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Predictors of relapse among pulmonary tuberculosis patients treated in a DOTS programme in South India

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SUMMARY

OBJECTIVE: To identify risk factors associated with relapse among cured tuberculosis (TB) patients in a DOTS programme in South India.

DESIGN: Sputum samples collected from a cohort of TB patients registered between April 2000 and December 2001 were examined by fluorescence microscopy for acid-fast bacilli and by culture for *Mycobacterium tuberculosis* at 6, 12 and 18 months after treatment completion.

RESULTS: Of the 534 cured patients, 503 (94%) were followed up for 18 months after treatment completion. Of these, 62 (12%) relapsed during the 18-month period; 48 (77%) of the 62 relapses occurred during the first 6 months of follow-up. Patients who took treatment irregularly were twice more likely to have a relapse than adherent patients (20% vs. 9%; adjusted odds ratio [aOR] 2.5; 95%CI 1.4–4.6). Other independent predictors of relapse were initial drug resistance to isoniazid and/or rifampicin (aOR 4.8; 95%CI 2.0–11.6) and smoking (aOR 3.1; 95%CI 1.6–6.0). The relapse rate among non-smoking, treatment adherent patients with drug-sensitive organisms was 4.8%.

CONCLUSIONS: The relapse rate under the DOTS programme may be reduced by ensuring that patients take their treatment regularly and are counselled effectively about quitting smoking.

KEY WORDS: tuberculosis; DOTS; India; relapse

IN THE REVISED National Tuberculosis Control Programme (RNTCP) of India, based on the DOTS strategy, patients are treated with an intermittent short-course regimen with drugs administered thrice weekly on alternate days.[1] The treatment consists of an initial 2-month intensive phase of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E), followed by a 4-month continuation phase of RH.[1] Under controlled clinical trial conditions, similar short-course treatment regimens have been found to be highly successful, with reported end-of-treatment cure rates of 95–100% and relapse rates of 3–8% over a 2-year follow-up period.[2]

The RNTCP has been remarkably successful and has achieved high cure rates of 80–85% nationally.[3] However, the relapse rate, which is also an important indicator of the success of any treatment regimen, has not been measured under programme conditions. We undertook a study in a newly introduced DOTS programme in South India to examine the rate of relapse and predictors of relapse among a cohort of sputum smear-positive pulmonary tuberculosis (PTB) patients who successfully completed treatment.

MATERIALS AND METHODS

Study design

This was a prospective study to measure the rate of relapse among patients who successfully completed treatment and were declared cured under the programme, and to identify the risk factors for relapse.

Study area and population

The study was conducted in Tiruvallur District, Tamil Nadu State in South India, where DOTS was implemented in mid 1999. Under the DOTS strategy, TB cases are detected at 17 governmental health centres where symptomatic patients are screened by examination of three sputum smears for acid-fast bacilli (AFB).

The study population was a cohort of new smear-positive PTB patients registered for DOTS between April 2000 and December 2001. All patients were treated with the $2H_3R_3Z_3E_3/4H_3R_3$ regimen.*[1] Of a

* Numbers in subscript indicate the number of times the drug is taken each week.

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total of 715 patients registered for treatment, 534 (75%) were declared cured, 114 (16%) defaulted, 29 (4%) died and 31 (4%) failed their treatment. For six (1%) patients the end-of-treatment sputum result was not available and they were considered as treatment completed. Only patients declared as cured were considered eligible for participation in the study.

Data collection

Field workers visited study subjects at their residence and collected one sputum sample from each patient at three time points during follow-up: 1) at 6 months from 480/510 (94%), 2) at 12 months from 423/456 (93%), and 3) at 18 months from 405/437 (93%). The sputum samples were transported to the Tuberculosis Research Centre (TRC), Chennai, Tamil Nadu, for AFB smear microscopy by fluorescence technique[4] and culture for *Mycobacterium tuberculosis* on Löwenstein-Jensen (LJ) medium.[5] Cultures positive for *M. tuberculosis* were subjected to drug susceptibility testing for H and R.[6]

A second sputum sample was collected from patients whose sputum was reported to be positive for AFB by smear. If the second sputum smear was negative we waited for the results of culture. If the culture was positive on either of the specimens, the patient was declared as relapsed. In addition, for quality check, a second specimen was collected from 10% randomly selected patients whose first sputum was reported to be negative to determine if any positive case was likely to be missed if only one sputum specimen was collected. This was in addition to the specimens collected on three occasions, i.e., at 6, 12 and 18 months after completion of treatment. Of the second sputum specimens collected for quality control assessment from 147/152 (97%) randomly sampled patients (who were negative on the first smear), only one was smear-positive, but this specimen was negative on culture.

Data for evaluating risk factors associated with relapse were collected from several sources. The patient's age, sex, initial smear grade, end of intensive phase sputum conversion and end-of-treatment outcome were obtained from the TB Register. Drug regularity was calculated from the patient treatment cards. Information on sputum culture and drug susceptibility was obtained from the TRC laboratory records. In addition, trained health workers interviewed patients within a week of starting treatment using a pre-coded interview schedule to elicit information on their socio-demographic profile and personal habits, such as smoking and drinking.

Case definitions

Standard international definitions were used to define treatment outcomes.[1] We defined as relapse a patient cured under DOTS who had two sputum samples positive for AFB by direct smear, one smear and one culture positive from separate samples, or two cultures positive.

Patients who habitually drank alcohol were considered alcoholics, and patients who habitually smoked and were currently smoking were considered smokers for the purpose of the analysis. In the RNTCP, a new smear-positive TB patient is expected to complete treatment within 7 months (6 months + 1 month grace period). For patients whose sputum does not convert at 2 months, the intensive phase is extended by one more month and the duration of treatment extended to 8 months (7 months + 1 month grace period). Patients who took longer than the RNTCP norms to complete treatment were considered irregular.

Statistical analysis

The data were computerised after scrutiny and further edited for completeness of all information relevant for analysis. For calculation of the relapse rate, the numerator was the number of patients who fulfilled the definition of relapse as above, and the denominator was the total number of patients in the cohort from whom a sputum sample was collected at at least one time point.

Univariate analysis was performed using Epi Info version 6.04d (Centers for Disease Control and Prevention, Atlanta, GA, 2001) to identify potential risk factors among patients who relapsed and those who did not. The χ^2 test of significance was used to test the difference in the proportion of relapse cases among patients with and those without risk factors. Stepwise logistic regression analysis was performed using SPSS/PC+, Version 4.0 (SPSS Inc, Chicago, IL, 1990) for those risk factors found significant in the univariate analysis to identify independent risk factors for relapse. A P value $\leqslant 0.05$ was considered statistically significant.

RESULTS

Rate of relapse

Of a cohort of 534 new sputum smear-positive PTB patients who were declared cured, 31 could not be contacted because they had died ($n = 8$), migrated ($n = 16$), or were not available despite two home visits ($n = 7$). Thus, sputum was collected from 503 (94%) patients at at least one time point during the 18-month follow-up period. Characteristics of the 31 patients who could not be followed up were similar to those of the 503 patients who were followed up with regard to age, sex, regularity of treatment, weight and smoking and drinking habits (data not shown).

As per our definition for relapse in this study the rate of relapse was 12.3% (62/503 patients). The majority of the relapses, 77.4% (48/62), occurred during the first 6 months after the completion of treatment; nine patients relapsed at 12 months and five patients at 18 months (Table 1). Based on the case definition of relapse used in the RNTCP, (i.e., a patient who has received full treatment and who is declared cured under

Table 1 Rate of relapse among new sputum smear-positive pulmonary tuberculosis patients treated between April 2000 and December 2001 in a DOTS programme, Tiruvallur District, South India

Month of follow-up	Died	Migrated	Absence (a)	Sputum collection (b)	COV % b/(a+b)	Relapse *n* (c)	Relapse % (c/b)
At 6 months	8	16	30	480	94	48	10.0
7–12 months	1	5	33	423	93	9	2.1
13–18 months	3	7	32	405	93	5	1.2
Total relapse (6–18 months)				503*	—	62	12.3

Note: Those who died, migrated or relapsed not included in the subsequent follow-up.
* Sputum collected at any time point.
COV = coefficient of variation (proportion [%] of sputum collected among those eligible).

the RNTCP returns and is found to have two positive sputum smear results), the relapse rate was 10%.

Drug susceptibility pattern at the time of relapse

Of the 487 patients for whom drug susceptibility results were available at the start of treatment, 455 (93%) had susceptible organisms, 30 (6%) had H resistance and only two had HR resistance (Table 2). Among the 455 patients who were susceptible, 51 (11.2%) relapsed. Drug susceptibility results were available for 49 of these 51 patients at the time of relapse: 39/49 (80%) relapses had drug-susceptible organisms and the remaining 10 patients had H-resistant organisms. Of the 32 patients with resistance to H or HR initially, 10 (31%) relapsed: 6 with H resistance and 3 with HR resistance (two of the three had initial resistance to HR).

Risk factors for relapse

On univariate analysis, drug irregularity, initial drug resistance, smoking and alcoholism were associated with a higher likelihood of relapse (Table 3). Overall, patients who were irregular on treatment were twice as likely to relapse as those who were regular (19.8% vs. 8.5%; odds ratio [OR] = 2.6, 95% confidence interval [CI] 1.5–4.7), $P < 0.001$). There was a linear relation between the extent of irregularity and the rate of relapse: 8.5% (28/329) among those who took 7–8 months to complete treatment, 14.5% (12/83) among those who took 9–10 months, and 25.3% (20/79) among those who took 10–12 months (χ^2 for trend = 16.9; $P < 0.001$).

Among patients who had organisms resistant to H and/or R, the relapse rate was 31.2% (10/32) compared to 11.2% (51/455) among those who had organisms sensitive to H and R (OR 3.6; 95%CI 1.5–8.5; $P < 0.01$). The relapse rate was 18.1% (41/226) among smokers compared to 7.3% (19/260) among non-smokers; the difference was statistically significant (OR 2.8; 95%CI 1.5–5.2; $P < 0.001$). Age, sex, weight, initial smear grade and end of intensive phase sputum conversion results did not influence the rate of relapse.

On stepwise logistic regression analysis, a higher relapse rate was independently associated with irregular treatment (adjusted OR [aOR] 2.5; 95%CI 1.4–4.7), drug resistance (aOR 4.8; 95%CI 2.0–11.6), and smoking (aOR 3.1; 95%CI 1.6–6.0). Among patients who were treatment adherent as per the RNTCP protocol, were non-smokers, and had susceptible organisms, the relapse rate was 4.8% (8/166).

Table 2 Drug sensitivity profile of patients on admission and at relapse among new smear-positive pulmonary tuberculosis patients treated from April 2000 to December 2001 in a DOTS programme in Tiruvallur District, South India

On admission	At relapse: H res	HR res	Sens	NA	Total
H res (30)	6	1	1	0	8
HR res (2)	0	2	0	0	2
Sens (455)	10	0	39	2	51
NA (16)	1	0	0	0	1
Total (503)	17	3	40	2	62

Figures given in parenthesis indicate the cohort of patients followed up.
H = isoniazid; res = resistant; R = rifampicin; sens = sensitive; NA = not available.

DISCUSSION

The findings of this study underscore the importance of regularity of treatment to ensure high cure rates without relapse. Patients who took treatment irregularly were twice as likely to relapse as those who were adherent. The performance of the RNTCP in the study site at the time of investigation was below the national average (cure rate of 75% in the study area compared to 85% at national level).[7,8] Nearly one third of the patients were irregular in this study, which contributed to an overall high relapse rate of 12.3%. Among patients who were adherent, the relapse rate was 8.4%, similar to the 6–7% found in other parts of India over the past 5 years,[3] but higher than the 3–6% relapse rates reported from randomised controlled clinical trials (RCT) using similar regimens.[9,10] The definition of relapse used in the study was more stringent than that used under programme conditions, but less stringent than that used in RCTs (two or more cultures positive for *M. tuberculosis*, at least one with a growth of ⩾20 colonies and associated with a positive smear). In the RCTs cited here, all drugs were given

Table 3 Risk factors for relapse among new smear-positive pulmonary tuberculosis patients treated from April 2000 to December 2001 in a DOTS programme in Tiruvallur District, South India

	n	Relapse *n* (%)	OR (95%CI)	*P* value	aOR (95%CI)
Sex					
Male	380	52 (13.7)	1.8 (0.8–3.9)	0.1	
Female	123	10 (8.1)			
Age, years					
<45	261	27 (10.3)		0.2	
⩾45	242	35 (14.5)	1.5 (0.8–2.6)		
Education					
Illiterate	209	24 (11.5)		0.7	
Literate	277	36 (13.0)	1.2 (0.6–2.1)		
Occupation					
Unemployed	150	21 (14.0)	1.2 (0.7–2.3)	0.5	
Employed	337	39 (11.6)			
Smoking					
No	260	19 (7.3)		<0.001	3.1 (1.6–6.0)
Yes	226	41 (18.1)	2.8 (1.5–5.2)		
Drinking (alcoholism)					
No	326	30 (9.2)		<0.01	
Yes	160	30 (18.8)	2.3 (1.3–4.1)		
Drug regularity					
Regular	329	28 (8.5)		<0.001	2.5 (1.4–4.6)
Irregular	162	32 (19.8)	2.6 (1.5–4.7)		
Drug sensitivity profile—0 months					
Sensitive	455	51 (11.2)		<0.01	4.8 (2.0–11.6)
Resistant to H and/or HR	32	10 (31.2)	3.6 (1.5–8.5)		
Smear conversion at 2 months					
Yes	403	49 (12.2)		0.9	
No	100	13 (13.0)	1.1 (0.5–2.2)		
Initial smear grading					
Scanty, 1+	224	27 (12.1)		0.9	
2+, 3+	279	35 (12.5)	1.0 (0.6–1.8)		
Initial weight					
<42 kg	241	33 (13.7)	1.3 (0.7–2.3)	0.4	
⩾42 kg	248	27 (10.9)			

OR = odds ratio; CI = confidence interval; aOR = adjusted odds ratio; H = isoniazid; R = rifampicin.

under supervision throughout treatment, ensuring that all patients were regular in taking their drugs, whereas in the programme all doses are supervised only in the intensive phase, while in the continuation phase the first dose of the week is given under supervision and the other two doses are supplied for self-administration. Also, in the RCTs, inclusion of patients is usually based on stringent criteria with the possibility of a lower frequency of risk factors. In our study, patients without risk factors, i.e., those who were adherent, non-smokers with susceptible organisms, had a relapse rate of 4.8%. Smoking was an independent predictor of relapse. Smoking has been associated with increased TB occurrence.[11,12] Some hypotheses have been put forward to explain this association: bronchoalveolar macrophages among smokers contain high levels of iron, promoting the growth of *M. tuberculosis*;[13,14] iron loading causes reductions in tumour necrosis factor-alpha (TNF-α) and nitric acid, which play a role in containing the intracellular growth of *M. tuberculosis*.[15] In this study, 68% of men were smokers and were thrice as likely to relapse as those who did not smoke. There is a need to devise effective strategies for counselling patients about the impact of smoking on their cure.

Our finding that the majority of relapses (77%) occurred during the first 6 months after completing treatment is corroborated by the results of several RCTs conducted in other parts of the world.[16–19] In our study, as in other studies, initial drug resistance was found to be associated with high relapse rates. Among patients with initial resistance to H and/or HR, 31.2% relapsed compared to 11.2% among those with susceptible organisms. Using a similar regimen, relapse among the drug-susceptible population was 9% compared to 13% among patients with initial H resistance in RCTs.[10] Mitchison et al. also reported a relapse rate of 4.6% among patients with initially sensitive organisms compared to 14% among patients with initially drug-resistant organisms.[20] In an earlier study, the prevalence of H resistance was 11.7% among 1324 patients without a history of prior treatment compared to 38% among 431 patients who had received more than 1 month of prior anti-tuberculosis

treatment.[21] This emphasises the importance of proper history taking to ascertain whether the patient has been previously treated for TB.

It is important to note that among the eight patients who had initial H-resistant organisms and relapsed, the emergence of drug resistance was very low, with only one patient developing HR resistance while 2% among the initially susceptible population developed H resistance. Similar findings have been reported from RCTs conducted at the TRC—emergence of resistance to H and R was less than 1% among patients who had a relapse.[21] This justifies treating patients who relapse after treatment with the currently recommended Category II regimen containing streptomycin, R, H and E for 2 months, R, H, E and Z for 1 month and R, H and E for the subsequent 5 months.

Our findings have several programme implications. The need to take a proper history of prior anti-tuberculosis treatment should be emphasised to the medical officers for correct categorisation of treatment. The relapse rate under the RNTCP can be reduced by ensuring that patients take their treatment regularly and are counselled effectively about quitting smoking. There is a need to develop effective communication strategies and health education materials to address these issues. All peripheral health centres must be provided with effective health education materials, and staff should be trained in counselling. Anti-smoking campaigns need to be strengthened to have far-reaching effects on the health of the population.[22,23] Further research is needed to develop and test local communication strategies to help smokers quit smoking and document its impact on the cure of TB.

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RÉSUMÉ

OBJECTIF : Identifier les facteurs de risque associés à la rechute parmi les patients guéris de tuberculose (TB) dans un programme DOTS en Inde du Sud.

SCHÉMA : Les échantillons d'expectoration provenant d'une cohorte de patients TB enregistrés entre avril 2000 et décembre 2001 ont été examinés par microscopie à fluorescence à la recherche de bacilles acido-résistants et par culture de *Mycobacterium tuberculosis* à 6, 12 et 18 mois après l'achèvement du traitement.

RÉSULTATS : Sur les 534 patients guéris, 503 (94%) ont été suivis pendant 18 mois après l'achèvement du traitement. Parmi ceux-ci, 62 (12%) ont rechuté durant la période de 18 mois ; 48 (77%) des 62 rechutes sont survenues au cours des 6 premiers mois du suivi. Les patients qui ont pris leur traitement de manière irrégulière ont eu un risque deux fois plus élevé de rechute que les patients adhérant au traitement (20% vs. 9% ; odds ratio ajusté [ORa] 2,5 ; IC 95% 1,4–4,6). D'autres facteurs prédictifs indépendants de rechute ont été une résistance initiale à l'isoniazide et/ou à la rifampicine (ORa 4,8 ; IC 95% 2,0–11,6) ainsi que le fait de fumer (ORa 3,1 ; IC 95% 1,6–6,0). Le taux de rechute parmi les patients adhérant au traitement, non-fumeurs et porteurs de germes sensibles aux médicaments a été de 4,8%.

CONCLUSIONS : Le taux de rechute dans un programme DOTS peut être réduit en s'assurant que les patients prennent leur traitement régulièrement et se voient conseiller effectivement d'abandonner le tabagisme.

RESUMEN

OBJETIVO : Identificar los factores de riesgo asociados con la recaída en pacientes con tuberculosis (TB) curada, en un programa DOTS en el sur de la India.

MÉTODO : Se recogieron muestras de esputo de una cohorte de pacientes con TB, registrados entre abril de 2000 y diciembre de 2001 y se examinaron en microscopio de fluorescencia en busca de bacilos ácido-alcohol resistentes y con cultivo para *Mycobacterium tuberculosis* a los 6, 12 y 18 meses después de haber completado el tratamiento.

RESULTADOS : Se realizó el seguimiento de 503 de los 534 pacientes curados (94%) durante 18 meses después de haber completado el tratamiento. De estos pacientes, 62 (12%) presentaron recaída durante el periodo de 18 meses ; 48 (77%) de las 62 recaídas tuvieron lugar durante los primeros 6 meses del seguimiento. Los pacientes que tomaron el tratamiento en forma irregular tuvieron una probabilidad doble de recaída, comparados con los pacientes con un buen cumplimiento terapéutico (20% contra el 9% ; aOR [cociente de posibilidades corregido] 2,5 ; IC95% 1,4–4,6). Otras variables independientes asociadas con la recaída fueron la resistencia inicial a isoniacida, a rifampicina o a ambas (aOR 4,8 ; IC95% 2,0–11,6) y el tabaquismo (aOR 3,1 ; IC95% 1,6–6,0). La tasa de recaída en los pacientes no fumadores con buen cumplimiento terapéutico y cepas sensibles a los medicamentos fue 4,8%.

CONCLUSIÓNES : La tasa de recaída en un programa DOTS puede reducirse procurando que los pacientes tomen regularmente el tratamiento y asesorándolos eficazmente sobre el abandono del tabaquismo.