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Major Article

Contributions of culture and antimicrobial susceptibility tests to the retreatment of patients with pulmonary tuberculosis

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ABSTRACT

Introduction: This study evaluated the efficacy of retreatment of pulmonary tuberculosis (TB) with regard to treatment outcomes and antimicrobial susceptibility testing (ST) profiles. **Methods**: This retrospective cohort study analyzed 144 patients treated at a referral hospital in Brazil. All of them had undergone prior treatment, were smear-positive for TB and received a standardized retreatment regimen. Fisher's 2-tailed exact test and the χ^2 test were used; RRs and 95% CIs were calculated using univariate and multivariate binary logistic regression. **Results:** The patients were cured in 84 (58.3%) cases. Failure was associated with relapsed treatment and abandonment (n=34). Culture tests were obtained for 103 (71.5%) cases; 70 (48.6%) had positive results. ST results were available for 67 (46.5%) cases; the prevalence of acquired resistance was 53.7%. There were no significant differences between those who achieved or not therapeutic success (p=0.988), despite being sensitive or resistant to 1 or more drugs. Rifampicin resistance was independently associated with therapeutic failure (OR: 4.4, 95% CI:1.12-17.37, p=0.034). For those cases in which cultures were unavailable, a 2nd model without this information was built. In this, return after abandonment was significantly associated with retreatment failure (OR: 3.59, 95% CI:1.17-11.06, p=0.026). **Conclusions**: In this cohort, the general resistance profile appeared to have no influence on treatment outcome, except in cases of rifampicin resistance. The form of reentry was another independent predictor of failure. The use of bacterial culture identification and ST in TB management must be re-evaluated. The recommendations for different susceptibility profiles must also be improved.

Keywords: Pulmonary tuberculosis. Retreatment. Drug resistance. Antimicrobial susceptibility testing. Treatment outcome.

INTRODUCTION

Although tuberculosis (TB) is among the oldest and most prevalent of human diseases, specific and effective treatment only became available in 1944 with the discovery of streptomycin[1-3]. Within a few years after this discovery, antimicrobial resistance could be recognized from the observation of reduced effectiveness[3-5]. Although there has been little progress in the development of new drugs since the introduction of isoniazid and rifampicin, TB remains a curable and preventable disease[6]. However, the management of resistant cases is complex and presents therapeutic limitations.

In this context, the most concerning situation is the retreatment of patients who are often exposed to conditions associated with future failures that are attributable to microbial resistance. The management of the most resistant forms requires the use of more complementary tests, as well as more expensive and toxic drugs, which are accompanied by diminished effectiveness[2,7,8]. In this sense, ongoing global efforts aim to reduce and control the disease. Special attention is being paid to reducing disease transmission and developing preventive measures, such as vaccines, and cures through new drugs.

Meanwhile, the occurrence of resistant forms of TB has increased significantly since the 1980s[2]. In the 1990s, outbreaks of multidrug-resistant (MDR) TB due to nosocomial transmission were characterized by late diagnosis, the use of inadequate treatment regimens and high transmission and mortality rates[2,9]. In the following decade, extensively drug-resistant TB (XDR-TB) was described. XDR-TB is underscored by a high mortality rate (98%) and shorter median survival period, suggesting poor TB control programs and potential adaptation of the bacteria[3,10-13]. Current studies acknowledge that patients infected with MDR strains are more prone to treatment failure, progression to chronic forms of the disease and death[14].

The latest Brazilian guidelines recommend that the retreatment of TB cases include a standard regimen of 4 drugs,

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as well as culture and susceptibility tests, although the benefit of this practice has yet not been sufficiently evaluated in Brazil[15,16].

This study's primary aim was to evaluate the efficacy of a retreatment regimen for patients referred to a referral hospital in Minas Gerais, Brazil, with regard to the measurements of cure (i.e., success) or abandonment and failure and these measurements' relationship with the bacterial susceptibility profile to the drugs used. The secondary aim was to determine possible exploratory associations between clinical variables and treatment outcomes.

METHODS

This was a retrospective cohort study of patients referred for retreatment of pulmonary TB at Hospital Júlia Kubitschek (HJK), a TB referral center located in Belo Horizonte, State of Minas Gerais, Brazil, from January 2004 to December 2007. The study enrolled patients with diagnoses of pulmonary TB, based on smear-positive results and a history of previous TB treatment. Patients were selected from the medical records of the hospital archives (Department of Medical Archives, SAME) and from the Hospital Admission System (SIH), Information System for Notifiable Diseases (SINAN) and Mortality Information System (SIM) databases.

Patients in retreatment with regimens other than the IR regimen (i.e., rifampicin, isoniazid, ethambutol and pyrazinamide) (n=912), cases of death from other causes (n=6) and cases with no information about treatment outcome (n=45) were excluded. From the database, 1,124 treatments were selected, and those cases with clinical indications for use of the 2RHZE/4RHE (two months of daily administration of rifampicin [R], isoniazid [H], pyrazinamide [Z] and ethambutol [E], followed by four months of daily R, H, E), standardized regimen were reviewed. After exclusions, 144 patients remained **(Figure 1).** In the case of multiple treatments, only the data for the later treatment were considered for analysis.

Mycobacterium tuberculosis was isolated using Lowenstein-Jensen (LJ) culture medium, and susceptibility testing (ST) was performed using the proportion method[17]. All of the tests were performed at the Central Laboratory (LACEN) of the State of Minas Gerais, which is internationally certified.

Outcomes were considered successful (i.e., cured) or treatment failures (i.e., death, failure or treatment abandonment), based on the medical records and review of the databases (SIH, SINAN and SIM). Both proven cures and unproven cures (2 negative smears at the end of treatment and when the patient could not perform the smear) were considered because the designations were made by the attending physician. Categorical variables were compared using the χ^2 test or Fisher's exact test when applicable. Multiple regression analysis was performed to estimate possible independent associations between variables and outcomes, including their relative risks (RRs) and 95% confidence intervals (CIs). Variables with a p-value less than 0.20 in univariate binary logistic regression were entered into the model. The database was created using Epidata for Windows, Entry 3.1 (EpiData Association, Copenhagen, Denmark); inconsistencies were checked by double entry. The analysis was performed using SPSS for Windows (version 13.0; SPSS Inc., Chicago, IL, USA).

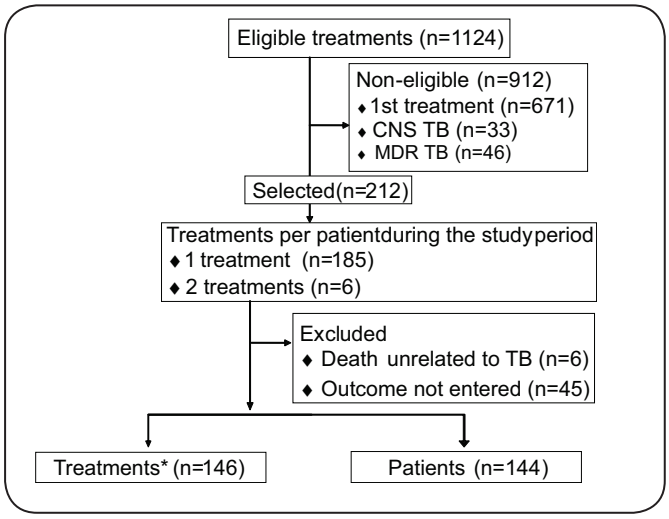

FIGURE 1 - Selection of retreatment cases, Hospital Júlia Kubitschek , from 2004 to 2007. MDR TB: multidrug-resistant tuberculosis; CNS TB: central nervous system tuberculosis. Note: *only the data for later treatments were considered for analysis.

Ethical considerations

This study was approved by the Ethics in Research Committees of HJK and the Federal University of Minas Gerais (COEP-UFMG), and a waiver of informed consent was obtained.

RESULTS

Demographic and epidemiological characteristics

The study included 144 patients, with a mean age of 38.8 years old (SD: ±12.4 y; range: 16-79 years old), and 70.1% were men (101/144). For 41 (28.5%) patients, there was no information on culture results. Data on skin color, educational level and weight and height were available in 54.2%, 26.4% and 17.4% of records, respectively. There were no statistically significant differences between groups with regard to demographic variables. In 123 (85.4%) cases, there were records of testing for human immunodeficiency virus (HIV), 10 (6.9%) of which were positive for the virus. Substance abuse was recorded in 105 (72.9%) cases: alcohol and tobacco (42.7% with more than 20 packs/year with a mean of 24.2 packs/year) in 86 patients each and illegal drug use in 11 (7.6%). Eight (5.5%) patients had both pulmonary and extrapulmonary TB. Comorbidities included prior liver disease, 9 (6.2%); silicosis, 7 (4.9%); chronic renal insufficiency, 2 (1.4%) and diabetes mellitus, 2 (1.4%) **(Table 1).**

The most prevalent cause of retreatment was the abandonment of treatment ([71.8%], mean of 1.9 prior treatments [range: 1-9]).

Almost 90% of the patients had their initial TB therapy in a hospital setting (89.6%), with an average hospital stay of

TABLE 1 - Demographic and epidemiological characteristics of 144 patients with pretreatment with regard to current treatment outcomes.

	Success		Failure		Total		
Age (years)	(n=84)		(n=60)		(n=144)		
Mean ± SD	39.9±13.3		36.4±10.7		38.8±12.4		
Min-Max	16-79		16-59		16-79		
	n	%	n	%	n	%	p
Male	59	70.2	42	70.0	101	70.1	0.975
HIV-positive, n (%)	5	7.1	5	9.4	10	6.9	0.645
Use of alcohol, n (%)	45	58.4	41	75.9	86	59.7	0.038
Smoking, n (%)	49	63.6	37	71.1	86	59.7	0.374
Other associated diseases	10	12.0	7	12.7	17	12.3	0.905
Extrapulmonary involvement	3	3.6	5	8.3	8	4.9	0.219
Five or more pretreatments	5	6.0	10	16.6	15	10.4	0.038
Relapse after cure	24	28.9	5	8.5	29	20.4	0.001
Readmission after failure	59	65.0	54	91.5	113	79.6	0.003
readmission after abandonment	50	60.2	52	88.1	102	71.8	-
readmission after failure	6	7.2	1	1.7	7	4.9	-
readmission for intolerance	3	3.6	1	1.7	4	2.8	-
Hospital/outpatient treatment	50	34.7	30	20.8	80	55.6	0.435
Availability of ST	60	71.4	37	61.7	97	67.4	0.218

SD: standard deviation; ST: susceptibility testing; HIV: human immunodeficiency virus.

approximately 2.5 months, which was followed by outpatient management. Fifteen (10.4%) patients were not admitted to the hospital **(Table 1).**

Susceptibility test results

The results of culturing were available for 103 (71.5%) of the 144 patients in retreatment: 70 (48.6%) were positive, and 33 (22.9%) were negative. Therefore, ST could be performed in 67 (46.5%) patients of the sample or 65% of the available results). The mean interval between the collection and provision of results was 3 months (range: 20 days to 8.9 months). In 25 (37.3%) patients, ST results were made available 4 months after collection. There was no significant difference in treatment outcomes with regard to the availability of ST results **(Table 1)**.

Among the available ST results, 32 (48.5%) cases were resistant to isoniazid (H), 19 (28.8%) to rifampicin (R), 9 (14.1%) to ethambutol (E), 7 (13.5%) to pyrazinamide (Z), 9 (13.8%) to streptomycin (SM) and 6 (9.7%) to ethionamide (ETH) **(Table 2)**. Fourteen patients were monoresistant to isoniazid (INHr-TB), 1 was monoresistant to rifampicin (RIFr-TB), and 18 were resistant to both drugs (RH) (MDR-TB). Of these, 8 patients exhibited resistance to RH and to 1 additional drug. The prevalence of acquired resistance was 53.7%. There was no significant difference between those patients who achieved therapeutic success and those who did not (p=0.988; χ^2 test) regarding being sensitive or resistant to 1 or more drugs **(Table 2)**.

Treatment outcomes

Success with the retreatment regimen (2RHZE/4RHE) was observed in 84 (58.3%) patients. Among the failures, 34 (23.6%) represented new abandonment, 15 (10.4%) failed the existing treatment, and 11 (7.6%) were due to deaths. Excluding the cases of new abandonment, the rate of success was 76.4%.

Univariate analysis revealed that the variables significantly associated with treatment failure were alcohol use, the presence of concomitant diseases, history of 5 or more treatments, retreatment due to abandonment, retreatment due to failure and rifampicin resistance (**Table 3**). These variables and the length of hospital stay were included in the multivariate logistic regression analysis. For this analysis, the variable of return due to failure replaced that of return due to abandonment because both represent the same phenomenon. In contrast, in the multivariate analysis, only rifampicin resistance was independently associated with therapeutic failure (OR: 4.4; 95% CI: 1.12-17.37; p=0.034; **Table 3**). In the second model in which information from ST was omitted, only return due to abandonment was associated with retreatment failure (OR: 3.59; 95% CI: 1.17-11.06; p=0.026; **Table 3**).

TABLE 2 - Profile of the drug susceptibility of 67 bacterial isolates from patients undergoing retreatment for tuberculosis.

	Success		Failure		Total		
	n	%	n	%	n	%	p
Sensitive	19	46.3	12	46.1	31	46.2	0.988
Resistant (one or more drugs)	22	53.7	14	53.8	36	53.7	-
isoniazid	19	28.8	13	19.7	32	48.5	0.843
rifampicin	9	13.6	10	15.1	19	28.8	0.162
pyrazinamide	3	5.8	4	7.7	7	13.5	0.275
ethambutol	4	6.2	5	7.8	9	14.1	0.227
streptomycin	7	10.8	2	3.1	9	13.8	0.281
ethionamide	3	4.8	3	4.8	6	9.7	0.550
Resistance to 1 drug							
isoniazid	11	16.7	3	2.1	14	21.2	0.262
rifampicin	1	0.7	0	0.0	1	0.7	0.480
Resistance to 2 drugs							
rifampicin/isoniazid	5	13.5	5	23.8	10	17.2	0.551
Resistance to 3 or more drugs							
rifampicin/isoniazid and other(s)	3	14.3	5	31.3	8	21.6	0.214

TABLE 3 - Univariate and multivariate analyses (Cox model), including odds ratios and 95% confidence intervals, of the tuberculosis retreatment outcomes.

		Univariate analysis		Multivariate analysis I†		Multivariate analysis II‡	
Variable	Category	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Resistance to rifampicin	Yes*	2.15 (0.73-6.36)	0.162	4.40 (1.12-17.37)	0.034	-	-
Form of reentry	After failure	4.39 (1.57-12.33)	0.003	3.07 (0.59-15.85)	0.181	3.51 (1.17-11.06)	0.026
	After success	reference					
Alcohol use	Yes*	2.24 (1.04-4.85)	0.038	1.71 (0.45-6.49)	0.432	1.99 (0.83-4.77)	0.122
Associated diseases	Yes*	1.06 (0.38-2.99)	0.086	1.33 (0.18-9.69)	0.780	1.66 (0.52-5.27)	0.392
Pretreatments	More than 5	3.16 (1.02-9.79)	0.038	5.55 (0.86-35.70)	0.071	3.72 (0.97-14.27)	0.055
	1 to 4	reference					
Admission shorter than 2 months	Yes*	1.50 (0.77-2.91)	0.235	1.47 (0.42-5.11)	0.547	2.09 (0.95-4.59)	0.068

OR: odds ratio; 95% CI: 95% confidence intervals; *Reference category: no; † Model I: susceptibility testing available; ‡ Model II: susceptibility testing not available.

DISCUSSION

The primary aim of this study was to evaluate the efficacy of the retreatment regimen available in Brazil for pulmonary TB patients who were managed at a referral center of a public hospital in Minas Gerais, according to the measurement of cure (i.e., success) or relapse and failure, and the regimen's possible association with the microbacterial susceptibility profile of the drugs. The secondary objective was to determine exploratory associations among clinical variables and treatment outcomes.

Despite the low availability of ST results, the high rate of acquired resistance and multiple forms of resistance, the main results showed a cure rate of 58% among retreatment cases and no associations between this outcome and the bacterial susceptibility profiles.

The results of the culture test, which represents a propedeutic breakthrough and which has been included in the national guidelines for all retreatment cases since 2004, were present in 71.5% of records[15]. Cultures were negative in 33 (32%) cases, while ST could be performed in only 67 cases, corresponding to 65% of available culture results.

The lack of information about culture exams in approximately 25% of the cases can be attributed to the absence of a request by the attending physician at the time of admission. This low yield of culture testing can also be explained by the limitations of the test itself and the scarcity of clinical specimens, which are often insufficient. However, these cases were considered representative of the sample because of their randomness.

In addition, the long period until the release of the ST results (approximately 3 months) can be attributed at least in part to the need to send materials to a laboratory not associated with the hospital and to the use of the proportion method.

A large number of patients exhibited polyresistance to 2 or more drugs (24/36, 66.6%). There were 18 patients resistant to MDR-TB, and 6 presented other combinations of multiple resistance. This finding could be due to the use of a state-level reference center, as is the case with HJK, which receives more referrals for complex cases. This finding might also have been a determining factor in the recognition of rifampicin as an independent predictor of failure because 18 of the 19 patients resistant to rifampicin exhibited MDR-TB **(Table 2).**

Secondary resistance was quite high, i.e., 53.7% of the sample. However, this rate is lower than the rate of secondary resistance of 69% reported by Fiuza de Melo et al. in São Paulo[18].

The delay in the recognition and identification of resistant forms of the disease or a satisfactory clinical response to unique forms of resistance, as reported in some studies, might also have been instrumental in this aspect[19]. Among the patients who obtained their ST results, 19 (28.1%) were resistant to rifampicin, 32 (48.5%) were resistant to isoniazid, and 10 (17.2%) were resistant to both simultaneously. According to Kritsky et al.[20], patients with dual rifampicin and isoniazid resistance receiving the 2RHZE/4RHE regimen for a long time until the release of ST results present a risk for the use of ethambutol as monotherapy in the maintenance phase of treatment[20].

In Belo Horizonte, Minas Gerais, 54% of all TB cases are diagnosed in hospitals, emergency services and outpatient referral clinics. According to unpublished data from the Municipal Health Department, the cure rate with retreatment was 51.8% between 2004 and 2007 with 13% abandonment. In the present study, the cure rate was 58.3%, which is very similar to the 51.8% mentioned above but higher than the cure rates recently published by the WHO, i.e., 26% and 38% for Brazil and the Americas, respectively, in 2005[21]; this difference might be due to the high proportion of patients not evaluated in those samples, i.e., 25% and 21%, respectively. Moreover, most (89.6%) of the patients in the present study initiated their treatment in a hospital setting, with an average that was stay longer than the first phase of treatment, which might have contributed to better results.

In 2007, Bierrenbach et al. reported a cure rate of 58.9% among retreatment cases throughout Brazil[22]. Regarding regional differences, the southeast region had the lowest (40.5%) cure rate[22].

In this study, the cure rate was 76.4% when patients who abandoned treatment were excluded. When MDR forms (e.g., RH) were excluded, the cure rate was 66.6%.

There was no information regarding the use of supervised treatment strategies for patients treated as outpatients. No resistance profiles were significantly altered because of treatment **(Table 2)**.

The prevalence of HIV was 6.9% among patients in this study, a rate that could be considered low compared to the HIV prevalence in Belo Horizonte in 2010 (12.5%) and compared to the most recent data published by the WHO for Brazil (16%)[22,23]. This finding might have been due to the patients with this diagnosis being managed at local HIV/AIDS referral hospitals.

This study had limitations associated with its retrospective design. There were many losses attributed to misinformation regarding the outcomes of many treatments and the yield of ST. Other limitations that are worth mentioning include only patients from one referral center being included, and the recurrence of resistant forms after cure was not evaluated.

In summary, the resistance profile presented by ST appears to be dissociated from the treatment outcome, namely cure or failure, of retreated TB pulmonary patients. The finding of resistance to rifampicin or the method of retreatment in the absence of ST should be analyzed as possible predictors of treatment failure.

The appropriate management of these patients regarding the use of the different microbacterial drug susceptibility profiles requires further research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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