Prevalence of primary drug resistance in pulmonary tuberculosis patients with no known risk factors for such*

Prevalência de resistência primária em pacientes com tuberculose pulmonar sem fatores de risco conhecidos para resistência primária

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Abstract

Objective: To estimate the prevalence of primary resistance to the drugs in the basic treatment regimen for tuberculosis in treatment-naïve patients with pulmonary tuberculosis and no known risk factors for such resistance, as well as to identify factors potentially associated with drug resistance. **Methods:** This was an exploratory cross-sectional study. We analyzed the medical records of the subjects enrolled in two clinical trials of treatments for drug-susceptible tuberculosis between November 1, 2004 and March 31, 2011 at the Prof. Newton Bethlem Outpatient Clinic of the Federal University of Rio de Janeiro Thoracic Diseases Institute, located in the city of Rio de Janeiro, Brazil. The inclusion criteria were being ≥ 18 years of age, testing positive for AFB in the first sputum sample, having a positive culture for *Mycobacterium tuberculosis*, having undergone drug susceptibility testing, and being treatment-naïve. Patients with a history of imprisonment or hospitalization were excluded, as were those who had been in contact with drug-resistant tuberculosis patients. **Results:** We included 209 patients. The overall prevalence of primary drug resistance was 16.3%. The overall prevalence of resistance to isoniazid and streptomycin was, respectively, 9.6% and 9.1%, compared with 5.8% and 6.8% for single-drug resistance to isoniazid and streptomycin, respectively. The prevalence of resistance to two or more drugs was 3.8%, and the prevalence of multidrug resistance was 0.5%. No statistically significant associations were found between the variables studied and drug susceptibility testing results. **Conclusions:** In this sample, the prevalence of primary drug resistance was high despite the absence of known risk factors.

Keywords: Tuberculosis, pulmonary; Tuberculosis, multidrug-resistant; Risk factors.

Resumo

Objetivo: Estimar a prevalência de resistência primária aos medicamentos do esquema básico de tratamento antituberculose em pacientes com tuberculose pulmonar virgens de tratamento sem fatores de risco conhecidos para resistência primária, e identificar os possíveis fatores associados à resistência medicamentosa. **Métodos:** Estudo transversal exploratório com a análise de prontuários de pacientes que participaram de dois ensaios clínicos de tuberculose sensível entre 1° de novembro de 2004 e 31 de março de 2011 no Ambulatório Prof. Newton Bethlem do Instituto de Doenças do Tórax da Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ). Os critérios de inclusão foram ter idade ≥ 18 anos, ter pesquisa direta de BAAR positiva na primeira amostra de escarro, ter cultura positiva para *Mycobacterium tuberculosis*, ter realizado testes de sensibilidade aos fármacos, ser virgem de tratamento para tuberculose e não ter história de prisão, hospitalização ou contato com caso de tuberculose resistente. **Resultados:** Foram incluídos 209 pacientes. A prevalência de resistência primária geral foi de 16,3%. A prevalência geral de resistência à isoniazida e à estreptomicina foi, respectivamente, 9,6% e 9,1%, enquanto a prevalência de monorresistência à isoniazida e à estreptomicina foi de, respectivamente, 5,8% e 6,8%. A prevalência de resistência a dois ou mais fármacos foi de 3,8%, e a prevalência de tuberculose multirresistente foi de 0,5%. Não foram observadas associações estatisticamente significativas entre as variáveis estudadas e resultados do teste de sensibilidade aos fármacos. **Conclusões:** Na amostra estudada, a prevalência de resistência primária foi elevada apesar da ausência de fatores de risco conhecidos.

Descritores: Tuberculose pulmonar; Tuberculose resistente a múltiplos medicamentos; Fatores de Risco.

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Introduction

In Brazil, the basic treatment regimen for all cases of adult and adolescent (over 10 years of age) tuberculosis, except for the meningoencephalitic form, consists of two months of treatment with rifampin, isoniazid, pyrazinamide, and ethambutol followed by four months of treatment with rifampin and isoniazid.[1] Culture for *Mycobacterium tuberculosis* and drug susceptibility testing at the outset of treatment are indicated only in patients considered to be at increased risk for primary drug resistance (those with recurrent tuberculosis, those with a history of hospitalization or imprisonment, homeless individuals, and those with comorbidities, such as HIV infection) or for acquired drug resistance (particularly those with a history of poor treatment adherence).[1] The theoretical substratum for not performing culture for *M. tuberculosis* or drug susceptibility testing in treatment-naïve patients is provided by drug resistance survey data published in a technical note by the Brazilian National Ministry of Health (NMH), as well as by the premise that the risk of primary drug resistance is not significant in patients who do not belong to the aforementioned groups.[2] However, the limited cure rate associated with the high rate of treatment dropout and the consequent poor treatment efficacy in many regions in Brazil, as shown by data from the *Sistema Nacional de Informação de Agravos de Notificação* (SINAN, National Case Registry Database), suggest that cases of primary drug resistance might not be restricted to the defined risk groups.[3]

The objective of the present study was to estimate the prevalence of primary resistance to the drugs in the basic treatment regimen for tuberculosis in the first sputum sample from patients with pulmonary tuberculosis and no known history of tuberculosis, imprisonment, hospitalization for any reason, or contact with patients with known drug-resistant tuberculosis.

Methods

This was an exploratory cross-sectional study in which we analyzed the medical records of the subjects enrolled in either of two clinical trials of treatments for drug-susceptible tuberculosis, one of which has been completed and one of which is ongoing.[4,5] Those trials were/are being conducted at the Laboratory for Clinical Research on Tuberculosis of the Prof. Newton Bethlem Outpatient Clinic of the *Instituto de Doenças de Tórax da Universidade Federal do Rio de Janeiro* (IDT/UFRJ, Federal University of Rio de Janeiro Thoracic Diseases Institute), which is located in the city of Rio de Janeiro, Brazil, and proactively treats patients referred there from primary health care facilities. The inclusion criteria for the present study were being ≥ 18 years of age, testing positive for AFB in the first sputum sample, having a positive culture for *M. tuberculosis*, having undergone drug susceptibility testing, and being treatment-naïve. The exclusion criteria were having an incomplete medical record, or having a history of imprisonment, hospitalization, or contact with patients with known drug-resistant tuberculosis.

The routine of care for the aforementioned trials included history taking, physical examination, and posteroanterior and lateral chest X-rays, as well as AFB smear testing, culture for *M. tuberculosis*, and drug susceptibility testing of all (spontaneous or induced) sputum samples collected during the initial evaluation.[6] All sputum samples were sent to the Mycobacteriology Laboratory of the IDT/UFRJ for testing. The results of AFB smear were available after 24 h. The culture results were available within 60 days, whereas the drug susceptibility testing results were available within 90 days. The sputum smear microscopy method employed was the Ziehl-Neelsen method, and culture was performed on Löwenstein-Jensen medium in accordance with a standardized protocol.[7] All samples with a positive culture for *M. tuberculosis* underwent biochemical testing in order to differentiate the *M. tuberculosis* complex from other nontuberculous mycobacteria.

Drug susceptibility testing was performed by the proportion method, on the basis of indirect tests, as described by Canetti et al.[8] We tested susceptibility to isoniazid, rifampin, ethambutol, streptomycin, and ethionamide, the final concentrations of which on Löwenstein-Jensen were 0.2 mg/mL, 40.0 mg/mL, 2.0 mg/mL, 4.0 mg/mL, and 20 mg/mL, respectively. All antibiotics were obtained in pure powder form (Sigma-Aldrich Chemie BV, Zwijndrecht, The Netherlands). All techniques were carried out in accordance with the guidelines of the Brazilian NMH.[9]

A data collection instrument was developed specifically for the present study, as well as being

pilot tested and adjusted by using data from 15 medical records (which were not included in the study). One single person, who had been trained for this purpose, reviewed the medical records and completed the instrument. Variables that have been described in the literature as potentially associated with drug resistance in tuberculosis (radiological extent of tuberculosis, alcoholism, residence in a low-income area, unemployment, diabetes mellitus, smoking, previous use of antibiotics, and illicit drug use) were recorded on the data collection instrument. An extensive radiological lesion was defined as that for which the total affected area exceeded that of one lobe or as that in which there was cavitation of 1 cm or more in diameter. Alcoholism was defined by means of the CAGE questionnaire, the name being an acronym for key terms in the instrument's four questions,[6] whereas current smokers with any smoking history or former smokers with a smoking history of 15 pack-years or more were considered smokers. These data were imported into a Microsoft Office Excel spreadsheet for subsequent analysis.

Results were analyzed with the Statistical Package for the Social Sciences, version 11.0 (SPSS Inc., Chicago, IL, USA). The chi-square test was used for analysis of dichotomous variables. The OR for the outcome resistance was calculated, as was the respective 95% CI. Results were considered significant when $p < 0.05$. The study protocol was approved by the Research Ethics Committee of the Federal University of Rio de Janeiro Clementino Fraga Filho University Hospital on August 22, 2008 (Process no. 596/08).

Results

The study included 211 patient medical records, 2 of which were excluded because they were incomplete. Therefore, 209 medical records of patients with pulmonary tuberculosis were considered eligible for data analysis. Of those patients, 34 (16%) showed primary resistance to at least one of the five drugs tested in the first sputum sample. Table 1 shows the gender and age of the 209 patients with pulmonary tuberculosis by patient group stratified by drug susceptibility testing result. There were no significant differences regarding these variables.

Table 2 shows the profile of drug resistance in the 34 patients. The overall prevalence of resistance to isoniazid (alone or in combination with other drugs) was 9.6%. The prevalence of resistance to streptomycin (alone or in combination with other drugs) was 9.1%.

Table 3 shows an analysis of the variables potentially associated with drug resistance in the study sample. None of the variables studied were found to be statistically associated with drug resistance.

Table 1 - Demographic data on the 209 patients with pulmonary tuberculosis.

Demographic data	Antibiotic drug susceptibility testing results (n = 209)		p
	Susceptible to all of the drugs tested[a] (n = 175)	Resistant to 1 or more of the drugs tested (n = 34)	
Gender			
Male, n (%)	113 (64.6)	18 (52.9)	0.1
Female, n (%)	62 (35.4)	16 (47.1)	
Age, years[b]	35 ± 13 [32 (25-45)]	39 ± 14 [37 (25-50)]	0.07

[a]Isoniazid, rifampin, ethambutol, streptomycin, and ethionamide. [b]Values expressed as mean ± SD [median (interquartile range)].

Table 2 - Prevalence of drug resistance in the study sample by drug, either alone or in combination.

Resistance to	Prevalence, %
Isoniazid (single-drug resistance)	5.8
Isoniazid + rifampin	0.5
Isoniazid + ethionamide	0.9
Isoniazid + streptomycin	0.9
Isoniazid + streptomycin + ethambutol	0.9
Isoniazid + streptomycin + ethionamide	0.5
Streptomycin (single-drug resistance)	6.8

Table 3 - Measures of association between resistance to at least one drug and the variables tested.

Variable	Susceptible to all of the drugs tested (n = 175)	Resistant to 1 or more of the drugs tested (n = 34)	p	OR (95% CI)
Presence of an extensive radiological lesion, yes/no	122/53	27/7	0.2	1.6 (0.6-4.0)
Residence in a low-income area, yes/no	127/48	24/10	0.8	0.9 (0.4-2.0)
Employment status, employed/unemployed	89/86	23/11	0.07	2.0 (0.9-4.3)
Presence of comorbidities,[a] yes/no	22/153	6/28	0.4	1.4 (0.5-4.0)
Smoking, yes/no	46/129	11/23	0.4	1.3 (0.6-2.9)
Alcoholism, yes/no	45/130	8/26	0.7	0.8 (0.3-2.1)
Previous use of antibiotics,[b] yes/no	21/154	4/30	0.9	0.9 (0.3-3.0)

[a]Comorbidity (N of patients): leukemia (n = 3) and diabetes mellitus (n = 26). [b]Previous use of antibiotics (N of patients): amoxicillin (n = 13), amoxicillin + clavulanate (n = 6), levofloxacin (n = 1), amoxicillin + clavulanate + cephalexin (n = 2), amoxicillin + clavulanate + clarithromycin (n = 1), amoxicillin + clavulanate + ciprofloxacin (n = 1), and amoxicillin + clavulanate + azithromycin (n = 1).

No statistically significant associations were found between the variables studied and drug susceptibility testing results. None of the patients reported using immunosuppressants.

Discussion

The rate of resistance to isoniazid in the study sample (9.6%) was more than 40% higher than that reported by the Brazilian NMH as having been found in the Second National Survey on Anti-Tuberculosis Drug Resistance (6%), whereas the rate of resistance to rifampin alone (0% vs. 0.5%) and the rate of multidrug resistance (0.5% vs. 1.4%) were lower.[2] The technical note published by the Brazilian NMH does not describe the methodology employed in conducting the Second National Survey, nor does it cite the survey in its reference list.[2] A search of the SciELO and PubMed databases for Portuguese-language and English-language articles published from 2008 onward also did not identify this reference, which prevented us from discussing potential differences or similarities between the samples or methodologies. The surprisingly high rate of resistance to streptomycin (9.1%) found in the present study sample suggests that, in Brazil, there has been endogenous reactivation of strains that emerged before the 1980s, since streptomycin is not used in new cases, except in cases of multidrug-resistant tuberculosis or in cases of intolerance to isoniazid or rifampin.[1,10] The absence of resistance to rifampin, however, is in contrast to the data reported in the technical note published by the Brazilian NMH and to what has been observed worldwide, since rifampin ranks third among drugs that cause resistance.[11] In fact, even in Central and Western Europe, where the rate of drug resistance is lower, resistance to rifampin is 1.1%.[11]

In a study conducted in the state of Mato Grosso do Sul, Brazil, and involving 645 samples collected from new cases between 2000 and 2006, the rates of primary drug resistance were 3.4% for streptomycin, 2.9% for isoniazid, and 1.7% for ethambutol,[12] i.e., the prevalence of primary drug resistance was approximately half of that found in our sample. As in our study, no resistance to rifampin was found. It is of note that the rate of resistance to ethambutol (which has recently been included in the basic treatment regimen because of the increasing rate of resistance to isoniazid) was 1.7%, whereas, in our sample, the rate of resistance to ethambutol, which was used in combination with isoniazid and streptomycin, was 0.9% (Table 2). Because that study was based on a review of data from SINAM, potential risk factors for drug resistance were not assessed, nor were there detailed information on the sample characteristics.

In a prospective study conducted in the city of Cabo de Santo Agostinho, located in northeastern Brazil, from 2000 to 2003 and involving 174 samples, the prevalence of primary resistance to at least one drug was 14%, whereas the prevalence of multidrug resistance was 8.3%.[13] However, in that study sample, previous tuberculosis treatment and treatment dropout were identified as variables associated with risk of drug resistance. The prevalence of primary multidrug resistance was higher than that reported

in the technical note published by the Brazilian NMH[2] and that found in our sample. In fact, the rate was comparable to that found in countries where the prevalence of multidrug resistance is high, such as Mozambique, Colombia, Lithuania, and Uzbekistan.[11] It is of note that the rate of treatment dropout in the region was higher than 10%, i.e., slightly above the national average.[3]

Two studies conducted in Brazil[14,15] and involving samples from patients admitted to either a referral hospital for tuberculosis and AIDS in Rio de Janeiro (samples collected between 2001 and 2005) or to a tertiary care hospital in Rio Grande do Sul (samples collected between 1997 and 2003) found prevalences of 16% and 18%, respectively, for primary resistance to at least one drug and prevalences of 4.3% and 2.0%, respectively, for multidrug resistance, i.e., the prevalence of resistance to at least one drug in the samples from those groups (which consisted of individuals with known risk factors for drug resistance) was the same as that found in our sample, which consisted of individuals with no known or perceived risk factors for drug resistance.

Between 2000 and 2002, a study conducted in the city of Rio de Janeiro and involving a group of 75 patients diagnosed with pulmonary tuberculosis who lived in the Complexo de Manguinhos found resistance to at least one drug in 10.6% of the new cases of tuberculosis.[16] The prevalence of single-drug resistance to isoniazid was 2.6%, and the prevalence of single-drug resistance to streptomycin was 4%. No rifampin-resistant or ethionamide-resistant strains were detected. Although the samples are not comparable, the fact that the Complexo de Manguinhos is located near the IDT/UFRJ Tuberculosis Outpatient Clinic and that the recorded prevalence of drug resistance was nearly half of that seen in our sample one decade later should be a cause for reflection.

In our study, we identified no association between the variable "cavitation on baseline chest X-ray" and the rate of drug resistance. However, a study conducted at a referral center for infectious diseases in the state of Minas Gerais, Brazil, between September of 2000 and January of 2004, found that the risk of multidrug resistance was higher in patients with cavitation of more than 4 cm in diameter and in those who had received previous tuberculosis treatment.[17]

A population-based, case-control study (134 cases and 185 controls) that was conducted in the state of Ceará, Brazil, between 1990 and 1999 and that also evaluated only cases of multidrug-resistant tuberculosis found that five variables (no home sewage treatment system, alcoholism + smoking, number of previous treatments, irregular treatment, and lung cavities) were associated with drug resistance.[18] In our sample, we evaluated only cases of primary drug resistance and we did not identify alcoholism or smoking as risk factors. Although the association between tuberculosis and smoking, as well as the increase in infectivity, morbidity, and mortality in active or passive smokers, has been demonstrated, the association between smoking and drug resistance has yet to be described.[19]

The high rate of primary drug resistance in patients with no known risk factors or in patients from areas where the rates of tuberculosis incidence and treatment dropout are high should be a cause for reflection by authorities in Brazil. The current practice of considering culture and drug susceptibility testing necessary only in patients with known risk factors is not justified, either from a medical or an economic standpoint. Despite the fact that, in 2009, the Brazilian NMH took a correct step in adding a fourth drug (ethambutol) to the then employed triple treatment regimen, reducing the risk of disease recurrence in patients with resistance to isoniazid, the possibility of emergence of resistance to ethambutol itself was not considered.[2] In addition, the high prevalence of resistance to streptomycin causes its use in patients with intolerance or single-drug resistance (to one of the drugs in the basic treatment regimen) to be a risk factor for disease recurrence or even for treatment failure.

The present study has some limitations. The sample studied was not random, is small, and included patients mostly from a health program area in the city of Rio de Janeiro, and, therefore, there might have been no statistical power to detect significant associations and it might not have been representative of other regions. This was a retrospective study that was based on data obtained from medical records, which may introduce information bias. However, this can be minimized by the systematic data collection, which was performed in an outpatient clinic with a strict routine of care for clinical research purposes.

Despite its limitations, the present study showed that there was a high prevalence of primary drug resistance in treatment-naïve patients with pulmonary tuberculosis and no known risk factors. This finding demonstrates the importance of performing culture for *M. tuberculosis* and drug susceptibility testing in the study sample and emphasizes the need to perform these tests in all patients with pulmonary tuberculosis in Brazil. Although there are only a small number of facilities performing solid medium culture for *M. tuberculosis* and even fewer facilities performing drug susceptibility testing, these methods are affordable and could be universally implemented, whereas more modern, rapid, and expensive methods, such as automated methods, would be reserved for patients with known risk factors.

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