# Clinical evolution of a group of patients with multidrug-resistant TB treated at a referral center in the city of Rio de Janeiro, Brazil*

## Evolução clínica de um grupo de pacientes com TB multirresistente atendidos em um centro de referência na cidade do Rio de Janeiro

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## Abstract

**Objective:** To analyze the clinical characteristics and evolution of a group of patients with positive sputum cultures for multidrug-resistant (MDR) *Mycobacterium tuberculosis* and treated at a referral center in the city of Rio de Janeiro, Brazil. **Methods:** Based on the positive results in sputum cultures for MDR *M. tuberculosis*, 50 patients were selected, and their clinical data were obtained from the Brazilian Ministry of Health MDR-TB Database. The frequencies of noncompliance, relapses, failures and previous treatments for TB up to diagnosis of MDR-TB were compiled. The radiological patterns were classified as unilateral or bilateral, and with or without cavitation. Two years after the end of the standard treatment for MDR-TB, the outcome (cure, failure, noncompliance or death) for each patient was evaluated and reassessed every two years. The post-treatment follow-up period was eight years. **Results:** The mean number of previous treatments was 2.3 ± 0.9. The mean interval between the initial diagnosis and the development of MDR-TB was 2.0 ± 1.7 years. Two years after the initial treatment for MDR-TB, 2 patients had abandoned treatment, 8 had died, 18 had been cured, and 22 had presented treatment failure. The bivariate analysis showed that bilateral pulmonary involvement and cavitary pattern markedly reduced the chances for cure, with a relative risk of 1-0.6 (40%) and 1-0.7 (30%), respectively. At the end of the follow-up period, 2 patients had abandoned treatment, 9 had presented treatment failure, 17 had been cured, and 22 had died. **Conclusions:** Bilateral pulmonary involvement and cavity pattern greatly reduced the chances for cure of the patients with MDR-TB. Most patients who presented treatment failure died within the 8-year follow-up period.

**Keywords:** Tuberculosis, multidrug-resistant; Treatment outcome; Disease-free survival; Treatment refusal; Treatment failure.

## Resumo

**Objetivo:** Analisar as características clínicas e a evolução de um grupo de pacientes com culturas de escarro positivas para *Mycobacterium tuberculosis* multirresistente (MR) e tratados em um centro de referência no município do Rio de Janeiro. **Métodos:** A partir dos resultados de *M. tuberculosis* MR em culturas de escarro, foram selecionados 50 pacientes cujos dados clínicos foram obtidos através do Banco de Dados TBMR do Ministério da Saúde. Foram considerados a frequência de abandono, as recidivas, as falências e os tratamentos prévios para TB até o diagnóstico de TBMR. O padrão radiológico foi classificado em uni- ou bilateral, e cavitário ou não. Dois anos após o término do tratamento padronizado para TBMR, o desfecho (cura, falência, abandono ou óbito) de cada paciente foi avaliado e repetido a cada dois anos. O período de seguimento foi de oito anos após o tratamento. **Resultados:** A média do número de tratamentos prévios foi de 2,3 ± 0,9. O tempo médio entre o diagnóstico inicial e o desenvolvimento de TBMR foi de 2 ± 1,7 anos. Após dois anos do tratamento inicial para TBMR houve 2 abandonos, 8 óbitos, 18 curas e 22 falências. A análise bivariada mostrou que o comprometimento pulmonar bilateral e o padrão cavitário reduziram acentuadamente a chance de cura, com risco relativo de 1-0,6 (40%) e 1-0,7 (30%), respectivamente. Ao final do seguimento, houve 2 abandonos, 9 falências, 17 curas e 22 óbitos. **Conclusões:** O comprometimento pulmonar bilateral e lesões cavitárias reduziram a possibilidade de cura dos pacientes com TBMR. A maioria dos pacientes com falha de tratamento evoluiu para óbito no período de 8 anos.

**Descritores:** Tuberculose resistente a múltiplos medicamentos; Resultado de tratamento; Sobrevivência livre de doença; Recusa do paciente ao tratamento; Falha de tratamento.

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## Introduction

Tuberculosis continues to be the single-agent infectious disease that kills the largest number of people worldwide.[1] The situation is aggravated by the emergence of bacteria that are resistant to the principal drugs used and by the high dissemination capacity of such bacteria.[2] In Brazil, there were 81,485 new TB cases in 2004, which corresponds to an incidence of 48.5 cases/100,000 population—with great regional variations—and the estimated mortality is 5,000 cases per year.[3] The state of Rio de Janeiro has the highest incidence of TB in the country: 87.5/100,000 population. In the city of Rio de Janeiro, this number increases to 105/100,000 population, reaching a much greater proportion in some pockets of poverty A nationwide epidemiological survey carried out by the Brazilian National Ministry of Health (NMH) from 1996 to 1997 showed that the rate of acquired resistance for the combination of isoniazid (INH) and rifampin (RMP) was 7.9%, whereas the rate of primary resistance was 1.1%.[6] Since this value is low, it allows, for TB cases not treated previously, the use of regimen I, which includes three drugs—INH, RMP and pyrazinamide (PZA)—unlike the regimen including four drugs, which is standardized in many countries.[7]

Poor compliance and noncompliance with treatment are the leading causes of multidrug-resistant TB (MDR-TB)-related deaths and of the progressive increase in primary resistance.[8] Internationally, MDR-TB is defined as resistance to at least INH and RMP. In Brazil, since there is regimen III—streptomycin (SM), PZA, ethambutol (EMB) and ethionamide—standardized by the NMH and administered in health care facilities,[7] MDR-TB is defined as resistance to INH, RMP and at least one more drug (SM, PZA or EMB) or as resistance to INH and RMP and failure of regimen III. These are the definitions of MDR-TB adopted in the present study.[9,10] The treatment for MDR-TB standardized by the NMH included the use of five drugs: clofazimine; EMB (or PZA); amikacin; terizidone; and ofloxacin. In 2005, clofazimine was withdrawn from the regimen, as recommended by the World Health Organization (WHO). The treatment, dispensed through the NMH Professor Hélio Fraga Referral Center for Tuberculosis and administered for 18 to 24 months, is known to be less effective than are first-line regimens, as well as presenting greater side effects and being much more expensive.[11]

The MDR-TB epidemiological surveillance database shows that, between 2000 and 2006, a total of 2,600 new cases of this form of TB were reported in Brazil. In 96% of the cases, resistance was acquired, with an average of 2.8 previous treatments. The rate of primary resistance was 4%, and the rate of TB/HIV co-infection was 8%. The data reveal that 66% of the cases presented bilateral pulmonary cavitations and 12% presented unilateral cavitations. Of the patients treated, 56% were cured, 8% abandoned treatment, 25% died, and 11% presented treatment failure and chronic disease. Between 2000 and 2002, 45% of the MDR-TB cases occurred in the state of Rio de Janeiro.[12]

The principal mechanism of *Mycobacterium tuberculosis* resistance to the drugs currently used is genetic mutation. This mechanism occurs whenever the bacterium remains in contact with the drug, for a variable period of time, at concentrations below the minimum inhibitory concentration, or the strain already presents a specific natural mutation that makes it resistant to the drug and is selected by an inappropriate treatment regimen.[13]

The present study originated from a survey, conducted in collaboration with Professor Hélio Fraga referral center, of MDR *M. tuberculosis* strains isolated from sputum samples—Löwenstein-Jensen (LJ) medium—using a molecular biology technique. Each culture corresponded to one patient. The objective was to determine the damage that those genetically modified bacteria caused to patients, as well as to analyze the clinical evolution of such patients.

## Methods

The survey from which the present study originated was approved by the Ethics in Research Committee of the Pedro Ernesto University Hospital, *Universidade Estadual do Rio de Janeiro* (UERJ, Rio de Janeiro State University).

Initially, the data of 58 patients living in the city of Rio de Janeiro and nearby towns were examined based on the identification of the respective cultures, whose sensitivity tests were performed on LJ medium using the propor-

tion method.[14] The information was obtained from the MDR-TB epidemiological surveillance database of the NMH. The fact that we opted to include only patients from Rio de Janeiro allowed us to review the charts and analyze the cases more properly. Eight cases were excluded due to missing data. The group of 50 patients became a cohort in which the observations were divided into two phases: the first phase, from the initial diagnosis of TB to the development of MDR-TB; and the second phase, from the diagnosis of MDR-TB to the final outcome (cure, failure, death or permanent noncompliance with treatment). In order to facilitate the analysis, the second phase was divided into two-year follow-up periods, up to eight years or more. In the first two years, the patients were treated for MDR-TB with the standardized regimen including the five drugs mentioned above, with some modifications, according to the needs of each case. The outcomes in this period were as follows: cure, with consistent negative conversion of cultures up to month 12 of treatment, and with cultures remaining negative for more than six months of treatment, with no clinical or radiological signs of active disease; permanent noncompliance; death; and treatment failure, with persistence of positive cultures up to month 12 of treatment.[11]

For the analysis, we considered the following: sensitivity test results; age of patients in the initiation of treatment for TB (pre-MDR-TB) and year of initiation; gender; race; level of education; comorbidities; results of the treatment with regimen I, regimen IR (regimen I plus EMB) and regimen III, as standardized by the NMH[9]; frequencies of treatments, noncompliance, cure followed by relapse and failure before the diagnosis of MDR-TB; type of resistance (acquired or primary); time taken to develop MDR-TB; radiological pattern (unilateral or bilateral lesion, with or without cavitation) at the moment MDR-TB was diagnosed; body weight fluctuation between treatment initiation and the final outcome; hospitalizations during the evolution of the case; and outcome. Primary resistance was defined as MDR-TB acquired from a known TB contact, usually familial, and absence of noncompliance during the initial treatment. The index cases are not part of our sample. The treatments were self-administered or partially supervised. In this group, none of the patients were submitted to surgery with the objective of curing MDR-TB.

As part of the routine of the referral center, the patients, during the treatment for MDR-TB, were monitored monthly, at which time sputum cultures were performed. Those presenting failure were monitored every three months, and continued using the terizidone-EMB-ofloxacin regimen throughout the follow-up period.

The information collected was compiled in an Excel® 2003 spreadsheet and analyzed using the programs Epi Info, version 3.4, which is a public domain program, and the Number Cruncher Statistical System 2000 (NCSS Inc., Kaysville, UT, USA). The results of the analysis of categorical variables are presented as percentages,

**Table 1 -** Drug resistance of the strains isolated from patients during the phase of multidrug-resistant TB.

| Number of drugs with resistant strains | Drugs tested and pattern of resistance[a] | Number of resistant strains (n = 50) |
|---|---|---|
| 5 | RMP-INH-PZA-EMB-SM | 12 |
| 4 | RMP-INH-PZA-EMB-SM[b] | 3 |
| | RMP-INH-PZA-EMB[b]-SM | 2 |
| | RMP-INH-PZA-/-SM | 1 |
| | RMP-INH-/-EMB-SM | 3 |
| 3 | RMP-INH-/-EMB-SM[b] | 7 |
| | RMP-INH-/-EMB[b]-SM | 6 |
| | RMP-INH-/-/-SM | 1 |
| | RMP-INH-/-EMB-/ | 4 |
| | RMP-INH-PZA-EMB[b]-SM[b] | 6 |
| | RMP-INH-PZA[b]-EMB-SM[b] | 1 |
| | RMP-INH-PZA-/-/ | 1 |
| 2 | RMP-INH-PZA[b]-EMB[b]-SM[b] | 3 |

RMP: rifampin; INH: isoniazid; PZA: pyrazinamide; EMB: ethambutol; SM: streptomycin. [a]The slash (/) indicates lack of result. There was no result for PZA in 21 strains, for EMB in 3 strains and for SM in 2 strains. [b]Sensitive drugs.

and those of continuous variables are presented as means and respective SD. The strength of the association between risk factors and the outcome studied was measured using relative risk (RR) and the respective 95% CI. The statistical significance of the differences observed among dichotomous variables was analyzed using Pearson's chi-square test and Fisher's exact test, when indicated, whereas the statistical significance of the differences observed among numerical variables was analyzed using the Kruskal-Wallis test. Figures are used in order to make the results more easily understood.

## Results

Table 1 lists the results of culture sensitivity tests to first-line drugs. In 21 cases, there was no result for PZA due to the difficulty in maintaining an acid pH on LJ medium during the sensitivity test. In 3 cases, there was no result for EMB, and, in 2, there was no result for SM. The initial TB treatment was administered between 1991 and 2003, and the diagnosis of MDR-TB was made between 1995 and 2003. Patient ages at treatment initiation ranged from 14 to 66 years (mean ± SD: 33.8 ± 13.3 years). Most patients (62.0%) were male. There was a predominance of mulatto and black patients over the other categories. It was observed that most patients (48%) had completed elementary school or junior high and only 8.0% were illiterate. Regarding comorbidities, 12 patients (24.0%) presented previous conditions, such as alcoholism (6 cases), HIV infection/AIDS (3 cases), asthma (1 case), COPD (1 case) and mental illness (1 case). All of the 50 cases initially received regimen I. Of those, 21 abandoned treatment, 18 presented failure (1 underwent retreatment with regimen I, regimen III and regimen IR, whereas the others underwent retreatment with regimen III), and 9 were cured and subsequently relapsed. We obtained no information about 2 cases. Of the remaining 48 patients, 34 received regimen III—29 of whom presented failure and 5 of whom abandoned treatment—whereas 14 patients did not receive regimen III. The mean number of treatments for TB was 2.3 (ranging from 1 to 6), whereas the mean number of patients who abandoned treatment was 0.8 (range, 0-3) and the mean number of patients who presented failure was 1.2 (range, 0-3). Resistance was acquired by 44 patients (84%), and 6 presented primary

**Table 2 -** Clinical and demographic variables of the 50 patients during the treatment for TB and during the treatment for multidrug-resistant TB.

| Variable | Result |
|---|---|
| Age, mean ± SD | 33.8 ± 13.3 |
| Gender, n (%) | |
| Mal | 31 (62.0) |
| Female | 19 (38.0) |
| Race, n (%) | |
| Caucasian | 21 (42.0) |
| Mulatto | 13 (26.0) |
| Black | 10 (20.0) |
| Not stated | 6 (12.0) |
| Years of schooling, n (%) | |
| 0 (illiterate) | 4 (8.0) |
| 1 to 3 | 13 (26.0) |
| 4 to 7 | 11 (22.0) |
| 8 to 11 | 8 (16.0) |
| Comorbidities, n (%) | |
| Yes[a] | 12 (24.0) |
| No | 38 (76.0) |
| Initial TB treatment, mean ± SD | |
| Number of patients who were cured or relapsed | 0.3 ± 0.6 |
| Number of patients who abandoned treatment | 0.8 ± 0.9 |
| Number of patients who presented treatment failure | 1.2 ± 0.8 |
| Time (in years) to the diagnosis of MDR-TB, mean ± SD | 2 ± 1.7 |
| Pulmonary involvement, n (%) | |
| Bilateral | 38 (76.0) |
| Unilateral | 12 (24.0) |
| Radiological pattern, n (%) | |
| With cavitation | 36 (72.0) |
| Without cavitation | 14 (28.0) |
| Hospitalization, n (%) | |
| Yes | 21 (42.0) |
| No | 21 (42.0) |
| Not known | 8 (16.0) |
| Clinical evolution after a 2-year period, n (%) | |
| Cure | 18 (36.0) |
| Failure | 22 (44.0) |
| Death | 8 (16.0) |
| Noncompliance with treatment | 2 (4.0) |
| Clinical evolution after an 8-year period, n (%) | |
| Cure | 17 (34.0) |
| Failure | 9 (18.0) |
| Death | 22 (44.0) |
| Noncompliance with treatment | 2 ( 4.0) |

MDR-TB: multidrug-resistant tuberculosis. [a]Comorbiditiess: alcoholism (6 cases), HIV infection/AIDS (3 cases), mental illness (1 case), asthma (1 case) and COPD (1 case).

resistance. The mean interval up to the diagnosis of MDR-TB was 2 years (ranging from less than 1 year to 6 years). The mean age of the patients at the time of MDR-TB diagnosis was 36.4 years (range, 14-69 years; the 14-year-old patient was a case of primary resistance, diagnosed early). Of the 48 patients who received treatment for MDR-TB and were evaluated in the first 2-year period (2 abandoned treatment in this phase), 12 (24%) initially presented unilateral lung disease and 36 (76%) presented bilateral lesions. In addition, 72% of those 48 patients presented cavitations. In this period, 6 (12.5%) of the 12 patients with unilateral disease were cured, 1 (2%) died after 26 days of treatment (HIV and mediastinal abscess due to MDR-TB), and the remaining 5 (10.4%) presented treatment failure. Within the same period, of the 36 cases with bilateral involvement, 12 (25%) were cured, 17 (35.4%) presented treatment failure, and 7 (14.6%) died (Figure 1). The remaining epidemiological and clinical aspects are presented in Table 2. The interval between the diagnosis of MDR-TB and the last piece of information obtained about the patient ranged from less than 1 year to 10 years (mean ± SD: 2.9 ± 2.4 years). The number of patients who were cured, presented failure or died by follow-up period is presented in Figure 2.

After the second year of treatment, the number of patients who were cured decreased slightly. One patient considered cured relapsed, underwent retreatment and presented failure. We preferred not to use the Kaplan-Meier survival curve since we believe that Figure 2 offers more information. This chart was constructed taking into account the follow-up period for each patient. The last period refers to an 8-year follow-up period or longer. At the end of this period, 2 (4%) of the 50 patients diagnosed with MDR-TB had abandoned treatment, 17 (34%) had been cured (effectiveness of treatment), 9 (18%) continued presenting treatment failure, and 22 (44%) had died.

Table 3 presents the results of the bivariate analysis performed to identify the factors associated with the cure of MDR-TB after the first 2-year follow-up period. The 2 cases, mentioned above, of patients who abandoned treatment were excluded. A statistically significant difference was found between the patients who were cured (cured group) and the others (uncured group) in terms of mean age (38.0 *vs.* 30.5 years, respectively; p = 0.04). There was a statistically significant difference in body weight between the cured and the uncured group in the initial phase of the treatment (58.0 *vs.* 49.0 kg; p = 0.02) and in the final phase (63.8 *vs.* 47.8 kg; p < 0.001).

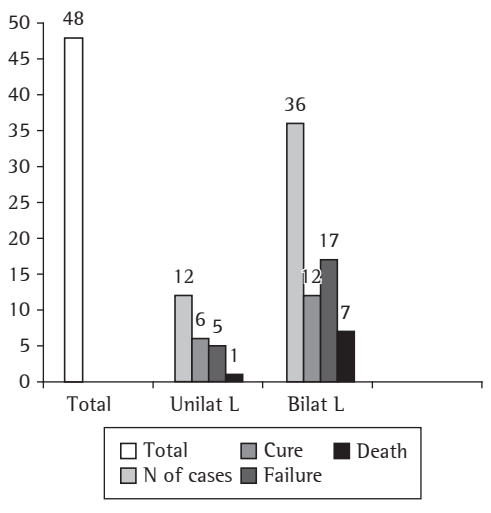


**Figure 1 -** Number of patients after two years of treatment for multidrug-resistant TB (two patients abandoned treatment) and type of outcome after these two years of treatment by type of pulmonary lesion diagnosed at treatment initiation: unilateral lesion (Unilat L) or bilateral lesion (Bilat L).

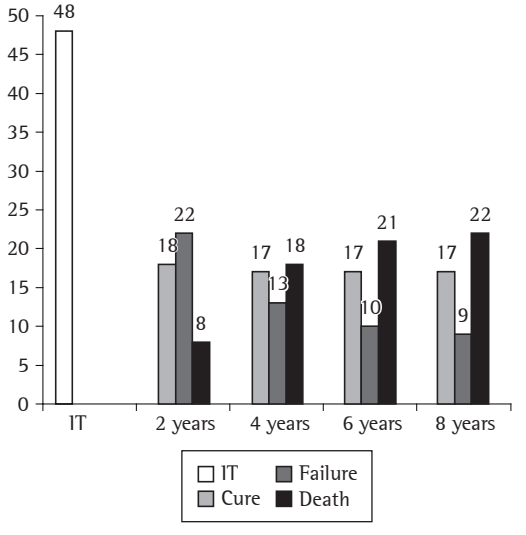


**Figure 2 -** Type of patient outcome from the initial period of treatment (IT) for multidrug-resistant TB up to an eight-year follow-up period. After the first two years, the number of patients who were cured decreased slightly. Only one patient presented recurrence.

Although there were no statistically significant differences between the two groups in terms of the other variables, it is of note that, among the patients who were cured, there was a lower percentage of bilateral pulmonary involvement (66.7% *vs.* 80.0%) and a lower percentage of cavitary disease (60.0% *vs.* 76.7%). Bilateral pulmonary involvement reduced by 40% the chance for cure within 2 years (RR, 1-0.6), whereas radiological cavitary pattern reduced this chance by 30% (RR, 1-0.7), as shown in Table 3.

## Discussion

Between 2000 and 2006, there were 2,600 new cases of MDR-TB in Brazil.[11] However, in the same period, approximately 30,000 patients died (5,000 per year),[4] many of whom were still possibly sensitive to regimen I or at least to regimen III, or were never diagnosed with TB.[15] The impossibility of seeking or finding appropriate medical treatment, noncompliance with treatment and relapse, which are often related to alcoholism, poor socioeconomic conditions and HIV co-infection, explain the high mortality and the development of MDR-TB.[16-18] The directly observed therapy, short-course strategy, has been the most successful method to reduce noncompliance, the number of deaths and the number of MDR-TB cases, and its implementation has been made a priority in the country, although, to date, this has happened slowly and in a nonuni-

**Table 3 -** Bivariate analysis of the factors associated with cure of multidrug-resistant TB after a two-year follow-up period (n = 48).

| Variable | Cure (n = 18) | No cure (n = 30) | RR | p |
|---|---|---|---|---|
| Age, mean ± SD | 38.9 ± 13.5 | 30.5 ± 12.2 | --- | 0.04* |
| Initial weight, mean ± SD | 58.0 ± 8.8 | 49.3 ± 11.1 | --- | 0.02* |
| Final weight, mean ± SD | 63.8 ± 8.2 | 47.8 ± 12.0 | --- | < 0.001* |
| Number of previous treatments, mean ± SD | 2.4 ± 1.1 | 2.2 ± 0.7 | --- | 0.96 |
| Number of patients who were cured, mean ± SD | 0.29 ± 0.5 | 0.26 ± 0.7 | --- | 0.56 |
| Number of patients who abandoned treatment, mean ± SD | 1.1 ± 1.0 | 0.59 ± 0.7 | --- | 0.09 |
| Number of patients who presented treatment failure, mean ± SD | 1.1 ± 0.8 | 1.4 ± 0.7 | --- | 0.18 |
| Gender, n (%) | | | | |
| Male | 13 (72.2) | 17 (56.7) | 1 | 0.28 |
| Female | 5 (27.8) | 13 (43.3) | 2.0 (0.5-8.5) | |
| Race, n (%) | | | | |
| Black | 4 (22.2) | 9 (30.0) | 0.7 (0.1-3.0) | 0.73 |
| Others | 12 (66.6) | 17(60.4) | 1 | |
| Comorbidities, n (%) | | | | |
| Yes | 4 (22.2) | 6 (20.0) | 1.1 (0.5-2.6) | 1.0 |
| No | 14 (77.8) | 24 (80.0) | 1 | |
| Type of resistance, n (%) | | | | |
| Primary | 2 (11.1) | 4 (13.3) | 0.9 (0.3-3.0) | 1.0 |
| Acquired | 15 (83.3) | 25 (83.3) | 1 | |
| Pulmonary involvement, n (%) | | | | |
| Unilateral | 6 (33.3) | 6 (16.7) | 0.6 (0.3-1.2) | 0.29 |
| Bilateral | 12 (66.7) | 24 (80.0) | 1 | |
| Pulmonary involvement, n (%) | | | | |
| With cavitation | 12 (60.0) | 23 (76.7) | 0.7 (0.4-1.6) | 0.51 |
| Without cavitation | 6 (40.0) | 7 (23.3) | 1 | |
| Hospitalization, n (%) | | | | |
| Yes | 8 (44.4) | 19 (63.3) | 0.6 (0.3-1.3) | 0.2 |
| No | 10 (55.6) | 11 (36.7) | 1 | |

RR: relative risk. *Statistical significance.

form manner.[19] It is of note that there were few HIV/AIDS cases and few cases of alcoholism in our sample. This is possibly due to the fact that the patients had already been selected from a larger group by having survived the initial manifestation of the disease. The gold standard for the diagnosis of primary resistance is the sensitivity test of the material obtained before the first treatment. Operationally, this is difficult, and that is why the definition presented was used, making it possible to diagnose MDR-TB more rapidly in the 6 patients, and only 1 patient received regimen III.[20] Techniques to identify clusters can definitely diagnose the identity of the strain exhibiting primary resistance with that of the index case.[21] Table 3 shows that there were only small differences between the cured and the uncured group in terms of the following items, which resulted in MDR-TB: number of previous treatments; number of patients who abandoned treatment; number of patients who relapsed; and number of patients who presented failure. Therefore, the great differential was the severity of pulmonary lesions, which depends on the virulence of the bacillus and the immunity of the patient in this phase.[22] In the initial 2-year period of treatment for MDR-TB, evolution was proportionally poorer and the number of deaths was proportionally greater among the patients with bilateral lesion and cavitation than among those with unilateral lesion. In addition, the number of deaths was 7 times greater among the patients with bilateral lesions. The incidence of TB is lower in females, and survival is higher in younger patients.[23] In the present study, patients in the older group were cured more often than were those in the younger group, and the number of females who were cured was 2 times lower than was the number of males cured (RR = 2). The severity of pulmonary lesions in the initiation of treatment for MDR-TB was more important than were natural protective factors. The initial 2-year period, in which the treatment for MDR-TB occurred, defined whether the outcome would be favorable (cure) or unfavorable (treatment failure or death). The patients who were cured clearly presented weight gain, whereas the worsening of the case and death were announced by a progressive weight loss throughout the follow-up period.[24]

In Brazil, a cohort study that analyzed cases of MDR-TB reported between 2000 and 2004 showed that the effectiveness of the treatment was 65% in the final phase of the study.[11] Our percentage of cure was 34% (considering 48 patients and 2 cases of noncompliance), and all cures occurred during the first 2 years of treatment. Since the city of Rio de Janeiro has one of the highest incidences of TB and MDR-TB in the country, the lower percentage of cure reported can be related to the greater severity of the cases. The greater association between hospitalization and death was obvious. Frequent relapses, such as those that occurred in the initial phase of the treatment for TB, are related to irregular drug intake, which results in apparent cure with the maintenance of a significant number of persistent bacilli that develop again, already exhibiting resistance.[25]

There is a clear contrast between the initial period of treatment for TB and the period of treatment for MDR-TB in terms of the number of patients who abandoned treatment, relapsed or presented failure. In the period of treatment for MDR-TB, 7 patients abandoned treatment, 2 of whom abandoned it permanently and 5 of whom abandoned it partially. This is due to the active search for cases of noncompliance carried out by the referral center and to the increased awareness of patients regarding the severity of MDR-TB. Only 1 patient relapsed, underwent retreatment and presented failure. The treatment routines of the referral center include a basic treatment for patients presenting treatment failure (terizidone, ofloxacin and EMB), since complete discontinuation of the drugs accelerates the progression of the disease. Given the unstable balance between the virulence of the bacillus and the immunity of the patient, promoted by drug maintenance, the patients who presented failure gradually died, and, after 8 years, the percentage of deaths was higher than the percentage of cure, only 9 patients surviving (Figure 2). The patient with the longest follow-up period (10 years in 2007) presented, in 2006, a chest X-ray with significant bilateral cavitations.

Treatment failure always brings the possibility of MDR-TB being transmitted to the families of patients, to health professionals and to the general population.[20,26] Epidemics of MDR-TB and the dissemination of MDR strains, produced by migratory movements, have been reported in the literature. Currently, the appearance of

strains designated extensively drug resistant tuberculosis (WHO), which are defined as initially resistant to INH, RMP, a quinolone antimicrobial agent and one more injectable drug (amikacin, capreomycin or kanamycin), represents a serious threat to the world.[2,27] Now, after a long period without investments in this domain by the pharmaceutical industry, there is the promise and the hope of new regimens or new drugs for the treatment of sensitive and resistant TB and the rescue of patients presenting failure.[28] The inclusion of drugs such as linezolid, new quinolones and capreomycin, to which TB strains are still sensitive, as well as new drugs still under research, represent the possibility of a cure for such patients, although, realistically, these new drugs will be available no earlier than 5 years from now.[29,30]

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