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Association of conversion & cure with initial smear grading among new smear positive pulmonary tuberculosis patients treated with Category I regimen

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***Background & objective*: Early diagnosis of tuberculosis (TB) is important for initiating treatment to gain cure. The present investigation was undertaken to study the association of conversion and cure with initial smear grading among pulmonary tuberculosis (TB) patients registered in a directly observed treatment – short course (DOTS) programme in Tiruvallur district, south India.**

***Methods*: All new smear positive cases registered from May, 1999 to December, 2002 were analysed for conversion and cure related to initial smear grading.**

***Results*: Of the 1463 patients, 1206(82.4%) were converted at the end of the intensive phase and 1109 (75.8%) were declared 'cured' after the completion of treatment. The cure rate decreased as the initial smear grading increased and the decrease in trend was statistically significant (*P*=0.01). Similarly, a significant decrease in conversion rate was also observed with increase in initial smear grading (*P*<0.001). In multivariate analysis, lower cure rate was significantly associated with patient's age (AOR=1.5, 95% CI=1.1-2.1), alcoholism (AOR=1.7, 95% CI 1.2-2.4) and conversion at the end of intensive phase (AOR=3.5, 95% CI= 2.6-4.8).**

***Interpretation & conclusion*: Cure and conversion rates were linearly associated with initial smear grading. High default and death rates were responsible for low cure and conversion. The proportion of patients who required extension of treatment and those who had an unfavourable treatment outcome were significantly higher among patients with a 3+ initial smear grading. This reiterates the need to pay more attention in motivating these patients to return to regular treatment and sustained commitment in the control of tuberculosis. There is a need to extend the treatment for one more month in the intensive phase of treatment.**

Key words Cure - default - DOTS - smear grading - tuberculosis

The Revised National Tuberculosis Control Programme (RNTCP) based on the World Health Organization's DOTS (directly observed treatment-short course) strategy was introduced in India in 1993. The goal of DOTS, which has emerged as the most cost-effective strategy and developed based on scientific evidence, is to cure at least 85 per cent new smear-positive cases and to detect at least 70 per cent of new smear-positive cases in the population. Patients diagnosed with

tuberculosis are treated under DOTS in accordance with the RNTCP guidelines[1]. Diagnosis of pulmonary tuberculosis is based on three sputum examination by smear microscopy in accordance with the guidelines[2,3]. Early diagnosis of TB and initiating treatment under DOTS would not only enable the patients to get cured but also reduce the transmission of infection and disease to others.

In RNTCP, the sputum smears are graded and reported based on the bacillary load. The present study was carried out on new smear-positive pulmonary tuberculosis cases treated with category I regimen under RNTCP in Tiruvallur district, south India, to find the association of conversion and cure related to smear grading at the start of treatment, and to examine other factors like sex, age, habit on smoking and alcoholism, patient delay, conversation rate, smear grade on admission *etc*. influencing the patient's treatment outcome 'cure' at the end of treatment.

Material & Methods

Study population, diagnostic algorithm and treatment regimens: The DOTS strategy was implemented in a rural population of 580,000 in Tiruvallur district, south India in May, 1999 and is being monitored by Tuberculosis Research Centre (TRC), Chennai. The area covered by 209 villages and 9 town blocks has 17 peripheral health institutions (PHI), of which seven have smear microscopy facilities.

The investigation was based on two types of patients – health facility and community survey. Patients reporting at one of the PHIs with symptoms suggestive of TB were diagnosed based on three sputum examinations. All patients diagnosed were given directly observed treatment as per RNTCP guidelines[1]. Patients detected by sputum examination based on symptom elicitation and chest X-ray in an ongoing epidemiological disease survey (community survey) in the same area were also referred for treatment if they satisfied the definition of a case as per RNTCP guidelines. The community survey was carried out to assess the epidemiological impact of DOTS implemented in this area. In community survey, case detection is early compared to passive case detection at health facility. So, cases detected in community would have reported voluntarily at health facilities for diagnosis, and cases detected by these methods can be merged. The anti- tuberculosis regimens used for category I, II, and III patients were $2H_3R_3Z_3E_3/4H_3R_3$, $2H_3R_3Z_3E_3S_3/1H_3R_3Z_3E_3/5H_3R_3E_3$ and $2H_3R_3Z_3/4H_3R_3$, respectively. (H= isoniazid; R= rifampicin; Z= pyrazinamide; E= ethambutol; S= streptomycin. Numbers before the letters indicate the duration of the treatment phase in months and numbers in subscript indicate the number of times the drug is given each week). Intensive phase (IP) treatment for category I and II patients was extended by another month if the sputum smear remained positive at the end of IP. The treatment was under observation for every dose in the IP and at least the first of the three doses of every week during continuation phase (CP). All category I patients registered from May, 1999 to December, 2002 formed the study population.

Procedure for sputum microscopy: When patients with chest symptoms suggestive of TB reported at the health facility, three specimens were collected by spot-morning-spot technique as per the procedures described elsewhere[4]. Direct smears were made immediately after sputum collection and read for acid fast bacilli (AFB) using Ziehl-Neelsen (ZN) technique[5]. In cases of discordant results, the highest smear grading was taken as per RNTCP guidelines. The smear readings were graded as negative (no AFB in 100 oil immersion fields), scanty (1 to 9 AFB in 100 oil immersion fields), 1+ (10 to 99 AFB in 100 oil immersion fields), 2+ (1 to 10 bacilli per oil immersion field in at least 50 fields) and 3+ (more than 10 AFB per oil immersion field in at least 20 fields).

Utmost care was taken to obtain three good quality specimens. The quality of the specimens

was also recorded in the relevant records. Quality assurances were followed to ensure the quality of sputum microscopy. This was done by a senior tuberculosis laboratory supervisor (STLS) who checked all positive slides and a 10-20 per cent random sample of negative slides in an unblinded fashion. In addition, another 10 per cent random sample of positive as well as negative slides was rechecked in a blinded fashion at TRC[6]. The quality assurance method adopted during the cohort period ensured the quality of sputum AFB microscopy.

Culture of Mycobacterium tuberculosis: Two samples of sputum specimen were collected from each patient immediately after diagnosis or within a week of starting treatment and transported these specimens in cetylpyridinium chloride (CPC) solution to the central laboratory for culture examination and susceptibility test to assess the drug sensitivity profile. The delay between the collection and processing of the specimen varied from 7 to 10 days. The isolated cultures were confirmed for *M. tuberculosis* by a Niacin test, a 68^0 C catalase test and growth on para-nitrobenzoic acid[7]. All the cultures were processed and confirmed independently. The culture results were graded as follows: colonies = 1 to 19 colonies, 1+ = 20 or more but less than 100 colonies, 2+ = innumerable colonies and 3+ = confluent growth.

Definitions: Standard international definitions[8] were followed to classify TB patients according to category and outcome as follows:

(i) Case— A case of category I patient is the one whose smear is positive on at least two sputum specimens and had no previous history of treatment of more than a month or one smear positive and chest X-ray abnormal suggestive of tuberculosis.

(ii) Conversion— A smear-positive patient is said to be 'converted' if his/her sputum collected and examined at the end of the intensive phase (or at the end of intensive extension phase) found to be smear negative.

(iii) Cure— A patient is declared 'cured' if his/her sputum smear is positive initially, completed treatment and had negative sputum smears, on at least two occasions, one of which was at the end of treatment.

(iv) Default— A patient is said to have defaulted if he/she discontinued taking anti-TB treatment for two months or more consecutively.

(v) Failure— A smear-positive case who is smear-positive at 5 months or more after starting the treatment or who was initially smear-negative but became smear-positive during treatment is a 'failure' case.

Data collection and statistical analysis: The data on the smear grading at the start of the treatment and at the end of the intensive phase of the treatment, and the treatment outcomes of the patients were collected from the Tuberculosis Register maintained in the Tuberculosis Unit (TU) of the study area. These patients were visited by trained health workers at the health facility or their residence to collect the socio-demographic profile, duration of symptoms, care seeking behaviour and treatment details using a structured questionnaire. Also, data on personal habits like smoking and alcoholism were collected. Informed consent was obtained from all patients included in the study. The data after scrutiny were computerized and edited incorporating all corrections. Statistical analysis and test of significance such as Chi-square and trend Chi-square were undertaken using Epi-Info version 6.04d (Centers for Disease Control, Atlanta, GA). $P<0.05$ was considered to be statistically significant for interpretation of the results. Crude odds ratio (OR) and 95 per cent confidence interval (C.I.) were used for the interpretation of factors analysed using univariate method. Logistic regression analysis was performed using SPSS/PC+, Version 4.0 (SPSS Inc, Chicago, IL, 1990) to find out the independent risk factors and adjusted odds ratio (AOR). The criterion

for inclusion of variables in the multivariate model was set at $P \leq 0.1$.

Results

Of the 1463 patients, 1206 (82.4%) became negative on smear microscopy at two months of the intensive phase of treatment or at three months in case of extension of treatment for another month (Table I). The conversion rate decreased as the smear grading increased and the decrease in trend was statistically significant (Trend Chi-square = 33.1; $P < 0.001$). Significantly more patients (13.2%; 64 of 484) remained smear positive at 3 months among those with a higher smear grading than that among patients with a lower smear grading (5.3%; 52 of 979) (Chi-square: 26.7 ; $P < 0.001$).

Table I. Smear and conversion of new smear positive patients registered in a DOTS programme from May, 1999 to December, 2002 in Tiruvallur district, south India

Initial grading	No. of patients	No. converted (%)
Scanty	43	40(93.0)
1+	562	486(86.5)
2+	374	325(86.9)
3+	484	355(73.3)
Total	1463*	1206(82.4)

* 141 patients from whom sputum was not collected due to default or death by the end of intensive phase were also included in the denominator for estimation of conversion as per the RNTCP policy.

Of the 1463 patients put on treatment, sputum was not examined for 99 (41% with 3+ smear grading) patients due to default or death by the end of two months of treatment. The remaining 1364 patients were subjected to smear examination and 354 (26.0%) patients remained smear positive at 2 months requiring extension for an additional month. Among those with positive smear at 2 months, 182 (41.1%) of the 443 patients had a high (3+) smear grading compared to 172 (18.7%) of 921 patients with a lower (scanty or 1+ or 2+) smear grading and the difference was statistically significant (Chi-square = 77.0; $P < 0.001$). This showed that more patients with a higher smear grading required extension of treatment compared to that with a lower grading.

Of the 1463 patients, 1109 (75.8%) patients were declared cured (Table II). It is observed that the cure rate decreased as the grading of the smear result increased and the decrease in trend was statistically significant (Trend Chi-square = 6.1; $P = 0.01$).

The distribution of cured patients for various factors is shown in Table III. Univariate analysis demonstrated that the proportion of patients cured was significantly lower among older patients ($\geq$45 yr), males, smokers, alcoholics, illiterates, those who had cough for 4 wk, those with 3+ smear grading and those who did not convert at the end of IP of treatment. In multivariate analysis, older

Table II. Treatment outcome among new smear-positive patients registered for treatment in a DOTS programme from May, 1999 to December, 2002 in Tiruvallur district, south India

Smear grading	Treatment outcome					
	Cured (%)	Defaulted	Expired	Failed	Others	Total
Scanty	38 (88.4)	5	-	-	-	43
1+	432 (76.8)	82	18	28	2	562
2+	292 (78.1)	44	13	21	4	374
3+	347 (71.7)	81	27	25	4	484
Total	1109 (75.8)	212	58	74	10	1463

Table III. Risk factors for cure among new smear positive patients registered for treatment in a DOTS programme from May, 1999 to December, 2002 in Tiruvallur, south India

Risk factor		No.	Cure (%)	OR (95%C.I.)	*P* value	AOR (95%C.I.)
Age	≥45 yr	699	490 (70.1)			
	<45	764	619 (81.0)	1.8 (1.4-2.3)	<0.001	1.5 *(1.1-2.1)
Sex	Male	1125	817 (72.6)			
	Female	338	292 (86.4)	2.4 (1.7-3.4)	<0.001	1.4 (0.9-2.3)
Education	Illiterate	599	488 (74.8)			
	Literate	766	611 (79.8)	1.3 (1.0-1.7)	<0.05	1.2 (0.8-1.6)
Smoking	No	708	599 (84.6)	2.4 (1.8-3.1)	<0.001	1.1 (0.8-1.7)
	Yes	659	461(70.0)			
Alcoholism	No	849	716 (84.3)	2.7 (2.1-3.6)	<0.001	1.7*(1.2-2.4)
	Yes	519	345 (66.5)			
Cough	<4 wk	383	317 (82.8)	1.6 (1.1-2.1)	<0.01	1.3 (0.9-1.9)
	≥4 wk	983	742 (75.5)			
Patient delay	<4 wk	901	708 (78.6)			
	≥4 wk	439	334 (76.1)	1.2 (0.9-1.5)	0.3	-
Body weight	> 40 kg	648	499 (77.0)			
	≤ 40 kg	632	466 (73.7)	1.2 (0.9-1.6)	0.2	-
Diagnosis	Com. survey	296	217 (73.3)			
	Health facility	1167	892 (76.4)	1.2 (0.9-1.6)	0.3	-
Smear grade	Low	979	762 (77.8)	1.4 (1.1-1.8)	<0.01	1.1 (0.8-1.5)
	High	484	347 (71.7)			
Conversion	Yes	1010	885 (87.6)	4.1 (3.1-5.5)	<0.001	3.5*(2.6-4.8)
	No	354	224 (63.3)			

* Statistically significant

patients, alcoholics and those who did not convert were more likely to have a less cure rate.

Culture results were available for 1387 of 1463 patients. The association between smear and culture grading is shown in Table IV. There was a linear association between the extent of smear grading and positive cultures (Trend Chi-square= 83.6; *P*<0.001).

Among the 1387 patients, 158 were culture negative and 3 were found to be contaminated on susceptibility test. Of the remaining 1226 patients for whom drug sensitivity results were available, 1094 (89.2%) had sensitive organism to izoniazid (H) and rifampicin (R), 111(9.1%) had resistant organism to H alone, 5 (0.4%) had resistant organism to R alone and 16 (1.3%) had multi-drug resistant (MDR-TB) organisms to H and R.

Table IV. Smear and culture gradings of patients registered for treatment in a DOTS programme from May, 1999 to December, 2002 in Tiruvallur, south India

Smear	Culture						Total
	Negative	Colonies	1+	2+	3+	NC*	
Scanty	23	7	6	3	0	4	43
1+	89	117	137	154	42	23	562
2+	27	51	72	145	56	23	374
3+	19	37	86	208	108	26	484
Total	158	212	301	510	206	76	1463

* NC- sputum not collected

However, no difference in the proportions between patients with low and high grades was found (data not shown).

Discussion

Our study shows that conversion and cure rates were associated with the smear grading of the patients at the time of start of treatment. Both the rates decreased as the grading increased and the trend was statistically significant. Smear positivity depends on the extent of lesion or the presence of cavitations and the smear grading is associated with the infectiousness of the case[9]. Smear positive cases are infectious cases transmitting the infection and disease to others especially those who are close contacts[10]. In our study, the conversion and the cure rates of the patients were 82 and 76 per cent respectively which were lower than the national average[1]. The defaulter rate was as high as 14.5 per cent compared to expected level of 5 per cent or less in RNTCP. A study[11] from a cohort of all patients from the same area has shown a default rate as high as 19 per cent of which nearly three-fourths did so by the end of the intensive phase, a period during which the symptoms usually declines. In that study, a higher default rate was reported to be associated with irregular drug intake, being male, having a history of previous treatment, being alcoholic and being diagnosed by community survey. It is observed that there was an annual decline of 12 per cent in the default rate over a four year period (data not shown) and it is an indication that the performance of the programme has improved. The death and the failure rates were 4.0 and 5.1 per cent respectively.

More patients with a higher smear grading had extension of one month's treatment in the intensive phase compared to those with a lower smear grading. In a similar study[12] conducted by the New Delhi Tuberculosis Centre to assess the importance of initial smear grading as a predictor of treatment outcome revealed that a larger proportion of previously untreated sputum positive patients with 3+ grading required extension of intensive phase. In addition to the above findings, we have observed that there was a linear association between smear grading and positive cultures. The proportion of culture positives among patients with scanty positives was 41 per cent only. The culture examination was done on using different samples collected from the same patients. The delay between collection and processing of these specimens for culture varied from 7 to 10 days. This might have contributed to the observed difference in the proportion of culture positives. The association between the smear microscopy by fluorescent technique and cultures

based on the same specimen showed that great majority (94%) of the smear positives were culture positives (data not shown).

A study[11] on an earlier cohort of patients from the same area has reported that high rate of default and deaths were responsible for low cure rates and found various risk factors for unfavourable treatment outcomes like default, failure and death of tuberculosis patients treated under the DOTS programme and recommended various measures to improve the programme performance. Among patients with a higher smear grading, the proportion of patients whose smear had not converted, was not only higher at two months of treatment but also at 3 months. We have further analyzed the data to identify other factors associated with cure rate of patients. Another important finding was that patients reported at health facilities with symptoms suggestive of tuberculosis and diagnosed were with high grades of smear compared to those identified through community survey (data not shown). This supports the findings of an earlier study[13] comparing the results of patients detected at health facility with those by community survey. Patients identified at the health facilities are more likely to be infectious due to the reason that they voluntarily report late after the onset of symptoms suggestive of tuberculosis. The need for early diagnosis after onset of symptoms should be popularized in the community. Since the inception of DOTS strategy in the area, health education programme through information, education and communication (IEC) has been ongoing to motivate symptomatic patients to report earlier for diagnosis. The awareness about tuberculosis and the need for early diagnosis and regular treatment is now on the increase in the area.

In conclusion, our findings showed that among patients with severe disease in terms of higher smear grade, the conversion and cure rates were lower compared to other patients and more had unfavourable treatment outcomes in terms of higher default and death. The smear grading that exists in RNTCP is to be viewed further in lieu of the above observations and necessitates more attention on patients with higher smear grading to motivate, counsel and ask them to come for treatment with sustained commitment in the control of tuberculosis. For these patients, there is a need to extend the treatment for one more month in the IP of treatment

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