear positive at two months were significantly more likely to have been ill for more than 2 months, to have lower BMI, to have cavity and far-advanced disease on chest X-ray, to have initial sputum smear grade 3+, and to be an interrupter than the controls.

On binary logistic regression (Table 2), it was found that more than 2 months' duration of illness, cavity on chest X-ray, far advanced disease radiologically, and occasional and frequent interruption were the risk factors independently associated with being smear positive at 2 months of treatment. However, low body mass index and initial sputum grade were not independent risk factors (not shown in Table 2).

The culture and DST results of 74 smear positive cases at two months are shown in Fig. 1. Among them, culture was positive in 30 (40.5%) patients; 7 had MDR-TB; 9 were pan-sensitive; and 9 had non-MDR-TB. In two patients the culture was contaminated. In five culture positive patients the DST was contaminated.

The culture positivity among smear positive patients represents the presence of live bacilli. On univariate analysis of a total of 148 cases and controls, it was observed that all the factors associated with smear positivity at two months

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