

Sputum smear conversion during directly observed treatment for tuberculosis

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SUMMARY. *Setting:* Treatment program for tuberculosis in a refugee camp in Thailand.

Objectives: To determine the cumulative frequency of conversion of sputum smears examined by direct microscopy by month of treatment and to identify factors predicting failure to convert.

Methods: Analysis of conversion based on three sputum smear examinations (performed monthly) in a cohort of patients with sputum smear-positive tuberculosis treated with a directly observed daily regimen containing rifampicin throughout. Nested case-control study of patients failing to convert definitively within four months compared to controls who did convert.

Results: Sputum conversion after the 2-month intensive phase was 75.0%, with a range from 61.7% to 90.9% in patients with initially strongly- and weakly-positive smears, respectively. The strongest predictor identified for no definitive conversion within four months of treatment was a positive sputum smear result at the end of the 2-month intensive phase (adjusted relative odds 4.2, 95% confidence interval 1.5–11.4). Of those patients who did not convert, positive smears were an isolated phenomenon in 15, repeatedly in four who definitely converted with a prolongation of treatment, and persistently positive in two requiring a re-treatment regimen.

Conclusions: Definitive sputum smear conversion is judged to be slower if a strict program of sputum smear examination is undertaken than under routine program conditions, but positive results late in the course are commonly an isolated phenomenon and possibly of little significance. Sputum smear results at two months strongly predict bacteriologic results beyond three months of treatment, and thus identify cases who might benefit from a prolongation of the intensive phase.

RÉSUMÉ. *Cadre:* Programme de traitement de la tuberculose dans un camp de réfugiés en Thaïlande.

Objet: Déterminer la fréquence cumulative de la négativation des frottis examinés par microscopie directe en fonction du mois de traitement, et identifier les facteurs laissant prévoir un échec de la négativation.

Schéma: Analyse de négativation sur la base de trois examens de frottis (effectués chaque mois) dans une cohorte de malades atteints d'une tuberculose frottis positif traités par un régime quotidien directement observé comprenant de la rifampicine pendant tout le traitement. Etude de cas et de leurs témoins parmi les malades qui n'ont pas montré de négativation définitive dans les quatre mois comparés aux contrôles négatifs.

Résultats: Le taux de négativation des frottis après la phase intensive de deux mois était de 75,0%, allant de 61,7% à 90,9% chez les malades montrant des frottis initiaux respectivement fortement et faiblement positifs. La valeur prédictive la plus forte pour l'absence de négativation dans les quatre mois de traitement était un résultat positif de l'examen des frottis à la fin de la phase intensive de deux mois (Odds relatifs ajustés 4,2, Intervalle de confiance 95% 1,5–11,4). Parmi les malades qui ne se sont pas négativés, un frottis positif s'est avéré un phénomène isolé chez 15, s'est répété chez 4 qui ont montré une négativation définitive après un traitement prolongé, et demeurait positif chez deux malades qui ont dû suivre un régime de retraitement.

Conclusion: Une négativation définitive de frottis est plus lente lors d'un programme stricte d'examens de frottis par rapport aux conditions de routine des programmes antituberculeux. Néanmoins des résultats positifs découverts dans les stades ultérieurs du traitement représentent habituellement un phénomène isolé, et peuvent être de peu de signification. Les résultats de frottis à deux mois de traitement ont une forte valeur prédictive des résultats bactériologiques au-delà de trois mois de traitement, et peuvent donc identifier des cas qui pourraient bénéficier de la prolongation de la phase intensive.

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RESUMEN. Marco de referencia: Programa de tratamiento de la tuberculosis en un campo de refugiados de Tailandia.

Objetivo: Determinar la frecuencia acumulativa de la negativización de las baciloscopias por mes de tratamiento e identificar los factores de predicción del fracaso de la negativización.

Método: Análisis de la negativización en base a tres baciloscopias (realizadas mensualmente) en una cohorte de pacientes con tuberculosis con baciloscopia positiva tratados con un esquema diario supervisado directamente y que contenía rifampicina durante todo el tratamiento. Estudio de casos/control en los pacientes que no lograban una negativización definitiva dentro de los 4 meses, comparados con los que negativizaban.

Resultados: La tasa de negativización del esputo después de la fase intensiva de dos meses era de 75,0%, con una dispersión de 61,7% a 90% en los pacientes con baciloscopias iniciales fuertemente positivas y débilmente positivas, respectivamente. El factor de predicción más fuerte para no negativizar definitivamente la baciloscopia dentro de los cuatro meses de tratamiento resultó ser la positividad de la baciloscopia al final de los dos meses de la fase intensiva (Odds relativos ajustados 4,2, DS 1,5–11,4, intervalo de confianza 95%). Entre los pacientes que no negativizaron, el hecho de tener una baciloscopia positiva era un fenómeno aislado en 15 de ellos, se repitió en 4, con una negativización definitiva después de un tratamiento prolongado y en 2 que continuaron siendo positivos y que necesitaron un esquema de retratamiento.

Conclusión: La negativización definitiva de la baciloscopia aparece como más lenta si se emprende un programa estricto de baciloscopia, que cuando se mantienen las condiciones de rutina de los programas antituberculosos. Pero los resultados positivos encontrados más tarde en el curso del tratamiento representan habitualmente un fenómeno aislado y posiblemente de escasa importancia. Los resultados de la baciloscopia a los dos meses de tratamiento tienen un fuerte valor predictivo con respecto a los resultados bacteriológicos más allá de los tres meses de tratamiento, y de esta manera pueden identificar los casos que podrán obtener beneficio de una prolongación de de la fase intensiva.

INTRODUCTION

The International Union Against Tuberculosis and Lung Disease (IUATLD) and the World Health Organization (WHO) both emphasize the necessity of monitoring treatment by bacteriologic follow-up examinations in sputum smear-positive tuberculosis patients.^{1,2} The result of the follow-up examination at the end of the 2-month intensive phase determines whether the regimen can be switched to the continuation phase or whether the patient should be given an additional month of intensive phase treatment. The follow-up examinations at 5 months and before completion of treatment allow a decision to be made to continue or complete the treatment, respectively, or to place the patient on a re-treatment regimen in case of failure.

In the setting of a camp for Cambodian refugees in Khao-I-Dang, Thailand, all tuberculosis patients were treated with a rifampicin-containing regimen of 6 months' duration with each dose of drugs given daily under direct supervision throughout the course of treatment.^{3,4} In sputum smear-positive patients, sputum smear examinations were made much more frequently than is generally recommended, and the data collected thus provide a unique source of information on sputum smear conversion under routine treatment in a setting in which drug intake was guaranteed throughout the course.

MATERIALS AND METHODS

The treatment regimen for new cases consisted of 6 months of daily rifampicin plus isoniazid, supplemented by pyrazinamide plus streptomycin during the first 2

months, first studied in Singapore.⁵⁻⁷ The regimen was strictly adhered to and changes, if any (completion, prolongation, or change to a second line re-treatment regimen), were made only after a full course.

In each patient, every effort was made to obtain three early morning sputum samples on consecutive days for follow-up examinations at the end of each month for as long as the patient remained on treatment. For each patient results were recorded on a special laboratory sheet and appended to the patient treatment card. If a patient was unable to produce a specimen, this was carefully recorded. Smear results were graded as internationally recommended.⁸

The data were computerized and analyzed with commercially available software.⁹ For each month, an average score of the up to three graded smear results was calculated. A sum of smear examination results was obtained by a mean score of all results available at each monthly examination. A mean score of 2+ or greater was designated strongly positive; 1+ to less than 2+ was moderately positive; less than 1+ but positive was weakly positive; and 0 was negative.

To determine the frequency of conversion each month, the numerator was the number of patients with a score of zero; the denominator for each month included the number of patients still available for sputum smear examination.

Within the cohort of patients available for analysis, a subgroup excluding patients who died, absconded or were transferred was selected for a nested case-control study. Cases were patients who had at least one positive smear examination at 4 months or later and controls were patients who had no positive smear examination at four months or later. Univariate and multivariate analyses

on the case control data sub-set were done to determine predictors for late smear positivity by using commercially available software.^{10,11} For the adjusted analysis a logistic regression model was used, where each of the four variables (age, gender, smear score at diagnosis, and smear score at 2 months) was adjusted for all the other variables in the model, e.g., the variable gender was adjusted for age, smear score at diagnosis, and smear score at 2 months.

Information on patients with any positive result at four months or later was further scrutinized for management and outcome.

RESULTS

Sputum smear conversion in the cohort

In the 3-year period from 16 April 1981 to 29 March 1984, a total of 259 new sputum smear-positive patients were admitted into the program in whom at least one of the first three sputa obtained was positive for acid-fast bacilli on a smear stained by the Ziehl-Neelsen method. Of these, 231 made up the cohort that should have completed the 6-month course by the end of the observation period (Table 1); the remaining 28 were not evaluated

because they were still on treatment at the time of data collection.

Cumulative losses by the end of treatment included seven deaths, 14 absconders and 34 transfers.

Of the 231 patients, 89 (38.5%) had strongly positive smears, 83 (35.9%) moderately positive smears, and 59 (25.5%) weakly positive smears at diagnosis.

Of patients with weakly positive smears, 90.9% had converted by the end of the 2-month intensive phase, 77.9% of patients with moderately positive smears, and 61.7% of patients with strongly positive smears (Fig. 1). Of all patients combined, conversion after 2 months was 75.0% and after six months of directly observed treatment, 95.5%.

A comparison between the results obtained on the first smear during each follow-up examination and any of the three follow-up examinations showed that 84.8% would have been classified as converters at 2 months had only a single smear been examined, compared to only 75.0% when three smears were taken (Fig. 2).

Case-control study on patients failing to convert

After exclusion of 55 patients from the cohort who died, were transferred to another camp, or absconded, a total

Table 1. Treatment outcome in 231 patients with sputum smear-positive tuberculosis, by month of treatment, Khao-I-Dang, Thailand, 1981-1984

Month	No. of patients with smear score available				Total	Died	Cumulative no. of patients lost		
	Negative	Weak	Moderate	Strong			Transferred	Absconded	Total
At diagnosis	0	59	83	89	231	0	0	0	0
End of 1st*	126	47	36	8	217	5	5	3	13
End of 2nd	153	37	14	0	204	6	12	9	27
End of 3rd	167	20	5	1	193	6	21	11	38
End of 4th	168	13	1	1	183	6	28	14	48
End of 5th	170	5	2	1	178	6	33	14	53
End of 6th	168	7	1	0	176	7	34	14	55

*1 additional patient had no result recorded at the end of the first month.

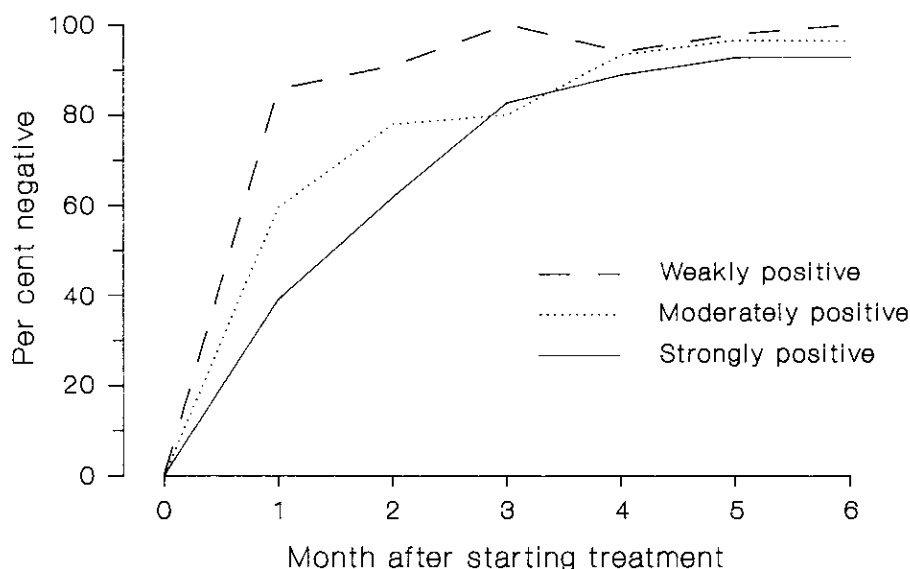


Fig. 1—Sputum smear conversion by microscopy (Ziehl-Neelsen technique) in 231 tuberculosis patients by initial amount of acid-fast bacilli, Khao-I-Dang, Thailand, 1981-1984.

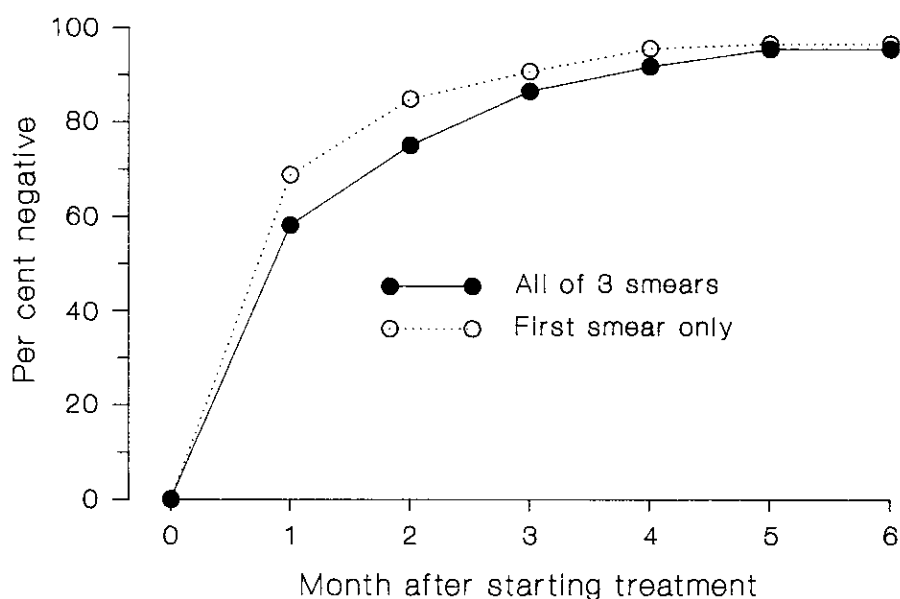


Fig. 2—Sputum smear conversion by microscopy (Ziehl-Neelsen technique) in 231 tuberculosis patients. Results with all three monthly smears considered compared with only the first smear result each month considered. Khao-I-Dang, Thailand, 1981–1984.

of 176 cases remained with complete monthly smear examinations throughout 6 months. Of these, the 155 who never had any positive smear during these last 6 months of treatment served as controls for the 21 cases who did (Table 2). Although the unadjusted odds increased with increasing initial grading of smear-positivity, the difference was not statistically significant, and in the adjusted analysis initial smear-positivity was not an independent predictor for subsequent positivity at four months or later. In contrast, the finding of any positive smear at 2 months was very strongly predictive for a positive smear at 4 months or later.

Outcome of patients failing to convert

Of the 21 cases with at least one positive smear at 4 months or later, 15 had one or two positive smears at the

end of month 4 or a single positive one at any time later, not exceeding a 1+ positivity. All of these patients were declared cured at the end of 6 months. Four of these had a positive result for the first of the 2 month specimens. In four patients with three or more positive smears during the last 3 months, treatment was prolonged without change for another 3 months. One had a positive result for the first of the 2-month specimens. None of these patients had positive smears during the 3-month period of prolongation, and all four were declared cured after a total of 9 months of treatment. Two patients were considered true treatment failures after 6 months of treatment and were given a re-treatment regimen, both because they had persistently positive smears during the last 3 months of the first-line regimen, and because they were frequently moderately to heavily positive. Both had been positive already on the first of

Table 2. Nested case-control study comparing patients with any positive smear at 4 months or later (cases) with patients never having any positive smear at 4 months or later (controls) during directly observed chemotherapy, Khao-I-Dang, Thailand, 1981–1984

Characteristic	Cases <i>n</i> (%)	Controls <i>n</i>	Total <i>n</i>	Crude OR	Adj. OR	(95% CI)	<i>P</i> value
Total	21 (11.9)	155	176	—	—	—	—
Age group							
up to 24	3 (8.8)	31	34	*1	*1	—	—
25–34	7 (12.1)	51	58	1.4	2.0	(0.5, 8.9)	0.36
35–44	5 (15.6)	27	32	1.9	2.2	(0.5, 11.0)	0.32
45+	6 (11.5)	46	52	1.3	1.6	(0.4, 7.3)	0.54
Gender							
male	11 (12.6)	76	87	*1	*1	—	—
female	10 (11.2)	79	89	0.9	0.9	(0.3, 2.3)	0.83
Smear score at diagnosis							
weak	4 (8.0)	46	50	*1	*1	—	—
moderate	7 (12.3)	50	57	1.4	1.2	(0.3, 4.8)	0.78
strong	10 (14.5)	59	69	1.9	1.2	(0.3, 4.5)	0.77
Smear score at 2 months							
negative	10 (7.6)	122	132	*1	*1	—	—
positive	11 (25.0)	33	44	4.1	4.2	(1.5, 11.4)	0.005

OR: Odds ratio; Adj. OR: adjusted odds ratio by logistic regression; CI = Confidence interval *1: defined as unity

the 2-month specimens. One of these patients responded favorably to the second-line treatment (employing ethambutol and kanamycin in addition to isoniazid, rifampicin and pyrazinamide) and was declared cured after completion of the course. The second patient absconded from the second-line regimen, was later found again, and was only cured with a 2-year third-line regimen elsewhere.

DISCUSSION

Initial sputum smear positivity is strongly correlated to the extent and form of pulmonary disease, and the agreement between culturally and microscopically identifiable bacilli is good.¹² However, sputum smear conversion on a rifampicin-containing regimen has been shown to be slower than culture conversion in a certain proportion of patients.¹³

In this refugee camp, tuberculosis was soon recognized by the authorities to constitute a major health problem and a single agency was put in charge of tuberculosis control.³ All drugs and reagents for smear microscopy were made available by the agency, but no funds for operational research were at their disposal. Thus, all work reported here was done on the regular budget. The camp had a clearly defined area³ which allowed daily and directly observed treatment for all patients with tuberculosis, provided in several small out-patient clinics within an acceptable walking distance from the patient's residence. Patients not attending in the morning were sought out in the afternoon, and as a result day-to-day adherence was excellent: during 1 month chosen at random, only 1.14% of treatment days were missed, and among the first 49 consecutive patients who completed the 6-month course, only 1.62% of the prescribed treatment days were missed, with a range from 0–5%.³ Thus, the results presented here are a close approximation of what can be achieved if drugs are taken exactly as prescribed.

Under program conditions, particularly in low income countries, the sputum smear examination must serve as a proxy, for cultures are neither available nor appropriate for such an assessment. It seems likely that the probability of relapse will be highest in those with the highest 2-month bacillary load. In this context, it is worth considering the findings of this study that 25.0% of patients had at least one positive result if three smears were examined, but 15.2% if only the first smear examination at 2 months was considered. Because a positive sputum smear result at 2 months strongly predicted smear results after 4 months in this study, the correlation between smears and cultures is generally good, and the 2-month culture findings are good predictors for the fate of the patient beyond treatment completion,¹⁴ the recommendation that patients with a single positive smear after 2 months of treatment could benefit from prolongation of the intensive phase¹ may be justified, considering that both patients ultimately considered to be failures already

had a positive result for the first specimen at the end of the second month.

Another finding of this study is that after 6 months of continuous directly observed rifampicin-containing treatment 4.5% of patients were still sputum smear positive on any, and 3.4% on the first, of the 6-month smear examinations. If the continuation phase did not contain rifampicin and drug intake were not directly observed, this proportion is expected to be similar or more likely even higher, and such patients would have to be considered programmatically as treatment failures.^{1,2} The proportion of treatment failures in IUATLD collaborative programs is, however, usually reported to be smaller.^{15–19} The higher frequency of positive results in this study might be attributable to the relatively high initial drug resistance in the Indochinese refugee population,^{20,21} an unlikely hypothesis, because initial isoniazid resistance can usually be overcome with the type of regimen that was employed.²² A more likely hypothesis is that follow-up examinations under routine program conditions are done less thoroughly than was possible in this refugee camp, and that the knowledge of the laboratory technician about the follow-up nature of the examination may bias the quality of reading. Again, it is not known whether paucibacillary findings during the last 3 months have any bearing on the risk of subsequent relapse. In patients with persistently positive smears or in patients exhibiting a clear-cut fall and rise phenomenon,²³ emerging resistance or poor adherence is likely. It is very probable that such patients are discovered even under routine program conditions.

A more detailed analysis of patients who failed to convert definitively by the end of the fourth month seemed to indicate that in the majority of these 21 cases the findings were an isolated phenomenon with seemingly little significance, and treatment was completed as planned. In four, a prolongation of treatment resulted in lasting conversion. Of the two failures, one was cured with a re-treatment regimen and the other ultimately with a third-line regimen. This testifies that the overall treatment results in this displaced population were excellent.

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