



## clinical investigations

# Retreatment Tuberculosis Cases\*

## Factors Associated With Drug Resistance and Adverse Outcomes

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**Study objective:** Risk factors associated with treatment failure and multidrug-resistant tuberculosis (MDR-TB) were examined among HIV-seronegative patients who were previously treated for tuberculosis (TB).

**Design:** Prospective, cohort study of patients referred to the study hospital for retreatment of TB between March 1986 and March 1990.

**Patients:** The patients belonged to three groups, according to outcomes following their previous treatment: 37 patients who abandoned treatment or suffered relapse after completion of therapy (group A), 91 patients who failed to respond to the first-line drug regimen (group B), and 78 patients who failed to respond to the second-line drug regimen (group C).

**Results:** Patients with *Mycobacterium tuberculosis* strains resistant to rifampin and isoniazid were found in 2 (6%) in group A, 29 (33%) in group B, and 49 (65%) in group C. Cure was achieved in 77% in group A, 54% in group B, and 36% in group C. Death occurred in none of the patients in group A, 8% in group B, and 24% in group C. In a multivariate logistic regression analysis, unfavorable response (failure to sterilize sputum culture, death, and abandonment) was significantly associated with infection with a multidrug-resistant *M tuberculosis* strain ( $p=0.0002$ ), cavitary disease ( $p=0.0029$ ), or irregular use of medications ( $p<0.0001$ ).

**Conclusion:** These observations show that a previous treatment outcome and current clinical and epidemiologic histories can be used to predict the development of MDR-TB and adverse outcomes in patients undergoing retreatment for TB. Such information may be useful for identifying appropriate patient candidates for programs such as directly observed therapy.

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**Key words:** DOT; multidrug-resistant TB; TB retreatment; tuberculosis

**Abbreviations:** DOT=directly observed therapy; EMB=ethambutol; INH=isoniazid; MDR=multidrug-resistant; MDR-TB=multidrug-resistant tuberculosis; PZA=pyrazinamide; RIF=rifampin; SM=streptomycin; TB=tuberculosis

Patients needing retreatment for tuberculosis (TB) present with a variety of previous TB treatment outcome histories. One such outcome is the devel-

opment of multidrug-resistant (MDR)-TB; previous treatment is an important risk factor for MDR-TB.<sup>1-4</sup>

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However, clearly not all such patients develop MDR-TB, and their previous treatment history and outcome may provide clues as to who are most likely to develop MDR-TB or have unfavorable outcome.

In most areas of the world, the routine use of drug susceptibility tests, let alone cultures to diagnose TB or MDR-TB, is beyond the scope of their health-care

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resources. If the clinical and epidemiologic background of a patient can be used to assess the likelihood of development of MDR-TB or adverse outcomes of retreatment, appropriate control measures may be instituted in these countries using already-existing resources and information. Programs such as directly observed therapy (DOT) to control MDR-TB may be prioritized according to patients' risks of developing MDR-TB.

In this study, we divided previously treated TB patients referred to our center according to whether they (1) abandoned their previous treatment or suffered relapse after completion of previous therapy, (2) failed to respond to their first-line drug regimen, and (3) failed to respond to their second-line drug regimen. We found that this grouping provided information highly predictive of their clinical outcomes after retreatment.

## MATERIALS AND METHODS

### *Patient Selection and Definitions*

From March 1986 to March 1990, 206 patients with pulmonary TB, who had prior anti-TB treatment, referred by Primary Health Services to Instituto de Tisiologia e Pneumologia da Universidade do Rio de Janeiro, were entered into the study. This hospital is the referral center for retreatment of TB serving the city of Rio de Janeiro and six neighboring municipalities. Eighty percent of the annual newly diagnosed TB cases in the state of Rio de Janeiro occur in this area.

In Brazil, the standard first-line regimen for treating TB is isoniazid (INH), rifampin (RIF), and pyrazinamide (PZA) for 2 months followed by INH and RIF for 4 months. Since 1981, the recommended second-line regimen has included streptomycin (SM), ethambutol (EMB), ethionamide, and PZA for 3 months followed by EMB and ethionamide for 9 months.

In Rio de Janeiro State, 17 to 20% of the TB patients require retreatment for one reason or another.<sup>5</sup> These prior-treatment patients fall into three groups: (1) group A, patients who suffer relapse or who return for treatment after abandoning therapy in the past; relapse is defined as recurrence of TB in which sputum becomes culture-positive for *Mycobacterium tuberculosis*  $\geq 12$  months following cure using any drug regimen; (2) group B, patients who fail to respond to the first-line regimen; and (3) group C, patients who fail to respond to the second-line regimen. In this study, presumed cure was defined as a treatment outcome in which patients who completed the therapy had two negative cultures for at least 4 weeks after the end of treatment. Failure was defined as an outcome in which sputum smear test remained positive for acid-fast bacilli after 5 months of treatment or became positive after an initial clearance during treatment. Treatment abandonment was defined as an interruption of treatment for a minimum of 8 consecutive weeks. A patient was defined as using medications irregularly if a family member reported that the patient failed to take the medications  $>20\%$  of the time or if the leftover medications at the time of clinic visit indicated that  $<80\%$  of the expected number had been consumed. Death was defined as death that occurred during the course of treatment among patients who received treatment for

at least 4 months. MDR-TB was defined as a case of TB caused by a strain of *M tuberculosis* resistant to two or more anti-TB drugs.

### *Patient Treatment*

All of the patients were retreated as outpatients, without direct supervision, with monthly ambulatory visits for clinical, radiologic, and bacteriologic examinations. They were placed on regimens of drug retreatment according to the results of drug susceptibility tests, following the National Tuberculosis Control Program recommendations. In Brazil, the access to different proved or experimental anti-TB drugs is difficult. The most frequently used retreatment regimen includes RIF, INH, PZA, EMB, SM, and in some occasions ofloxacin, clofazimine, and rifabutin. Whenever possible, we attempted to use at least three drugs to which the strain was susceptible, prescribing a regimen with tolerable side effects.

Surgical treatment was used if the strain was resistant to all available drugs, the drugs produced toxic side effects, or the patient's sputum remained positive after 5 months of the second-line or other retreatment regimens. Preoperative studies were performed on those deemed potential surgical candidates, including simple spirometry, arterial blood gas determinations, perfusion radionuclide lung scans, and pulmonary arterial pressure measurements.

### *Laboratory Tests*

Serum samples were screened for HIV antibody by enzyme-linked immunosorbent assay (Organon Teknika; Boxtel, the Netherlands), and confirmed by the Western blot method (DuPont; Wilmington, Del). Drug susceptibility testing was performed on cultures of *M tuberculosis* isolated from Lowenstein-Jensen medium by the proportional method of Canetti and Grosset.<sup>6</sup> A patient was considered to harbor drug-resistant *M tuberculosis* if the number of colonies growing on a medium containing 0.2  $\mu\text{g/mL}$  of INH, 5  $\mu\text{g/mL}$  of EMB, or 1  $\mu\text{g/mL}$  of RIF exceeded 1% of the growth on a drug-free culture plate; SM resistance was defined as the growth exceeding 10% on a medium containing 4  $\mu\text{g/mL}$  of the drug.

### *Statistical Tests*

The data were collected and analyzed by a software program (EPI-INFO version 5.01b; Centers for Disease Control; Atlanta, Ga). A  $\chi^2$  or Fisher's Exact Test was used to compare proportions. Rates were compared according to a method described by Smith and Morrow.<sup>7</sup> Variables found to be significantly associated with unfavorable outcomes in univariate analyses were reexamined in a logistic regression model.

## RESULTS

### *Study Patients*

Between March 1986 and March 1990, 1,152 newly diagnosed and previously treated patients were referred to the study hospital. Two hundred six HIV-seronegative patients, whose *M tuberculosis* isolates were available and tested for susceptibility, and who consented to the study, were included in this study. They were all previously treated for TB and referred to the study hospital

for retreatment from 29 primary health service clinics in the city of Rio de Janeiro and six neighboring cities. Others were not included because they were not retreatment cases (732), they were HIV seropositive (57), their cultures were not available (142), or they refused to participate (15). Of 206 previously treated patients, 37 (18%) were referred because of relapse or recurrence of TB after previously abandoning their therapy (group A); 91 patients (44%) had previously failed to respond to the first-line regimen treatment course (group B); 78 patients (38%) had previously failed to respond to the second-line regimen (group C).

### Demographic Characteristics

Of 206 patients, 144 (70%) were men. The mean age was 42 years (range, 19 to 79 years). One hundred thirty-nine (67%) were identified as non-white of African heritage, and 67 were white. No significant differences in these demographic characteristics were observed among the three study groups (Table 1).

### Clinical Characteristics

Most patients had advanced pulmonary disease; 148 (72%) had bilateral disease, and 152 (74%) had multiple cavities (Table 1). Forty-five (22%) met the CAGE (Cutting down; Annoyance to criticism;

Guilty feelings; Eye-openers) definition of alcoholism,<sup>8</sup> while 124 (60%) were smokers.

### Susceptibility Tests

Susceptibility information on the patient isolates was available for 196 patients. For the other 10 patients, the susceptibility data were not available. Of 196 patients, 108 (55%) had strains resistant to INH, 81 (42%) to RIF, 46 (23%) to SM, and 36 (18%) to EMB. *M tuberculosis* strains resistant to two or more drugs were isolated from two patients (6%) in group A, 34 patients (39%) in group B, and 52 patients (68%) in group C. Strains resistant to RIF and INH were found in two patients (6%) in group A, 29 (33%) in group B, and 49 (65%) in group C ( $p=0.00002$ , Fisher's Exact Test) (Table 2).

### Outcomes of Chemotherapy

Of 206 patients, 34 were excluded from the analysis of chemotherapy outcome measures because of the following reasons: one died after receiving therapy for 1 month, and 33 were unavailable for follow-up before they were observed long enough (<4 months). Of 172 patients, 88 (51%) were cured, 52 (30%) abandoned treatment, 22 (13%) died, three (2%) were classified as treatment failure, and seven (4%) were transferred to another institution (Table 3). Overall, 80 patients (46%) remained free of disease throughout a mean follow-up period of 20.5 months (range, 2 to 87 months). However, only 21 (27%) of 77 MDR-TB patients remained disease free during this follow-up period ( $p<0.05$ ,  $\chi^2$ ); 18 (25%)

**Table 1—Demographic Features, Disease Characteristics, and Susceptibility of *M tuberculosis* Isolated From Pulmonary TB Patients According to Previous Treatment Groups\***

	Group A (%) (n=37)	Group B (%) (n=91)	Group C (%) (n=78)
Age, yr			
16-30	3 (8)	18 (20)	14 (18)
31-45	17 (46)	45 (50)	34 (43)
46-60	14 (38)	22 (24)	22 (28)
>60	3 (8)	6 (6)	8 (11)
Mean	42.8	40.6	41.8
Male	25 (68)	58 (64)	61 (78)
Female	12 (32)	33 (36)	17 (22)
White	18 (49)	29 (32)	20 (26)
Nonwhite	19 (51)	62 (68)	58 (74)
Chest radiograph images			
Bilateral	26 (70)	65 (71)	56 (72)
Cavities	24 (65)	67 (74)	61 (67)
Extension of disease to >2 areas of lung	22 (59)	57 (63)	55 (60)
Required surgery	1 (3)	8 (9)	17 (22)

\*Group A=patients who abandoned or suffered relapse after their first therapy; group B=patients who failed to respond to the first-line drug regimen; and group C=patients who failed to respond to their second-line drug regimen.

**Table 2—Drug Susceptibility of Isolates From 196\* Patients With Retreated TB**

Category	Group A (n=31)	Group B (n=89)	Group C (n=76)
Susceptible	22	45	13
Resistant to 1 drug	7	10	11
INH	5	7	7
SM	1	3	3
RIF	0	0	1
Resistant to 2 drugs	1	22	21
INH/RIF	1	18	18
INH/SM	0	2	3
SM/RIF	0	1	0
INH/EMB	0	1	0
Resistant to 3 drugs	1	7	13
INH/EMB/RIF	1 <sup>†</sup>	4	6
INH/RIF/SM	0	2	7
INH/EMB/SM	0	1	0
Resistant to 4 drugs	0	5	18
INH/EMB/RIF/SM	0	5	18

\*Drug susceptibility test not available for 10 cases.

<sup>†</sup>Patient used first- and second-line regimen.

**Table 3—Results of the Chemotherapy in 172 Patients With Pulmonary TB Who Were Retreated According to Their Previous Treatment Status**

	Group A (%) (n=31)	Group B (%) (n=74)	Group C (%) (n=67)
Cured	24 (77)	40 (54)	24 (36)
Failed	0 (0)	1 (1)	2 (3)
Died	0 (0)	6 (8)	16 (24)
Abandoned	7 (23)	25 (34)	20 (30)
Transferred	0 (0)	2 (3)	5 (7)

of 72 who had strains resistant to INH and RIF, and three (60%) of five who had strains resistant to INH and non-RIF drugs remained disease free during the same follow-up period ( $p=0.12$ , Fisher's Exact Test, two-tailed).

The 88 presumably cured patients were followed up for a total of 1,955 person-months. Of these, eight (9%) suffered relapse, and three of them suffered relapse within 2 years after the cessation of therapy. Relapse was observed only among patients from groups B and C ( $p=0.002$ , Fisher's Exact Test). Drug susceptibility tests of the new isolates from these eight relapse cases showed that six (75%) had patterns of resistance identical to those of the isolates before the initiation of the new chemotherapy.

Unfavorable outcome (failure to sterilize the sputum culture during therapy, death, and abandonment of therapy) was significantly associated with patients (1) belonging to groups B and C ( $p<0.01$ ), (2) having an MDR *M tuberculosis* isolate ( $p<0.0001$ ), (3) having cavitory disease ( $p<0.001$ ), (4) running out of medication ( $p<0.01$ ), and (5) taking medication irregularly ( $p<0.001$ ). The logistic-regression analysis that included these variables revealed that resistance to two or more drugs ( $p=0.0002$ ), cavitory disease ( $p=0.0029$ ), and irregular use of medication ( $p<0.0001$ ) were each significantly associated with unfavorable outcome.

#### Adjunctive Surgery

Twenty-six (15%) patients underwent surgical procedures. Of these patients, 14 (54%) had bilateral lesion on chest radiograph. Fourteen patients had pneumonectomy, four had lobectomy, six had lobectomy with thoracoplasty, and two had thoracoplasty. Seventeen of these patients were from group C, eight from group B, and one from group A. Of the surgical patients, 12 (46%) were cured and seven (27%) died. Death was attributed to pulmonary embolism that occurred the second day after surgery in one patient, respiratory insufficiency in the second and fourth months after

surgery in two, and complications from broncho-pleural fistula in four patients.

#### DISCUSSION

Previous treatment for TB has been identified as an important risk factor for the acquisition of drug-resistant TB, especially in HIV-seronegative patients.<sup>1-4</sup> In this study, several categories of patients who had received prior treatment for TB were examined for the risk of developing MDR-TB and other adverse outcomes. We found that the risk for MDR-TB varied greatly among these different groups. Those who took but failed to respond to the second-line drug regimen had more than 10 times the risk for developing MDR-TB than those who abandoned their therapy or had recurrence of TB after completing the first treatment, and twice the risk compared to those who continued to take the drugs but failed to have the sputum culture sterilized by the first-line drug regimen.

A study by Costello et al<sup>1</sup> found that 41% of 4,017 patients with previous treatment for TB developed drug-resistant TB, and that the percentage of those excreting drug-resistant strains increased with increasing duration of the previous treatment. Another study found that equally favorable retreatment outcomes can be achieved among patients previously treated for <30 days compared to patients treated adequately for >30 days.<sup>9</sup> The present study further refined the grouping of previously treated patients and found that TB patients who previously failed to respond to the first-line or second-line treatment course are much more likely to have MDR-TB and poorer outcomes than those who abandoned or had relapse after their therapy. Since group A patients could have included those who took first- or second-line drugs (the information was usually not available), the history of abandonment or relapse was the primary reason for the initiation of retreatment. The low rate of occurrence of MDR-TB in this group suggests that these patients may not have had exposures to many drugs in the past or had had an incomplete treatment.

Of 172 patients with follow-up information, only 80 (47%) remained disease free without relapse during the follow-up period. This is lower than the rate (56%) reported by Goble et al<sup>10</sup> in the United States in their treatment of 134 MDR-TB patients who had previously received TB drugs. Our study showed that among those infected with documented MDR *M tuberculosis* strains, the cure rate was only 32% (25/77). The low rates observed in the present study may be explained by the high rate (30%) of treatment abandonment, which was

not included in the study of Goble et al. That is, the population studied in Rio is quite distinct from the type of patients examined by Goble et al.

The retreatment of group A patients was successful in 77%; this success rate is within the range of successful treatment rates for patients with drug-susceptible strains or for patients who suffer relapse, whose isolates are not necessarily tested for susceptibility.<sup>9,11</sup> Patients infected with strains resistant to at least RIF and INH comprised the most common MDR-TB cases in this study (37%). In this group, among those who did not abandon treatment or were not unavailable for follow-up, 17 (41%) died, and two (5%) failed to sterilize sputum cultures. The cure rate in this group was similar to that achieved in comparable groups of MDR-TB patients observed by Manalo et al<sup>12</sup> (43%).

In this study, although the patients with strains resistant to INH and a non-RIF drug fared slightly better than MDR-TB patients with INH/RIF resistance, the overall cure rate was still low at 60%. This stresses the point that in nonoutbreak studies, the case definition of MDR-TB should not be restricted to those resistant to at least INH and RIF, as is often advocated by some investigators.

Using a combination of resectional surgery and chemotherapy, Iseman<sup>13</sup> has achieved bacteriologic conversion in >90% of MDR-TB patients. In the present study, 26 patients underwent surgical treatment. Group C patients were seven times more likely to receive surgery than group A patients. Favorable outcome was observed in only 46%. Surgery appears to have a role in the management of MDR-TB, but may require specialized institutions with long-term experience in the surgical management of TB.

In a multivariate model, unfavorable outcomes (failure to sterilize the sputum culture during therapy, death, and abandonment of therapy) were significantly associated with *M tuberculosis* isolates resistant to two or more drugs ( $p=0.0002$ ), cavitory disease ( $p=0.0029$ ), and irregular use of medication ( $p<0.0001$ ). Cavitory disease has been shown previously to be associated with MDR-TB,<sup>4,14</sup> but, in the present study, this clinical manifestation was associated with poor outcome independent of drug resistance. Goble et al<sup>10</sup> found male gender and the number of drugs received previously to be significantly associated with treatment failure. Accurate information about the number of previously administered drugs could not be obtained in the present study.

In developed countries, the management of patients previously treated for TB may be facilitated by the drug-susceptibility information of the patient's new *M tuberculosis* isolate. Unfortu-

nately, in most developing countries, such data are not easily obtained. Our present study suggests that clinical outcomes and the likelihood of development of MDR-TB may be predicted by grouping previously treated patients into those who abandon treatment or suffer relapse after treatment, those who fail to respond to the first-line drug regimen, and those who fail to respond to the second-line drug regimen. In addition, cavitory disease and irregular use of medication provide positive predictive values of 54% and 83%, respectively, for unfavorable outcome. Patients who exhibit these characteristics may be good candidates for measures such as DOT to reduce the likelihood of poor outcome of their retreatment. DOT is an effective method to prevent and reduce the occurrence of MDR-TB if applied properly, and does not require drug susceptibility testing.<sup>15,16</sup> However, in places like Brazil where the annual incidence of TB in a single city like Rio de Janeiro may exceed that of most developed countries, DOT can become an enormously expensive undertaking. By utilizing the type of predictive information identified in this study and incorporating such data into a DOT program, an effective TB control program may be devised.

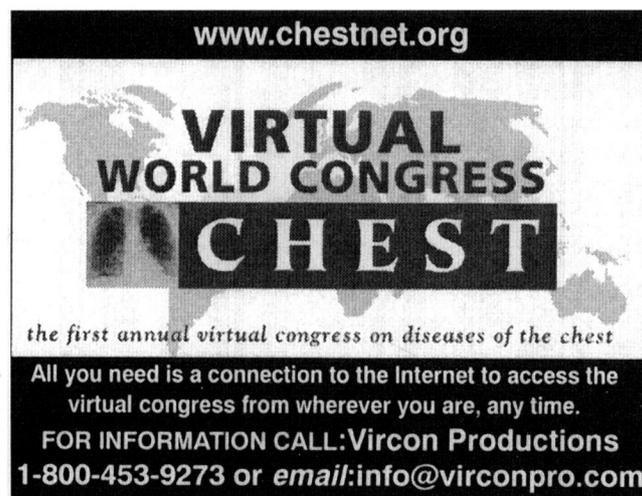
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