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Primary bacillary resistance in multidrug-resistant tuberculosis and predictive factors associated with cure at a referral center in São Paulo, Brazil

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ABSTRACT

Objective: To identify transmitted or primary resistance among cases of multidrug-resistant tuberculosis and predictive factors for cure in multidrug-resistant tuberculosis after the first treatment. **Method:** Descriptive study of a cohort from 2006 to 2010, in a reference unit of tuberculosis in São Paulo, Brazil. The data were obtained by the revision of medical records. Clinical criteria were used to classify transmitted and acquired resistance. Extended primary resistance was also defined, in this study, as cases initially treated with a standardized scheme, but with no therapeutic success, and the pre-treatment drug susceptibility test (DST) showed presence of resistance. **Results:** 156 patients with multidrug-resistant tuberculosis and their respective sputum samples were eligible for the study. Only 7% of the patients were positive for the human immunodeficiency virus (HIV). Previous treatment occurred in 95% of the sample. The cure rate after the first treatment was 54%. The median bacteriological conversion time of those who healed was one month. Bacillary resistance was considered acquired resistance in 100 (64%) and transmitted resistance in 56 (36%). By logistic regression, patients who presented primary multidrug-resistant tuberculosis (*odds ratio*—OR = 6,29), without comorbidity (OR = 3,37) and with higher initial weight (OR = 1.04) were associated with cure after the first treatment. **Conclusion:** The early detection of bacillary resistance and appropriate treatment are in favor of healing. Thus, it is crucial to know exactly the primary resistance rate avoiding the use of inadequate treatments, amplification of bacillary resistance and its transmission.

Descriptors: Multidrug-resistant tuberculosis; Drug resistance; Treatment outcome.

INTRODUCTION

The appearance of multidrug-resistant tuberculosis (MDR-TB) in the world has become a public health issue. Therefore, the strategic adjustments to raise the cure rate and the measurements to prevent the dissemination of the disease must be adopted fast.[1]

Bacillary multi-resistance is a biological phenomenon that can be considered as iatrogenic and multifactorial, considering that the exposure of Mycobacterium tuberculosis to drugs during the treatment of the disease causes selective pressure, which favors the permanence of resistant bacillary lineages.[2]

Factors that contribute with the existence of bacillary resistance are deficient tuberculosis-control programs, hard access to the system, lack of or delayed diagnosis, little adherence to treatment, low healing percentage, which leads to persistent transmission, and increasing number of individuals with latent infection (TBLI) with resistant bacillus, who might become sick.[1]

Drug-resistance is classified as: natural resistance, which appears during the process of bacillary multiplication; primary resistance, in patients who were never treated for tuberculosis, infected by previously resistant bacilli; and, finally, resistance acquired by patients with initially sensitive tuberculosis, who became resistant after exposure to the drugs.[3]

The World Health Organization (WHO), in 2015, reported that the susceptibility test (ST) for the diagnosis of bacillary resistance was carried out in only 58% of the patients who had been previously treated for TB, and in 12% of new cases, therefore missing the chance of an early diagnosis of the resistance.[4] In 2012, the institution had already estimated that 3.7% of the new cases, and 20% of the previously treated for TB in the world, were cases of MDR-TB. In some regions, that proportion was even higher.[5,6]

In Brazil, it is formally recommended to perform culture and phenotypic ST for all cases of retreatment, however, this rule is not always fulfilled.[7] Therefore, the magnitude of the problem is not totally known, which makes it difficult to assess the reality of the situation. [3,7] Even if no phenotypic ST is completely accurate,[8] its importance is undeniable.[9] The complexity of these patients associated with the difficulty in management, both aggravated by the association of the coinfection

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tuberculosis and the human immunodeficiency virus (HIV) – which was 10.4% in Brazil, in 2013 —,[7] turns this process into a huge challenge.

The knowledge of the characteristics and peculiarities of these patients with MDR-TB, in some regions of the country, constitutes an important database for the elaboration of new measures of control, diagnosis and therapeutic proposals.

São Paulo is the second state of the country in number of MDR-TB cases. In the study period, from 2006 to 2010, 453 cases were notified, of which 190 (42%) were registered and treated at Instituto Clemente Ferreira, which is a reference outpatient clinic for MDR-TB of the State Health Secretariat in São Paulo.[10,11]

This study aimed at identifying the extended primary resistance among cases of MDR-TB and predictive factors, among demographic, clinical and radiological variables, associated with the cure of MDR-TB after the first treatment.

METHOD

Study population

In Instituto Clemente Ferreira, 190 patients were diagnosed with phenotypic ST, and, according to the definition by the WHO,[12] patients with MDR-TB were those showing resistance to isoniazid and rifampicin, from January 2nd, 2006, to December 31st, 2010.

This project was approved by the Research Ethics Committee of Universidade Federal de São Paulo (UNIFESP), and conducted according to the ethical principles established by the Declaration of Helsinki.

Inclusion criteria

- Aged 18 years or more;
- Both genders;
- Diagnosis of MDR-TB according to the WHO;[12]
- Treatment of MDR-TB in Instituto Clemente Ferreira.

Exclusion criteria

- Initial resistance to quinolone and/or initial resistance to an injectable second line drug;
- Previous use of quinolone for the treatment of tuberculosis.

Study protocol

Descriptive study of a cohort nested in a structured database for the follow-up of adult patients with MDR-TB.

The following was pointed in the medical chart:

- Demographic variables, such as sex, age at the time of phenotypic ST, positive for MDR-TB, age of tuberculosis onset, hospitalization;
- Social variables, such as freedom deprivation, homeless patients;
- Clinical history, such as interval of time between date of the first possible episode of drug-sensitive tuberculosis and the onset of MDR-TB (first episode of TB/TB-MDRTB), number of previous treatments, number of previous treatments with first line drugs, and other treatments, time of culture negativation, contacts with tuberculosis (sensitive or resistant), primary resistance and acquired resistance.

Regarding the clinical data, the following were analyzed: initial weight, presence of comorbidities referred to in the medical chart (HIV, diabetes mellitus and hepatopathy), changes in the thoracic x-ray (lesion in the lung and cavity, uni or bilateral), besides the results of several cultures from each patients, their phenotypic STs and identification of the mycobacterium using the phenotypical or molecular method, during the follow-up period, without a pre-established periodicity. The phenotypic STs were carried out in the automated system Bactec MGIT Sire kit (SAT/Sire), and, for second line drugs, the methodology to determine the minimum inhibitory concentration (MIC). The non-performance of ST for second line drugs together with the first line was occasional.

Phenotypic TSs occurred in the microbiology laboratory of Instituto Clemente Ferreira and in Instituto Adolfo Lutz, both reference centers maintained under rigorous quality control.

At the end of the first MDR-TB treatment, that is, 18 months, the initial outcome events were assessed: abandonment, failure, cure and death, according to the definitions by the WHO[13] and the Ministry of Health.[3]After observing the records in the medical chart, bacillary resistance was categorized in:

- extended primary resistance: in our study, it was defined in three different situations: patients who had never been treated for tuberculosis; individuals who had been treated for less than 30 days,[3] and those who were never treated for tuberculosis who began the first treatment with first line drugs (isoniazid, rifampicin, ethambutol and pyrazinamide); however, with unsatisfactory clinical, radiological and microbiological evolution, and posterior confirmation of the MDR-TB pattern, in a sputum culture collected before the treatment began;[8,14]
- acquired resistance: established in patients with initially drug-sensitive tuberculosis who became resistant after exposure to drugs.[3,12]

The treatment plan for MDR-TB was the one established by the National Tuberculosis Control Program (PNCT), of the Ministry of Health, for the study period.[3]

Statistical analysis

Concerning the convenience sample, the categorical variables were expressed in absolute and relative frequencies (percentage), and numerical variables were expressed in mean, standard deviation (SD), medians and interquartile range.

For the analysis of demographic, clinical and radiological characteristics, the following were used: χ^2 and Fisher's exact tests, or the ANOVA One-Way test, with Bonferroni post-hoc test, and the Kruskal-Wallis

test with Mann-Whitney post-hoc test, depending on the nature of the variable's distribution.

A univariate logistic regression analysis was used to know the association of the factors that favor the cure among the demographic, clinical and radiological variables, and the ones that presented $p < 0.10$ were selected to test the multiple logistic regression model, using the Stepwise method.

The 5% value was considered for rejecting the nullity hypothesis in all tests, and the Statistical Package for the Social Sciences (SPSS), version 19.0, was used for statistical calculations.

RESULTS

From 2006 to 2010, in Instituto Clemente Ferreira, 531 sputum samples with presence of bacilli resistant to rifampicin and isoniazid, from 190 patients, were isolated using the phenotypic ST.

Nine patients were excluded (12 samples) due to transfer from the health unit; nine patients (25 samples), for previous use of second line injectable drug; and 16 patients (34 samples), for phenotypic ST showing pattern of pre-XDR TB, that is, in vitro bacillary resistance to rifampicin and isoniazid, added to the resistance to quinolone or a second line injectable drug (amikacin, kanamycin or capreomycin),[15] and with pattern of extensively resistant tuberculosis (XDR-TB), defined as in vitro bacillary resistance to rifampicin and isoniazid associated with resistance to both drugs, to quinolone and to a second line injectable drug.[12]

Therefore, 156 patients and their respective sputum samples were eligible for the study (Figure 1).

In this cohort, composed of patients with MDR-TB, mean age was 39.5 years (SD ± 12.5), most were male (60%), and mean basal weight was 57.2 kg (SD ± 11.8). The first diagnosis of tuberculosis was reported with mean age of 35.8 years (SD ± 13.2). Hospitalization caused by tuberculosis was mentioned by 1/3 of the patients. Only 11 individuals (7%) were freedom deprived at some point because of the disease, and six (4%) were homeless (Table 1). Only 6% of the patients were treatment naive.

Table 1 presents the median of the number of previous treatments with first line drugs. Also, the median time of evolution from the first episode of tuberculosis to the diagnosis of MDR-TB and time for negativation of the sputum in patients who were cured were described.

Most patients (72%) denied having previous contact with individuals with tuberculosis. On the other hand, 19 (12%) confirmed their contact with a drug-sensitive tuberculosis patient, whereas 25 (16%) mentioned the contact with a person with MDR-TB.

Of the 156 patients, 100 (64%) and 56 (36%) were classified as acquired and primary resistance, respectively (Table 1).

A higher proportion of patients without a lung cavity was associated with cure, whereas in the event of abandonment and failure, the association was higher with the presence of a lung cavity (uni or bilateral) ($p = 0.008$). The presence of unilateral parenchymal lesion was associated with cure ($p = 0.040$) (Table 2).

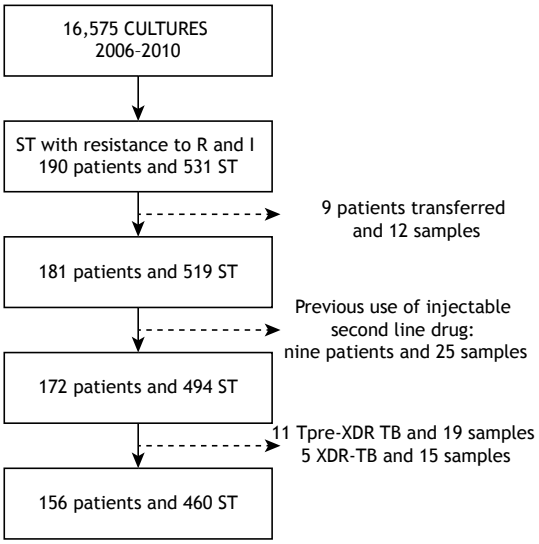

Figure 1. Flowchart of the study sample about multi-drug resistant tuberculosis (MDR-TB). ST: sensitivity test; pre-XDR TB: pre-extensively drug-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis.

Cure was associated with treatment naïve patients, whereas the negative events (failure and abandonment) were associated with patients who had been treated previously ($p < 0.001$) (Figure 2).

Among the individuals who healed, 56% had primary resistance, and 79% of the individuals in the failure group, and 86% in the abandonment group had acquired resistance ($p < 0.001$).

Multiple analysis was used to assess the association of the factors that favored the cure adjusted for probable confounding variables. Therefore, after the adjustment of the model for time between the date of the first supposedly drug-sensitive tuberculosis episode and the onset of MDR-TB (first episode tuberculosis/TB-MDRTB), and lack of bilateral cavity, the patients who presented with higher initial weight (odds ratio – OR = 1.04), without comorbidity (OR = 3.37), and with primary MDR-TB (OR = 6.29) were associated with cure at the end of the first treatment for MDR-TB (Table 3).

DISCUSSION

In four years of analysis in Instituto Clemente Ferreira, 16,575 sputum cultures for Mycobacterium tuberculosis were performed, of which only 3.2% showed resistance to the rifampicin-isoniazid binomial, which is lower in relation to specific regions of the world.[5,16]

The sample of 156 patients with MDR-TB was mainly composed of male patients, with mean age of 39 years.

In groups of patients in a special situation, such as the ones who required hospitalization, both for the

Table 1. Demographic characteristics of the 156 patients with multi-drug resistant tuberculosis (MDR-TB) included in the study.

Variable	
Age (years) mean ± SD	39.5 ± 12.5
Age of onset of the disease (years) mean ± SD	35.8 ± 13.2
Male n (%)	94 (60)
Weight (kg)	57.2 ± 11.8
Hospitalization n (%)	50 (32)
Freedom deprived n (%)	11 (7)
Homeless n (%)	06 (4)
T. drug-sensitive TB – MDR-TB (Years) Md [IQR]	1.0 [0.5 - 2.5]
Previous treatments	
Number of treatments Md [IQR]	2.0 [1 - 3]
n (%) previous plan with first line drugs	
Treatment naive	09 (06)
1	53 (34)
2	49 (31)
3 or more	45 (29)
Time for negativation (months) Md [IQR]	1 [1 - 2]
Contact with TB n (%)	
No contact	112 (72)
Contact drug-sensitive TB	19 (12)
Contact with MDR-TB	25 (16)
Resistance n (%)	
Acquired	100 (64)
Primary	56 (36)

SD: standard deviation; n: number; T.: time; TB: tuberculosis; Md: median; IQR: interquartile range.

Table 2. Clinical and radiological characteristics of patients regarding the initial outcome events.

Variables n = 156	Initial outcome					
	A (23)	F (37)	C (85)	D (11)	P	Total n (%)
Previous treatments n (%)	23 (96)	37 (100)	77 (91)	10 (91)	0.25§	146 (94%)
Number of treatments Md [IQR]	3 [2-3]	3 [2-3]	1 [1-2]	2 [1-3]	< 0.001¥	2 [1-3]
Contact TB n (%)					0.64§	
No contact	18 (78)	29 (78)	56 (66)	9 (82)		112 (72)
Drug-sensitive TB	01 (4)	04 (11)	13 (15)	1 (9)		19 (12)
MDR-TB	04 (18)	04 (11)	16 (19)	1 (9)		25 (16)
Parenchymous lesion					0.040	
Unilateral	02 (9)	04 (11)	25 (30)	03 (30)		34 (22)
Bilateral	21 (91)	33 (89)	59 (70)	07 (70)		120 (78)
Cavity					0.008	
Absent	00 (0)	01 (03)	15 (18)	03 (30)		19 (12)
Unilateral	11 (50)	15 (40)	45 (54)	04 (40)		75 (49)
Bilateral	11 (50)	21 (57)	24 (28)	03 (30)		59 (39)
Comorbidities	11 (50)	13 (35)	23 (28)	10 (91)	< 0.001	57 (37)
Diabetes mellitus	02 (9)	04 (11)	13 (16)	01 (9)	0.77	20 (13)
Hepatitis	02 (9)	01 (3)	03 (4)	01 (9)	0.59	07 (5)
HIV	04 (19)	03 (9)	00 (0)	03 (37)	< 0.001	10 (7)

n: number of patients; Md: median; TB: tuberculosis; MDR-TB: multi-drug resistant tuberculosis; HIV: human immunodeficiency virus; A: abandonment; F: failure; C: cure; D: death; §: χ^2 test (complemented by partitioning); ¥: Kruskal-Wallis.

severity of the disease or for their social condition, those who were freedom deprived[17,18] at some point because of the disease and those who were homeless were a minority, but elevated the complexity of conduct, considering the clinical and the social points of view. These groups require special care, since they are exposed to locations with high incidence of tuberculosis, with higher chances of exogenous reinfection, that is, primary resistance, which may require specific strategic.[19,20]

The median time between the first diagnosis of tuberculosis and the confirmation of resistance

compatible with the definition of MDR-TB was one year, creating the possibility of using different treatments with first line drugs,[21] perpetuating the transmission of the drug-sensitive and/or drug-resistant bacillus. This scenario confirms the identification of the fragilities of the tuberculosis control program and the management of unfavorable post-treatment events.[22]

Only 1/3 reported contact with tuberculosis, and not specifically with patients who had MDR-TB; however, the report of contact with MDR-TB was prevalent. These findings remain similar with time in the institution where the previous analysis was carried out by Melo et al.[23]

For 89% of the patients in this study, negativation occurred in up to six months. This results suggests the benefit of creating criteria for the early diagnosis of treatment failure, thus preventing the maintenance of an inadequate plan, and the consequent increase of bacillary resistance.[24]

It was amazing to find the proportion of 36% of primary MDR-TB in this sample, once, in Brazil, the rate of this descriptor is very low, around 4%.[3,11,23,25-27] It is worth to remember that many patients who showed resistance came from other services and were, afterwards, assisted at the reference center mentioned here, which characterizes that the percentage of the general population is lower than what is shown in the sample.

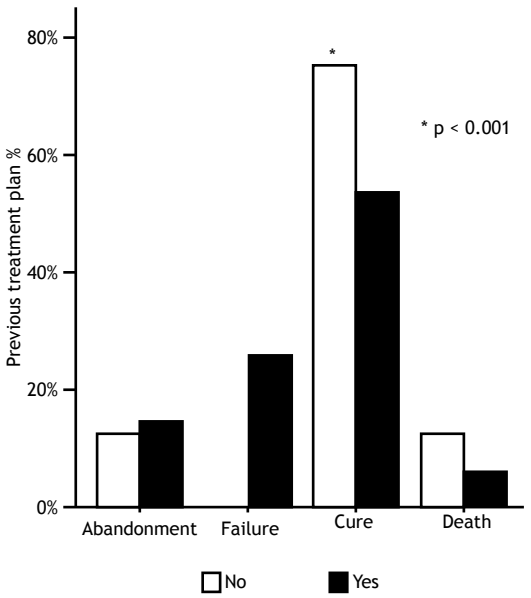

Figure 2. Association of the number of previous treatments of patients with multi-drug resistant tuberculosis (MDR-TB) with first line drugs in relation to the initial outcome events: χ^2 test added to the partitioning χ^2 test. *: significance.

The referred rate of primary resistance, of 4%, was based on the classic definition,[3,8] the most applied one, however, it may underestimate its presence,[8,14,28] since the ST is not universally offered before the beginning of the first therapeutic plan for tuberculosis.[26,29]

Therefore, the definition applied in this study was the extended primary resistance. The following cases were added to the classic definition group: patients who had never been treated for tuberculosis, but started the first treatment with a triple or basic plan, as established by the PNCT, Ministry of Health, supposedly patients with tuberculosis for bacilli who are sensitive to first line drugs, however, with unsatisfactory clinical, radiological and microbiological evolution who were not healed, with posterior confirmation of compatible bacillary resistance with MDR-TB pattern, using the phenotypic ST, in a sample collected before the beginning of the treatment.[8,14,30-32]

This extended definition could only be proposed because in the institution where this study took place, before the beginning of any treatment, the sputum culture for Mycobacterium tuberculosis and phenotypic ST[33] for first line drugs was routine for all of the patients. In case MDR-TB was confirmed, ST was performed for second line drugs.

According to this orientation from PNCT, only eight patients (5%) denied having undergone previous treatment with anti-tuberculosis drugs. In this scenario, there were possibly patients who could be cases of undiagnosed primary MDR-TB. Unfortunately, the maintenance of this recommendation, from our point of view, leads to the delayed diagnosis of bacillary resistance, and the use of an inadequate treatment plan, which can increase resistance, and, consequently, worsen the clinical conditions, besides the maintenance of transmission of multi-drug resistant bacilli.[26,30,34,35]

In thise sense, Günther et al., in a study carried out in 16 European countries, also reported high rates of MDR-TB, probably due to the transmission of the multi-drug resistance bacillus, because 52.4% of the patients had not undergone a previous treatment.[33]

In Brazil, a study performed in Espírito Santo showed primary resistance rate of 19.3%.[36] With molecular method resources, a similar situation occurred in a study conducted in São Paulo, with patients with

Table 3. Risk factors associated with cure, after 18 months of treatment, for the 156 patients with multi-drug resistant tuberculosis (MDR-TB): -2-Log-likelihood 138.271.

Variable	Odds Ratio (OR)	95%CI	P
Initial weight	1.04	0.99-1.08	0.072
T. Drug-sensitive TB - MDR-TB	1.03	0.89-1.18	0.716
No comorbidity	3.37	1.41-8.09	0.006
No bilateral cavity	2.60	1.14-5.91	0.023
Primary MDR-TB	6.29	2.35-16.79	< 0.001

T. time; TB: tuberculosis; 95%CI: 95% confidence interval.

HIV[37] and in Minas Gerais. Dantas et al. reported cases of MDR-TB for primary transmission in 20 to 30% of the patients.[28]

Such a variability is also owed to the existence of different tools to define the same parameter. Therefore, associating genotyping methods of Mycobacterium tuberculosis makes it possible to explore the dynamic transmission of the bacillus, besides distinguishing the disease by exogenous reinfection or endogenous reactivation.[33,36,38]

The broad use of rapid molecular test (Xpert RIF/MTB) as the first approach should collaborate with a quick diagnosis and the adequate conduct for bacillary resistance.

It is very important to distinguish primary resistance from acquired resistance, since there may be implications in the strategy to control the transmission of the multi-drug resistant bacillus.

Also, it is essential to perform a phenotypic ST for all cases of tuberculosis before the treatment, because, without it, it is impossible to assess and take adequate and accurate measures for transmission control. This characterization can be an indicator of efficiency of the tuberculosis control program, helping with the adjustments and the development of tools to control the MDR-TB.[32,34]

In conclusion, after the adjustment for confounding variables, the multiple analysis showed that patients with MDR-TB with primary resistance, without comorbidities and higher initial weight were the ones with higher chances of cure after the initial 18-month treatment. Logistic regression confirmed the expected in the daily clinic. Therefore, early diagnosis and adequate treatment in patients with good clinical conditions favor the cure.[21,38,39]

The treatment plan for MDR-TB in Brazil is standardized by PNCT, and is composed, in the study period, by five drugs, accounting for 18 to 24 months, according to the time for culture negativation and radiological clinical assessment. In the first six months, the following are administered: amikacin, levofloxacin or ofloxacin, ethambutol, terizidone, and pyrazinamide); in the following 12 months, ofloxavin or levofloxacin, ethambutol and terizidone.[6] In some situations, an alternative plan for MDR-TB was used and composed of three or four first line and second line drugs (all of them had ofloxacin), or, as aforementioned, with first line drugs. This plan changed in 2017. Currently, the plan established by the Ministry of Health for Brazil is different, according to the institution's information note.[40]

Study limitations are the fact that it is retrospective and carried out in a single center, where the information was taken from the charts of patients assisted by different physicians, so the data was provided by the patient. However, all relevant information was described in a structured, previously established report, in order to minimize possible bias. Besides, even if occasionally, phenotypic ST was not performed for first line or second line drugs concomitantly for all patients in the beginning of the treatment for MDR-TB, which could lead to more precision in primary resistance rate.

Studies with prospective design and phenotypic and genotypic ST should add more accurate data to this study.

The conclusion is that primary resistance among cases of MDR-TB was higher, and the predictive factors associated with healing after the first treatment ere: presence of primary MDR-TB, lack of bilateral cavity and lack of comorbidity after the adjustment for the initial weight of the patient, and time between drug-sensitive tuberculosis and diagnosis of MDR-TB.

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