

Sputum microscopy results at two and three months predict outcome of tuberculosis treatment

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SUMMARY

OBJECTIVE: To assess the importance of monitoring sputum conversion as an early treatment indicator of treatment success.

METHODS: Retrospective analysis of sputum conversion in a cohort of 'cured' tuberculosis patients.

RESULTS: Of 65 (95%) patients whose sputum converted in the third month of treatment, 62 were cured; only 21 of 35 (60%) patients whose sputum was still pos-

itive at the end of three months of treatment were ultimately cured.

CONCLUSION: Sputum conversion during the third month of treatment is an important predictor of treatment success; failure to convert predicts treatment failure.

KEY WORDS: tuberculosis; China; diagnosis; treatment outcome; sputum

THE RECOMMENDATIONS of the International Union Against Tuberculosis and Lung Disease (IUATLD) are that patients with confirmed tuberculosis should have three sputum smears, stained by the Ziehl-Neelsen method, examined by microscopy for *Mycobacterium tuberculosis*:¹

- two months after the commencement of treatment,
- five months after the commencement of treatment, and
- prior to the completion of treatment.

If mycobacteria are identified at two months, an extra examination at three months is recommended.

The World Health Organization has endorsed this protocol,² which is being followed throughout the World Bank-assisted Infectious and Endemic Diseases (Tuberculosis Component [IEDC-TB]) Programme in China.

De Cock and Wilkinson recently stated that one of the disadvantages of the implementation of tuberculosis control programmes was the heavy load of smear examinations.³ They identified that the purpose of follow-up smear examinations is to:

- identify treatment failures, and
- offer retreatment with a different (treatment) regimen.

Further, they stated that in areas of high human immunodeficiency virus (HIV) infection, laboratories would be unable to sustain the increased workload required for initial and follow-up smear examinations. They propose that where rifampicin-based regimens

are used in environments with low levels of primary drug resistance, follow-up smear examination is of low priority and that regular assessments of epidemiologically valid samples of patients for microbiological cure would be sufficient to monitor programme efficacy.

In a subsequent letter to the editor, Wilkinson and Gilks thought that the experience of the China-World Bank project could test the necessity for the sputum examination at two months.⁴ (The IEDC-TB operates in an environment of low HIV prevalence, and presumed low primary drug resistance.)

We report the treatment outcomes and intermediate treatment results for 726 new sputum smear positive patients from Liaoning Province, China, recruited during 1993.

METHODS

Subjects were those persons who were sputum smear positive at diagnosis, had never received anti-tuberculosis treatment previously, and had completed treatment. The cohort was assembled retrospectively from a group of 755 cases.

All patients had received fully supervised treatment. The standard regimen was an initial two-month treatment of thrice-weekly isoniazid (H), rifampicin (R), pyrazinamide (Z) and streptomycin (S), followed by four months of thrice-weekly isoniazid and rifampicin (2H₃R₃Z₃S₃/4H₃R₃). Patients who remained sputum-smear positive at two months were given the following regimen—3H₃R₃Z₃S₃/4H₃R₃. Further de-

tails of the tuberculosis control programme have been reported elsewhere.⁵

All patients were:

- assessed at two months, and if sputum-smear positive at that time reassessed at three months;
- reassessed at five months after the commencement of treatment, and if sputum-smear positive were re-tested at six months, and
- tested at the completion (of six or eight months) of treatment.

Classification of treatment outcome was based solely on microscopy, there being no access to routine culture and sensitivity testing, and results were reported as 'positive' and 'negative.' Without quantification of smear results there was no distinction between patients with a fall and subsequent rise in bacilli (treatment failure) and scarce, perhaps dead, bacilli.

A cured case was defined as a case that was:

- sputum positive at the commencement of treatment,
- became sputum negative during treatment, and
- was still negative at five months (or later) after commencement of treatment.

RESULTS

A total of 726 of the 755 (96%) patients completed treatment. Patients who ceased treatment were excluded from the study—eight died from tuberculosis, 15 died for other reasons, five transferred out and one refused treatment at the outset.

All 726 patients had been assessed at two months: 626 (86%) were sputum negative and 100 (14%) remained sputum positive. These two groups are reported separately.

Outcome of patients who were sputum negative at two months

Of the 626 sputum negative patients, 623 (99.5%) were reassessed in the fifth month, and all 626 were assessed at the sixth month.

At five months, 607/623 patients (97%) were negative, and only 16 (3%) were positive. At six months, 615/626 were sputum smear negative (98%) and 11 (2%) were sputum smear positive (i.e. treatment failures).

Outcome of patients who were sputum positive at two months

Only 82 of the 100 patients were reassessed at three months. Of these, 65 patients (79%) had converted to sputum smear negative during the third month, leaving only 17 (21%) patients still sputum smear positive (Table).

At five months all but three patients were examined (including all those who had not been examined at three months). A total of 75 patients were sputum smear negative and 22 were positive.

Table Treatment outcome of patients who were sputum positive at two months, by sputum smear result at three months

	Total <i>n</i>	Sputum (-) at end of treatment <i>n</i> (%)	Sputum (+) at end of treatment <i>n</i> (%)
Sputum negative at 3 months	626	615 (98)	11 (2)
Sputum positive at 2 months	100	83 (83)	17 (17)
Negative at 3 months	65	62 (95)	3 (5)
Positive or not done at 3 months	35	21 (60)	14 (40)
Total	726	698	28

At the completion of treatment (at 6 or 8 months) 83 patients were negative while 17 patients were still sputum smear positive.

DISCUSSION

One limitation of this study is that cases may have been misclassified as 'new' when in fact they were re-treatment cases. The programme was expanding at the time of the study, and experience from other programmes suggests that previously treated patients also seek treatment, even if they do not qualify.

The results of this study demonstrate a correlation between a positive sputum examination at two months with treatment failure; the correlation is, not surprisingly, stronger after three months of treatment.

We therefore disagree with De Cock and Wilkinson in eliminating this examination from patient management protocols. Where limited culture and drug sensitivity facilities are available, two and three month sputum microscopy is the critical discriminator of 'high' and 'low' risk patients for treatment failure. In our study, patients who were still sputum smear positive at two and three months were 1.59 times ($1.2 < RR < 2.09$) more likely to be treatment failures than patients who sputum converted during the third month. These patients will require more intense follow-up throughout their treatment—including the continuation phase.

We feel that these data support the continuation of second and third month sputum examinations in routine monitoring of treatment. They also suggest that the most cost-effective approach may be a single sputum examination at three months. The results of this study could support the early commencement of 're-treatment' regimen in patients who are still sputum-smear positive at three months; this proposal should, however, be tested within a larger prospective study.

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RÉSUMÉ

OBJECTIF : Evaluer l'importance de la surveillance de la négativation des crachats comme indicateur précoce du succès du traitement.

SCHÉMA : Analyse rétrospective de la négativation des crachats dans une cohorte de malades tuberculeux 'guéris'.

RÉSULTATS : De 65 (95%) malades dont les crachats ont viré au troisième mois de traitement, 62 ont été guéris ;

seulement 21 sur 35 malades (60%) dont les crachats étaient encore positifs à la fin de trois mois de traitement ont atteint une guérison.

CONCLUSION : La négativation des crachats au cours du troisième mois de traitement est un facteur prédictif important de la réussite du traitement ; une absence de négativation présage l'échec du traitement.

RESUMEN

OBJETIVO : Evaluar la importancia del control de la negativización de los exámenes de esputo como un indicador precoz del éxito del tratamiento.

MÉTODO : Análisis retrospectivo de los exámenes de esputo en una cohorte de pacientes tuberculosos «curados.»

RESULTADOS : De los 65 (95%) pacientes cuyo esputo se negativizó durante el tercer mes, 62 habían curado ; sólo

21 de los 35 (60%) pacientes cuyo esputo era aún positivo al fin del tercer mes de tratamiento lograron finalmente una curación.

CONCLUSIÓN : La negativización del esputo durante el tercer mes de tratamiento es un factor predictivo importante para el éxito del tratamiento ; la ausencia de negativización presagia el fracaso del tratamiento.