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Multi-drug resistant tuberculosis in the Netherlands

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Chapter 3

Individualised MDR-TB treatment

a | Multidrug-resistant tuberculosis: long-term treatment outcome in the Netherlands.

Geerligs WA, Van Altena R, De Lange WCM, Van Soolingen D, Van Der Werf TS.
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SETTING: Tuberculosis units (Beatrixoord, Haren; and Dekkerswald, Groesbeek) in the Netherlands.
OBJECTIVE: To study the long-term treatment outcome of patients with multidrug-resistant tuberculosis (MD-RTB).
DESIGN: Descriptive analysis of all consecutively admitted patients with MDR-TB between 1 January 1985 and 1 September 1998, with follow-up until 1 August 1999.
RESULTS: Of 44 patients (31 male) enrolled in the study, 33 were foreign born and none were human immunodeficiency virus positive. At diagnosis 38 patients had sputum-smear positive pulmonary TB, and converted culture negative after a mean of 6 weeks, while six converted to negative later (mean 69 weeks). Most patients had micro-organisms resistant to several antimycobacterial drugs (mean _ median: 5), including resistance to isoniazid and rifampin. In-patient treatment lasted a mean of 164 days (range 31–481), and patients were treated with six drugs on average. Side effects were common.
Treatment lasted for a mean of 608 days (range 268– 1626); five patients are still on treatment. Four patients were operated for TB, and two others were operated for post-TB sequelae. During the follow-up period six patients died, of whom three had active TB; 33 (75%) were considered cured.
CONCLUSION: Mortality was only 14% after a mean follow-up period of 53 months. MDR-TB can be successfully treated, but requires much effort from both patients and carers, and the costs may be higher than is affordable in resource-poor countries.

KEY WORDS: multidrug-resistant tuberculosis; tertiary care centre; outcome; survival

MULTIDRUG-RESISTANT tuberculosis (MDR-TB) is defined as a form of tuberculosis (TB) caused by strains of *Mycobacterium tuberculosis* that are resistant to at least isoniazid (INH) and rifampin (RMP). Drug resistance results from mutations in the genetic material of these mycobacteria.[1] One in every 10^6 mycobacteria is naturally resistant to INH because of spontaneous mutations in the katG gene,[2–5] which encodes for the katalase-peroxidase reaction, or the inhA gene.[3,4] One in every 10^8 –10^{10} mycobacterial divisions, mutations of the genes which encode for the RNA polymerase subunit B (rpoB) occur, resulting in RMP resistance.[6,7] The overall incidence of RMP-resistant mutants is estimated at one in 10^7 .

MDR-TB can emerge in several ways.[8–10] The chance of spontaneous mutations occurring, resulting in simultaneous resistance to INH and RMP, is exceedingly small. The chance of developing primary multiple drug resistance can be calculated by multiplying the mutation rates for the individual drugs, and is estimated to occur in one in 10^{13} mycobacteria.

Even in patients with high bacterial loads, i.e., in smear-positive pulmonary tuberculosis with an estimated mycobacterial load of 10^8 –10^9 micro-organisms, the chance of harbouring simultaneous INH and RMP-resistant tubercle bacilli resulting from spontaneous mutation is negligible, and would occur in only one in 10^4 –10^5 patients. Drug resistance is therefore believed to result from inadvertent monotherapy. Once resistance mutation has occurred, these resistant mutants soon replace the drug-sensitive bacterial population, and if monotherapy is in effect given to a patient with a high bacterial load, resistant mutants will again replace the microbial population, resulting in acquired drug resistance. Combination anti-tuberculosis treatment is therefore only effective in overcoming the problem of drug resistance if the mycobacterial population remains sensitive to at least two compounds.[11] Inadequate treatment may result from several sources: inaccurate prescription by a physician, inaccurate delivery of medication by the pharmacy, poor intrinsic quality or poor bioavailability of the drugs delivered by the pharmacy, bowel absorption disorders, and patient non-compliance. In a personal communication by Vegter, quoted by Lambregts-van Weezenbeek,[10] it was noted that 56% of all major errors in TB treatment observed during home visits were due to mistakes made by physicians and pharmacists. Another way of acquiring MDR-TB is by transmission of multiresistant mycobacteria. In the Netherlands, most cases of MDR-TB are imported from other countries, due to fugitive migration and international travel of the local and immigrant populations. In a 1993–1994 cohort study in the Netherlands, the majority of MDR-TB patients appeared to be foreign-born.[12] MDR-TB is notoriously difficult to treat for a number of reasons. Because of resistance to the most powerful bactericidal agent available, INH, sputum conversion is delayed in patients with MDR-TB compared to those infected with normally sensitive tubercle bacilli. Resistance to RMP is attributed to the fact that MDR-TB patients have a greater risk of relapse because this agent has not only bactericidal properties, but also a sterilising effect. As the first-line drugs RMP and INH cannot be used, patients with MD-RTB have to be treated with the so-called second-line agents. These drugs are generally less effective, i.e., their sterilising capacity is limited, and they are therefore not suitable for short-course chemotherapy (SCC). These drugs also have considerably more side-effects. The need to treat patients with MDR-TB over considerably longer periods of time than 6 months, with drug schedules that have a considerably higher toxicity profile, reduces the chance of patients complying with the prescribed treatment. Prolonged time for sputum conversion carries yet another risk—a prolonged period of transmission of the disease. It has been shown that MDR-TB patients

are equally likely to infect persons in their direct environment—as evidenced by a positive tuberculin skin test—as patients with drug-susceptible tuberculosis.[13] Directly observed therapy, short course (DOTS) has proved successful in many TB programmes throughout the world, both in poor-resource countries [14–17] and in affluent societies.[18,19] MDR-TB can be seen as a failure to supervise drug compliance in TB treatment, and therefore DOTS has become a standard approach for combating drug-susceptible TB.[20,21] Supervised treatment of MDR-TB is even more critical as reserve drugs are being used as a last resort.[22,23] In this paper we describe the results of intensive, predominantly in-patient, fully supervised treatment for MDR-TB patients in the Netherlands.

METHODS

Sites

Beatrixoord and Dekkerswald are the two specialized referral centres for tuberculosis in the Netherlands. Because of the complicated treatment that MDR patients require, and the need to prevent nosocomial transmission of MDR-TB, many physicians in the Netherlands refer MDR patients to one of these two centres for treatment.

Data retrieval

Retrospective data were collected of all patients who were admitted and treated for MDR-TB during the period 1 January 1985 to 1 September 1998. Most patients had received treatment prior to admission to Beatrixoord or Dekkerswald, but it was impossible to obtain valid data about this period. Data were collected on demographics, hospitalisation and treatment, the number of drugs used, duration of treatment and serious side-effects, disease localisation, symptoms and results of sputum smears and cultures with drug susceptibility test results. Risk factors for MD-RTB were assessed as follows: a history of TB treatment, recent immigration, close contact with patients with known MDR-TB, and non-compliance with anti-tuberculosis treatment. In vitro sensitivity test results were retrieved from the WHO/IUATLD-recognised National Reference Laboratory for Tuberculosis, National Institute of Public Health and the Environment, Bilthoven, the Netherlands. The modified absolute concentration method with 99% growth inhibition using Middlebrook 7H10 culture medium was used to determine sensitivity (NCCLS document M24-pV, 110:10. Antimycobacterial susceptibility testing). Breakpoints used for in vitro susceptibility are given in Table 1.

TABLE 1 Breakpoints for in vitro sensitivity and resistance

	Upper limit	Lower limit
Agent	for sensitivity	for resistance
Isoniazid	< 0–2 mg/L	>1 mg/L
Rifampin	< 1 mg/L	>1 mg/L
Pyrazinamide	< 50 mg/L	>100 mg/L
Ethambutol	< 5 mg/L	>10 mg/L
Streptomycin/kanamycin/ amikacin	< 5 mg/L	>10 mg/L
Ciprofloxacin/ofloxacin	< 2 mg/L	>2 mg/L
Rifabutin	< 2 mg/L	>2 mg/L
Prothionamide/ethionamide	< 5 mg/L	>5 mg/L
Cycloserine	< 50 mg/L	>50 mg/L
Thioacetazone	< 2 mg/L	>2 mg/L
Clofazimine	< 2 mg/L	>2 mg/L
Clarithromycin	< 16 mg/L	>16 mg/L

Side-effects were considered present if they were serious enough to discontinue medication or adjust the dosage. The time to sputum conversion was defined as the time from admission to the time of collection of the first in a series of two or more consecutive negative culture results, at least 2 weeks apart.[24] Treatment failure was defined as a positive culture after 5 months of adequate therapy;[25] and adequate therapy was defined as a regimen of drugs containing at least two drugs with in vitro susceptibility against the isolate;[24] such therapy was invariably instituted within 2 weeks after admission. Patients were considered compliant with therapy if they reported on a regular basis to the out-patient clinic and if they took their medications regularly according to their physician, family or specialised TB nurses.

Patients were followed until 1 August 1999. When these patients were no longer followed up by our tuberculosis unit out-patient departments, their general practitioners were contacted by telephone about their current state of health. Patients were considered cured if they had no clinical or microbiological signs of TB at the moment of follow-up. The costs of drug treatment, admission fees, and out-patient treatment were estimated based on 1999 prices in US$.

RESULTS

Patient characteristics

During the study period, 44 patients (31 males and 13 females) were treated for MDR-TB in the two centres. Eleven were indigenous to the Netherlands, two came from other European countries, 13 from Africa, nine from the Middle East and eight from the Far East. We were unable to trace the native country of one patient. The mean age at diagnosis was 33 years (range 10–82). Twenty-five patients were proven human immunodeficiency virus (HIV) negative; the remaining 19 were not tested as they did not belong to any of the known risk groups for HIV infection.

Disease characteristics

Most (38) of the patients had pulmonary tuberculosis, four had extra-pulmonary tuberculosis, and the remaining two had both pulmonary and extra-pulmonary disease. Only four were asymptomatic at hospitalisation, while the others had obvious symptoms.

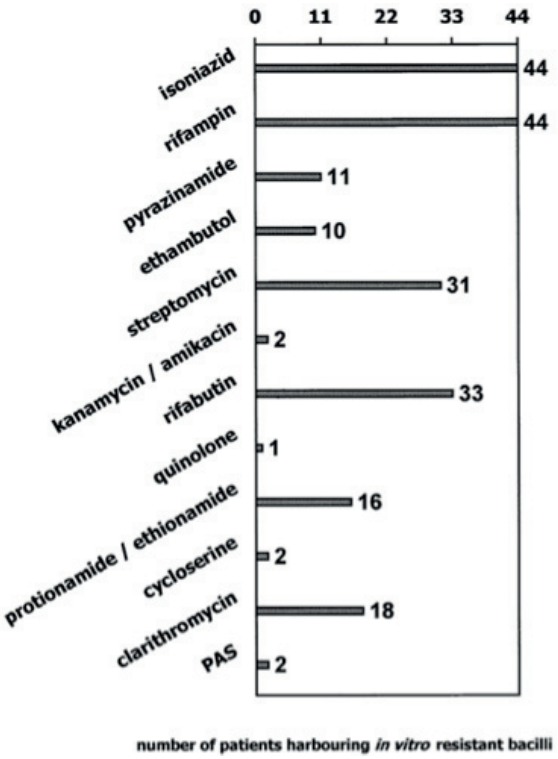

FIGURE 1 In vitro resistant tubercle bacilli recovered from 44 MDR-TB patients.

Twelve patients had fever, 34 had pulmonary complaints and 35 had constitutional symptoms. Most patients had organisms that were resistant to more agents than only INH and RMP, with resistance to a median and mean number of five drugs. Data on in vitro resistance to the separate agents are listed in the Figure.

Twenty-four of the patients had immigrated to the Netherlands less than two years before diagnosis; 34% had a history of previous treatment for TB and 36% had had close contact with a known TB patient.

Treatment and costs

At the start of treatment all patients were admitted to one of the units (39 to Beatrixoord, and five to Dekkerswald), and were discharged home after a mean admission episode of 164 days (range 31–481). All patients received an individually tailored combination of anti-tuberculosis drugs, depending on the drug susceptibility reports, and based on previously prescribed anti-tuberculosis drugs, when known. In the latter period of the study, the general policy was to start with a regimen of an aminoglycoside, a quinolone and two to three additional drugs, but for patients treated in the 1980s the drug prescribing policy was less specific. The number of different compounds for each individual patient was six on average (range 4–9).

Drug therapy was continued for a mean period of 608 (268–1626) days. Five patients had not completed treatment at the time of writing, but were responding well. Their drug therapy was scheduled to be continued for a mean of 124 days. Twenty-four patients suffered significant side effects. An overview of all drugs prescribed, all experienced side effects and the duration of drug treatment is given in Table 2.

In Table 3, the number and range of antimycobacterial agents are given for each pattern of in vitro test results against five first-line antimycobacterial agents. Despite the recorded drug resistance, most patients were still treated with INH because it was assumed that if the in vitro catalase reaction proved positive, a subset of the micro-organisms in the clinical isolate were still INH-susceptible. Three patients underwent a pneumonectomy because of treatment failure; shortly after the operation, their cultures became negative.

One patient underwent an elective pleuropneumonectomy in order to reduce the risk of relapse from a destroyed lung. Two other patients underwent a lobectomy after they were considered cured of their TB, because of an aspergilloma in an old cavernous lesion. Forty-one patients had sputum examination on a regular basis.

TABLE 2 Anti-tuberculosis drug treatment in 44 patients with MDR-TB; duration of treatment and reported side effects

Agents	Patients (N)	Duration in days (range)	Total side effects (n)	Side effect
Isoniazid	36	471 (20-1684)	3	N, S, L
Rifampin	5	341 (85-534)		
Pyrazinamide	38	461 (18-1001)	5	L, J
Ethambutol	42	526 (44-1474)	4	I, K, V
Aminoglycoside	40	108 (20-383)	6	H, I, N, K
Quinolone	38	504 (31-898)	4	L, I, J, K
Rifabutin	9	276 (14-1474)	1	S
Prothionamide	16	244 (6-617)	6	P, L, I
Thioacetazone	4	511 (415-651)		
Cycloserine	5	193 (16-478)	2	N, P
Gamma interferon	1	21		
Clofazimine	39	533 (75-1474)	2	S, K
Clarithromycin	2	520 (443-596)		
Co-amoxiclav	1	61		

N = neurological disorders; S = itching; L= liver-test abnormalities; J = joint complaints; I = gastro-intestinal complaints; K = renal dysfunction; V = visual disorder; H = acoustic symptoms; P = mental disturbances.

At the time of admission, 29 patients were sputum culture positive, and 22 of these also had a positive direct sputum smear. After a mean period of 6 weeks (range 1–20), 23 patients converted to sputum culture negative. Therapy failed initially in six patients, but after a period of 69 weeks on average (range 24–181), their sputum also converted. The total costs per patient for treatment amounted to US$60,000.

Follow up

The mean follow-up period from the first day of hospitalization was 1610 days (range 268 4288)— about 53 months. The mean survival from the day of diagnosis was 1904

days (range 421–5382)—about 62 months. Six patients (14%) died during the follow-up period. In only one patient was the cause of death directly related to TB: he died of a relapse. Two other patients dying during treatment for active TB died from other causes, one from *Staphylococcus aureus* sepsis and the other from complications of pancytopenia in concomitant Gaucher's disease. The remaining three patients died of progression of pulmonary carcinoma and other unrelated conditions after completion of their TB treatment, without any evidence of TB relapse.

Five patients had not yet completed therapy, but had no clinical or microbiological signs of active TB. The remaining 33 patients (75%) are considered cured of their MDR-TB. Only one patient had a relapse, 2 years after completion of treatment; this was the only patient to die as a result of active TB.

TABLE 3 Drug resistance patterns to first-line anti-tuberculosis agents and subsequent treatment decisions

		Number of patients for whom each of the listed drugs was prescribed										
Patterns of multiple drug resistance	**No. of patients with each resistance pattern**	**Isoniazid**	**Rifampin**	**Pyrazinamide**	**Ethambutol**	**Aminoglycoside***	**Quinolones†**	**Rifabutin**	**Prothionamide**	**Cycloserine**	**Thioacetazone**	**Clofazimine**
INH/RMP	7	6		7	7	6	5	2	1	1	1	7
INH/RMP/SM	16	13	2	16	16	14	14	3	3	2	1	11
INH/RMP/EMB	4	2		4	4	4	4		1	1	1	4
INH/RMP/PZA	2	2	1	2	2	1	2		2			2
INH/RMP/SM/EMB	6	5	1	6	5	6	5	2	2		1	6
INH/RMP/PZA/SM	6	5		3	6	6	6	1	5			6
INH/RMP/SM/EMB/PZA	3	3	1		2	3	2	1	2	1		3
All patterns	44	36	5	38	42	40	38	9	16	5	4	39

* amikacin, kanamycin or streptomycin.

† Ciprofloxacin or ofloxacin.

INH = isoniazid resistance; RMP = rifampin resistance; SM = streptomycin resistance; EMB = ethambutol resistance; PZA= pyrazinamide resistance.

DISCUSSION

This study shows that MDR-TB can be cured in the vast majority of cases in the setting described. MDR-TB has been referred to as the 'new tuberculosis' which is more often than not a deadly scourge for mankind.[26] This view is largely based on several earlier reports on long-term treatment outcome in MDR-TB.

One large study in 171 patients showed poor outcome after a mean follow-up period of 5 years, in which only 56% of patients responded, and 20% of mortality was attributed to TB.[27] Another report by Park et al. showed that HIV-positive patients have a particularly poor prognosis: 77% of HIV-positive MDR-TB patients died, whereas HIV-negative patients had a mortality of 20%.[28] Another important factor influencing prognosis in this study was the institution of inadequate treatment. One South African study showed that only 27% of the patients were considered cured after a follow-up period of 5 years.

Treatment outcome of MDR-TB was therefore comparable with the treatment outcome of (drug-sensitive) TB in the period before antimycobacterial drug treatment was available.[29]

Not all of our pulmonary TB patients (29 of 40 patients with pulmonary involvement) were sputum culture or smear positive. This may reflect the possibility that in 11 of these patients the treatment started by their referring doctors had converted them to negative, and that the pre-hospital treatment period should be added to estimate the total time required for their treatment.

Not all the patients were tested for HIV co-infection, notably in the initial years of the study. We have assumed that these patients were HIV-negative, both because they did not belong to any known risk group for HIV infection, and because they remained in good health after completion of TB treatment in the absence of retroviral therapy. We have no data to suggest any measurable benefit from some of the medications prescribed such as clofazimine, clarithromycin and co-amoxiclav (Tables 2 and 3, Figure), and we are well aware of the controversy about their effectiveness. The data presented merely suggest that the care provided appeared effective for most of the patients. Although the costs involved for treatment compared favourably with a report from the United States by Mahmoudi, who calculated an average of US$180000 (in 1993) per patient,[30] it is clear that such costs cannot be afforded in most resource-poor countries. We believe, however, that not all reports of poor treatment outcome of MDR-TB are disappointing due to financial restraints.[31,32]

Our results confirm the hypothesis that MDR-TB can be cured, provided that patients are treated with an adequate drug combination, by a committed team who apply the principles of close supervision.[22,23] Mortality after a median follow-up of 53 months was 14%, with half of the patients dying during TB treatment, and only one death (2–3%) directly caused by active TB. Because patients are treated with drugs that are known to be potentially toxic and have significant side-effects, and because of the need for

prolonged use of the drugs, it is even more important to motivate patients to comply with treatment than in normally drug-sensitive TB.[33,34] Despite the serious side-effects in 22 patients, only nine appeared to be non-compliant with therapy at any one time during the treatment period. We believe that this is an important aspect of the treatment of MDR-TB.[35] Our practice has been to emphasise education and psychosocial support of patients. The DOTS-plus strategy implies close treatment supervision by our nurses, a practice that is continued after discharge from the unit by a specialised nurse from the Municipal Health Service. Special care is taken so that patients feel free to call or contact health staff informally whenever they experience any problems.

A limitation of the study is that our patients agreed to be admitted—some patients might not have agreed to be referred to one of the units in the first place, and might have absconded. Compulsory treatment is not possible under Dutch law, and some MDR-TB patients may have experienced difficulties due to cultural or language barriers. Dutch immigration authorities have agreed to allow illegal immigrants who subsequently appear to suffer from disease to complete their medical treatment before any court sentence to expel them from the Netherlands is implemented. In the earlier quoted national Dutch cohort survey, six of 19 patients defaulted, four were transferred outside the Netherlands, and only nine were considered cured.[12]

In the Netherlands, the number of TB cases has been low. The 1997 incidence was 9.5/100 000 population (Tuberculosis Index 1997, Royal Netherlands Tuberculosis Association, The Hague, 1999), and this figure has changed little over recent years. The problem of resistance is also limited—12% of TB patients have bacilli with resistance to one or more agents, and only 1% have multiresistant bacilli.[10] Although MDR-TB may not be a major health problem in the Netherlands, it certainly is a large problem world-wide. Pablos-Mendez et al. showed that few countries participating in the global study on the prevalence of drug-resistant TB were free from the problem of MDR-TB, [25] with prevalence rates ranging from nearly 0 to 22% (mean 2.2%). The highest prevalence of MDR-TB was found in Asia, the former Soviet Union, the Dominican Republic and Argentina. The higher prevalence rates for MDR-TB appeared to correlate with the lack of a well organised national anti-tuberculosis programme, with implementation of the WHO-TB control strategy. The best way to combat MDR-TB is to prevent it.[22] Migration and international travel have rendered regional and national efforts futile. To fight MDR-TB and TB in general requires both a global and a holistic approach.[36]

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