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Residual lung damage after completion of treatment for multidrug-resistant tuberculosis

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SUMMARY

SETTING: Limpopo Province, South Africa.

OBJECTIVE: To assess the residual lung damage of patients who completed treatment for multidrug-resistant tuberculosis (MDR-TB).

DESIGN: Chest radiograph and lung function tests were performed at the end of treatment. The radiographs were read by two independent observers who attributed a zonal score of between 0 and 18, depending on the extent of radiographic abnormalities (opacification or cavitation), counted the number of visible cavities and measured the diameter of the largest cavity.

RESULTS: The mean zonal score was 6.5. Cavitation was present in more than half of the patients. Of 33 patients, 31 (94%) had abnormal lung function tests. The median FEV_1 was 63% and FVC was 57% of the predicted value. Restrictive and combined restrictive-obstructive lung function patterns were the predominant abnormalities.

CONCLUSIONS: Residual lung damage in MDR-TB patients who completed treatment is common and extensive. This may increase the risk of relapse of tuberculosis and reduce the quality of life and life expectancy of these patients. Additional efforts are warranted to diagnose MDR-TB early to reduce the extent of residual lung damage. Close follow-up of MDR-TB patients completing treatment will have to be ensured to detect relapses.

KEY WORDS: multidrug-resistant tuberculosis; lung functions; chest radiograph

THE TREATMENT of multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid (INH) and rifampicin (RMP), is costly and has an uncertain outcome. Cure rates of between 56% and 85% have been reported by different centers.[1–4] Successful treatment is likely to reduce the risk for further spread of MDR-TB. However, for countries with limited resources, the question arises as to whether it is worthwhile to treat MDR-TB. It has indeed been questioned whether treatment of MDR-TB should be integrated into the national TB control programmes of these countries, as it might divert resources away from the programmes for drug-sensitive tuberculosis and other important health issues.

The discussion on MDR-TB has mainly focused around these two points of cure rate and affordability. We were interested in the extent of residual lung damage after completion of treatment for MDR-TB, which might add another dimension to the discussion, as evidence of extensive residual lung damage might affect further morbidity and mortality of patients considered as cured. The objective of this study was to assess dynamic lung volumes and chest radiograph appearances as measures of the extent of residual lung damage in patients from the Limpopo Province, South Africa, who completed treatment for MDR-TB. Although previous studies have assessed lung function and chest radiograph in patients with drug-sensitive tuberculosis, no similar evaluation has been done in patients with MDR-TB.

METHODS

The Limpopo Province, South Africa, formerly called Northern Province, has a population of about 4.3 million; the incidence of tuberculosis based on the number of reported cases was estimated at 128/100 000 in 1998. There are no data on the incidence of MDR-TB for this region, but in two other South African provinces the incidence of MDR-TB has been estimated at 1–2% in new TB patients and 4–8% in retreatment cases.[5,6] Limpopo Province established a MDR-TB control programme in October 1997, and by October 2001, 142 patients with culture-proven tuberculosis resistant to RMP and INH had been registered. They were put on standardised treatment as

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proposed by the World Health Organization (WHO) and the South African guidelines for the management of MDR-TB.[7,8] In short, the treatment comprised an initial phase with five drugs for 3–4 months and a continuation phase with three drugs. The recommended total duration of treatment was at least 18 months. The drugs used for the initial phase were kanamycin, pyrazinamide, ethionamide (ETH), ofloxacin (OFL) and ethambutol (EMB) or cycloserin (CS), depending on the sensitivity of the strain to EMB. The drugs used for the continuation phase were ETH, OFL and EMB or CS, again according to the sensitivity results. All patients received treatment at their local hospital and were reviewed at the centralised MDR-TB clinic in Polokwane (previously Pietersburg), Limpopo Province, on a 3–4 monthly basis. Patients were considered as having completed treatment if they had received at least 18 months of treatment and had been sputum smear and culture negative for a minimum of 12 months.

All patients registered in the MDR-TB control programme of the Province, and who completed treatment between September 1999 and October 2001, were eligible. For each patient a chest radiograph and lung function tests were performed on the day treatment was stopped.

Two observers scored the chest radiographs independently, without knowledge of the lung function measurements. Both lungs on the postero-anterior chest radiographs were divided into upper, middle and lower zones, which were delimited by the upper border of the second and fourth anterior ribs, and assessed for disease. Disease was defined as the presence of opacification or cavitation. Each zone was attributed a value between 0 and 3, depending on the extent of the disease: 0 = no disease, 1 = disease affecting less than one third of the zone, 2 = disease affecting one to two thirds of the zone, 3 = disease affecting more than two thirds of the zone. The zonal score was defined as the sum of the values of all six zones, with a minimum value of 0 (normal radiograph) and a maximum value of 18. The number of cavities was counted and the diameter of the largest cavity was recorded.

Lung function tests were performed using two similar spirometers from Schiller (Dietikon Switzerland); ten patients had a lung function test performed on the Schiller Cardiovit AT-10, and 27 on the Schiller Spirovit SP-200. Temperature was entered manually to correct volumes for body temperature pressure saturation. Both spirometers were calibrated as required with a 2 l syringe prior to each test. Ethnicity, age, weight and height in bare feet were recorded. Each patient performed at least three and a maximum of eight forced expiratory maneuvers. The quality of the tests was categorized according to the consensus statement of the National Lung Health Education Programme.[9] Only patients with at least two acceptable maneuvers with forced expiratory volume of the first second (FEV_1) matching within 200 ml were included in the final analysis. The highest values of the FEV_1 and forced vital capacity (FVC) were recorded. To determine the predicted values we used the equations proposed by Hankison et al. for African-American subjects, which were based on the third National Health and Nutrition Examination Survey (NHANES III).[10] Obstructive disease was defined as a ratio of FEV_1 and FVC <0.8, with a FVC $\geqslant 80\%$ of the predicted value. Restrictive disease was diagnosed if both the FEV_1 and the FVC were $<80\%$ of the predicted values. Combined disease was defined as a FVC $<80\%$ of the predicted value and a FEV_1/FVC ratio <0.8.

RESULTS

Forty-two patients completed treatment for MDR-TB during the study period. For five patients the lung function tests were not done, and another three patients were not able to produce acceptable and reproducible forced expiratory maneuvers. Chest radiographs were available for 33 of the 34 patients with acceptable lung function test results.

All 33 patients were black Africans and 76% were men. The mean age was 40.2 years (range 16–66 years). Twenty-seven patients underwent testing for human immunodeficiency virus (HIV); three (11%) were positive. The patients received an average of 20.6 ± 4.4 months of chemotherapy for MDR-TB. One patient received only 15 months of treatment because he was diagnosed with MDR-TB very rapidly (within 3 months of onset of symptoms) and had a good response to treatment (all sputum smears and cultures negative within 1 month of start of treatment). The mean time between the first diagnosis of TB and completion of MDR-TB treatment was 51.8 months (range 18–113).

Respectively 33 and 31 patients had a zonal score >0 according to observer 1 and observer 2 (Table 1). Observer 1 identified cavitation on 23 and observer 2 on 17 radiographs.

Table 2 summarizes the result of the lung volumes and shows a predominance of restrictive and combined restrictive-obstructive patterns. The median FVC was 63% of the predicted value, and the median FEV_1

Table 1 Results of chest radiograph readings

	Observer 1	Observer 2	Mean
Number of patients with abnormal chest radiographs (zonal score > 0) (%)	31 (94)	33 (100)	
Mean zonal score	5.7	7.4	6.5
Number of chest radiographs with cavities (%)	23 (70)	17 (52)	
Mean number of cavities on chest radiographs with at least one cavity	2.1	1.9	2.0
Mean size of largest cavity (in cm)	5.3	8.1	6.7

Table 2 Types of abnormality on lung function testing among 33 patients completing treatment for MDR-TB

Type of disease	Patients *n* (%)
Restrictive disease (FEV_1 and FVC <80%, FEV_1/FVC ⩾0,8)	14 (42)
Combined disease (FEV_1 and FVC <80%, FEV_1 /FVC <0,8)	13 (39)
Obstructive disease (FEV_1/FVC <0.8 and FVC ⩾80%)	4 (12)
Normal (FEV_1 and FVC ⩾80%, FEV_1/FVC ⩾0.8)	2 (6)
Total	33 (100)

MDR-TB = multidrug-resistant tuberculosis; FEV_1 = forced expiratory volume of the first second; FCV = forced vital capacity.

was 56% of the predicted value. In comparison to the predicted values, the average loss of FVC was 1.13 ± 0.84 l and the average loss of FEV_1 was 1.2 ± 0.64 l; 12% (4/33) of patients had a FEV_1 <1 l/sec.

Linear regression analysis showed that the zonal score, the FEV_1 (% predicted) and the FVC (% predicted) were related to the time between the first TB diagnosis and completion of MDR-TB treatment (Table 3).

DISCUSSION

This cohort of MDR-TB patients, who completed treatment with second-line anti-tuberculosis drugs, showed extensive residual radiological abnormalities and significant lung function impairments. Almost all patients were considered as having an abnormal chest radiograph. The average zonal score was 6.5 of a maximum of 18. In other words, our patients had radiographic abnormalities affecting an average of 36% of their lung fields. A particularly disturbing finding was the high number of patients with residual cavitation. A study in South African mineworkers showed that the presence of cavitation at cure from tuberculosis was a risk factor for relapse, and the rate of recurrence was estimated at 22.9 per 100 person-years at risk (PYAR).[11] Although this latter study specifically excluded MDR-TB patients, we think that it is reasonable to speculate that cavities represent a risk for relapse in both drug-sensitive and MDR-TB. To ensure the timely detection of possible relapses, regular follow-up visits after completion of treatment will therefore have to be scheduled for these MDR-TB patients.

Table 3 Regression coefficient *b* and correlation coefficient *r* for zonal score, FEV_1 (% predicted) and FVC (% predicted) in relation to time between first TB diagnosis and completion of MDR-TB treatment

	Time between first TB diagnosis and completion of MDR-TB treatment (months)	
	Regression coefficient *b* (95%CI)	Correlation coefficient *r* (*P* value)
Zonal score	+0.069 (0.013–0.124)	+0.40 (0.020)
FEV_1 (% predicted)	−0.004 (−0.002–−0.006)	−0.51 (0.003)
FVC (% predicted)	−0.004 (−0.002–−0.006)	−0.48 (0.005)

FEV_1 = forced expiratory volume of the first second; FCV = forced vital capacity: MDR-TB = multidrug-resistant tuberculosis; CI = confidence interval.

Our data also show serious lung function impairments. Thirty-one of 33 patients (94%) had abnormal lung functions. Restrictive and combined restrictive-obstructive lung function patterns were predominant. Lung function tests were not done after bronchodilation, and the reduced FEV_1 may have been reversible in some cases. Several studies have investigated lung function after treatment for tuberculosis. Most of these studies have observed an obstructive, and less often a restrictive lung function pattern in a considerable proportion of patients. A study from Pretoria, South Africa, showed that 28% had obstructive and 24% had restrictive lung disease in a group of 76 patients cured of severe pulmonary tuberculosis.[12] Another study showed that the severity of lung function impairment was related to the number of episodes of pulmonary tuberculosis. Among South African gold miners, 18% of subjects with one episode, 27% with two episodes and 35% with three episodes of pulmonary tuberculosis had impaired lung function.[13] Even after cure from tuberculosis it seems that patients have a steeper decline in lung function with age than people who have never suffered from pulmonary tuberculosis. In a study from Cape Town, South Africa, 68% of patients had chronic obstructive lung disease an average of 16 years after cure of tuberculosis.[14] Our lung function results suggest that a large proportion of our patients have or will develop prematurely disabling respiratory disease, possibly affecting their quality of life and life expectancy.

The extensive residual lung damage documented by our data can probably be explained by the fact that our patients had active tuberculosis for prolonged periods. The duration of tuberculosis, defined as the time between the date of first diagnosis of tuberculosis and the date of completion of treatment for MDR-TB, was 51.8 months. Linear regression showed a direct relationship between FEV_1 (% predicted), FVC (% predicted), zonal score and duration of tuberculosis, as defined above. There were two main reasons for the long duration of active disease. Firstly, we estimate that the majority of our patients had acquired and not primary MDR-TB. The incidence of primary MDR-TB in South Africa is relatively low (1–2% of newly diagnosed TB patients). This means that most of our patients had first had at least one episode of drug-sensitive tuberculosis with either treatment failure or subsequent relapse. Secondly, in resource-limited countries mycobacterial sensitivity sputum testing is not done on newly diagnosed TB patients. The WHO and the South African guidelines for the treatment of drug-sensitive tuberculosis recommend collecting specimens for sensitivity

testing if there is no sputum AFB conversion after the initial and/or continuation phase of anti-tuberculosis treatment, as well as before starting patients on the retreatment regimen. This leads to relatively late recognition of MDR-TB. In addition, in our experience these recommendations are not followed consistently, mostly due to lack of knowledge among health care workers and logistical problems. Even more worrisome, annual surveys done in the Southern region of the province have recently shown a deterioration in the rate of sputum testing done at the recommended intervals (F J C Millard and R D Barker, personal communication).

There are some limitations to our data. A selection bias is possible, as nine patients were excluded due to missing data. Compared with the other 109 MDR-TB patients registered in the program since 1997, our study population did not differ with regard to sex distribution, mean age and proportion of HIV-positive individuals. Several confounding factors may have affected the results, including pneumoconiosis and smoking. However, none of the chest radiographs showed typical features of pneumoconiosis. Smoking habits were not recorded. There is no widely accepted scoring system for chest radiographs of tuberculosis patients; the scoring system we designed was essentially based on two parameters: the extent of the abnormalities and presence and size of cavitation. We used such a simple scoring system to ensure reproducibility. Despite the simplicity of the scoring system there was some disagreement between the two observers, especially with regard to the evaluation of cavities. However, the correlation between the zonal score and both the FEV_1 (% predicted) and the FVC (% predicted) were relatively good, with correlation coefficients r of 0.65 and 0.63. This suggests that there was internal consistency between the estimated extent of abnormalities on the chest radiograph and the degree of lung function abnormalities.

For the interpretation of the lung function test results we used the prediction equations from the NHANES III survey, as no population-based survey has established normal values for the whole South African population. To our knowledge only normal values for adult South African males have been established.[15] The comparison of the normal values for men predicted by the equations from the NHANES III and this latter study of South African males showed very small differences. Indeed there were average differences of only 3.1% between the predicted FVC and of 3.0% between the predicted FEV_1. As our study included also women, we chose the prediction equation for African Americans established by the NHANES III survey.

Our findings have important implications for the establishment of MDR-TB control programs in resource-limited countries. It has been questioned whether health services of poor countries should invest in the treatment of MDR-TB, considering the variable cure rates and high costs. Such programs might indeed prove to be a waste of effort and resources if the majority of cured patients have severe lung damage, high rates of recurrence and poor life expectancy.

We remain convinced that treatment of MDR-TB patients is necessary both for the benefit of the individual patients and to avoid a growing epidemic of MDR-TB. Indeed the cure rates of MDR-TB patients treated with short-course chemotherapy based on RMP and INH have been shown to be low.[16] Furthermore, mathematical models and population surveys suggest that the MDR-TB epidemic is likely to expand if no effective treatment is available.[17,18] However, it is essential that the establishment of MDR-TB control programs should go hand in hand with reinforcement of the DOTS strategy for drug-sensitive tuberculosis. Firstly, properly implemented DOTS-based programs reduce the incidence of patients with acquired MDR-TB, as has been pointed out previously. Secondly, it is important that sputum microscopy is done systematically after the completion of the initial and continuation phase of any anti-tuberculosis regimen, and if the result is positive, to perform a culture with sensitivity testing. Only the enforcement of this policy will ensure the timely detection of non-converters and possible MDR-TB cases. In the Limpopo Province these sputum verifications are often not done, mostly because of organizational problems. Thirdly, an MDR-TB program should include the establishment of a readily available TB culture and sensitivity testing facility. Finally, efforts should be made to ensure that health care workers know the indications for mycobacterial sensitivity testing.

In summary, our MDR-TB patients showed severe residual lung damage after completion of treatment. Further studies are needed to evaluate the long-term outcome of those MDR-TB patients who are considered as cured.

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RÉSUMÉ

CONTEXTE : Province de Limpopo, Afrique du Sud.
OBJECTIF : Apprécier les dégâts pulmonaires résiduels chez les patients qui ont achevé leur traitement pour une tuberculose à germes multirésistants (TB-MR).
SCHÉMA : A la fin du traitement, on a pratiqué un cliché thoracique et des examens fonctionnels pulmonaires. Les clichés ont été lus par deux observateurs indépendants qui ont attribué un score par zone entre 0 et 18 en fonction de l'étendue des anomalies radiologiques (opacifications ou cavités) et qui ont compté le nombre de cavités visibles et mesuré le diamètre de la plus grande d'entre elles.
RÉSULTATS : Le score moyen par zone est de 6,5. Une cavité est présente dans plus de la moitié des cas. Les tests fonctionnels pulmonaires donnent des résultats anormaux chez 31 de 33 patients (94%). Le VEMS médian atteint 63% et la capacité vitale forcée 57% des valeurs prédites. Les anomalies principales ont été des troubles fonctionnels restrictifs ou une combinaison de troubles restrictifs et obstructifs.
CONCLUSIONS : Les dégâts pulmonaires résiduels sont fréquents et étendus chez les patients atteints de TB-MR qui ont achevé leur traitement. Ceci peut accroître le risque de rechute de tuberculose et diminuer la qualité et l'espérance de vie de ces patients. Des efforts supplémentaires sont justifiés pour diagnostiquer précocement la TB-MR afin de réduire l'étendue des dégâts pulmonaires résiduels. Un suivi étroit des patients TB-MR achevant le traitement doit être assuré pour détecter les rechutes.

RESUMEN

CONTEXTO : Provincia de Limpopo, Sudáfrica.
OBJETIVO : Evaluar el daño pulmonar residual de los pacientes que completan el tratamiento de una tuberculosis multirresistente (TB-MR).
DISEÑO : Al final del tratamiento se practicaron una radiografía de tórax y pruebas funcionales respiratorias. Las radiografías fueron leídas por dos observadores independientes que atribuyeron un score por zona entre 0 y 18, dependiendo de la extensión de las anomalías radiográficas (opacificación o cavitación), que contaron el número visible de cavidades y que midieron el diámetro de la cavidad más grande.
RESULTADOS : El escore promedio por zona fue de 6,5. Se observó una cavitación en más de la mitad de los pacientes. De 33 pacientes, 31 (94%) tenían pruebas funcionales respiratorias anormales. La mediana del FEV_1 era de 63% y la capacidad vital forzada (FVC) era igual al 57% del valor esperado. Las anormalidades predominantes de la función respiratoria eran de tipo restrictivo y tipo combinado restrictivo-obstructivo.
CONCLUSIÓN : En los pacientes que completan el tratamiento de la TB-MR el daño pulmonar es frecuente y extenso. Este hecho puede aumentar el riesgo de recaída de tuberculosis y disminuye la calidad de vida y la esperanza de vida de estos pacientes. Se requiere hacer esfuerzos adicionales para el diagnóstico precoz de la TB-MR a fin de disminuir la extensión del daño residual pulmonar. A fin de detectar las recaídas, se debe asegurar un seguimiento estrecho de los pacientes que terminan el tratamiento de la TB-MR.