Artigo Original

Drug-resistant *Mycobacterium tuberculosis* strains isolated at an AIDS reference center general hospital in Rio de Janeiro*

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Background: Tuberculosis become important challenge to health care settings. Brazil has high prevalence of the disease and Rio de Janeiro has high incidence rates with 30% of cases notified at hospitals.

Objective: To evaluate prevalence of initial and acquired drug resistance at a general hospital, reference for aids treatment in Rio de Janeiro and to identify associated factors.

Methods: *Mycobacterium tuberculosis* strains from 165 patients were analyzed, between August 1996 and February 1998.

Results: Twenty per cent (33/165) were resistant to at least one drug; 13% (12/165) to isoniazid; 3.64% (6/165) to rifampin and 3.64% (6/165) to both. Among HIV seropositive subjects (52/165); 28.85% (15/52) were resistant to at least one drug. Acquired resistance occurred in 15.79% of 19 patients that mentioned previous antiTB treatment. Association statistically significant was found with non cavitation on X-ray in bivariate analyses (P=0.05). Eighty four patients refereed no previous treatment (NPT). Resistance to 1 or more drugs was found in 28.57% (24/84) of NPT patients. Association statistically significant with initial resistance was found with health care workers (P=0.004), unemployment (P=0.03), and diarrhea (P=0.01) in bivariate analyses. On multivariate analyses, health care workers (P=0.002) remained significantly associated with initial resistance.

Conclusions: High resistance rates was found. It corroborates that hospitals needs attention for TB control especially which concerns to health care works infection.

Key words: Mycobacterium tuberculosis. Drug resistance. Disease transmission, patient to professional. Hospitals.

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INTRODUCTION

Tuberculosis (TB) represents a great challenge in various regions in the world today. Internationally, incidence has been increasing by approximately 0.4% every year[1]. It is estimated that one-third of the world population is infected with *Mycobacterium tuberculosis* (Mtb). Approximately 95% of these cases, and 98% of TB-related deaths, have occurred in developing countries[2].

According to the World Health Organization, Brazil ranks fifteenth among nations with the highest rates of TB.[1] In 2001, there were an estimated 111,000 new cases of the disease, for an incidence rate of 64/100,000 inhabitants. Control of the disease is poor in various regions of the country, and the implementation of supervised treatment strategies is still in the incipient phase[1]. In 1999, the cure rate was 75.40%, and there was a 13.81% rate of noncompliance with treatment. Over the past few years, the highest negative impact on TB control has occurred in large cities – as a result of worsening socioeconomic conditions and the dismantling of the health system. Data are more alarming in the southeastern part of the country, where co-infection with human immunodeficiency virus (HIV) is the highest.[3]

There are approximately 6 million people in the city of Rio de Janeiro, the largest metropolitan area in the state of Rio de Janeiro. In 2000, 9223 TB cases were reported (6680 new cases), for an incidence rate of 114/100,000 inhabitants, and the mortality rate was 6.53%.[4] In 1995, one third of the 9500 TB cases reported in the city of Rio de Janeiro occurred in hospitals, where most reported TB/HIV co-infection cases (63%) also occurred.[5]

Primary and acquired resistance to anti-TB drugs has been reported since the introduction of antimicrobial drugs for TB treatment.[6,7] Developed countries have been concerned about the increase of primary and acquired resistance, especially in large urban areas. Most cases of primary resistance are caused by contamination of indoor environments (hospitals, prisons, shelters) and HIV co-infection.[8-10] Very few data have been collected concerning this subject in developing countries. On the one hand, TB control programs have emphasized the use of sputum smear microscopy in patients treated in basic health units. On the other hand, there are no guidelines for the use of mycobacteria culture and susceptibility tests in patients treated in general hospitals.[11,12]

It is believed that resistance has also been increasing in developing countries, especially in large urban centers, if we consider the high incidence of noncompliance with treatment and the high number of patients treated in hospitals.[12] Since there are few reports on primary resistance in these countries, especially in environments such as hospitals and prisons (where higher incidence is expected), surveys have been performed in order to characterize drug-resistance profiles.[13-15]

There are very few data on resistance to anti-TB drugs in our country. A multicenter study performed by the Ministry of Health between 1995 and 1996 showed a primary resistance rate of 8.5% and an acquired resistance rate of 21.0%. Primary resistance to the rifampin and isoniazid combination (RIF+INH) occurred in 1.1% of the cases studied, and acquired resistance to this combination was 7.9%. The patients in that study had not been submitted to anti-HIV serology tests. In addition, patients treated in hospitals were not included in the study in a representative fashion.[7] Between 2000 and 2003, 1214 multidrug-resistant TB cases were reported in Brazil, 45.4% of these in the state of Rio de Janeiro. Of these patients, 95% presented with acquired resistance. Of the total number of patients diagnosed with multidrug-resistant TB and submitted to anti-HIV testing (988 patients), 8% presented with HIV co-infection.[16]

Siglas e abreviaturas utilizadas neste trabalho:
95% CI – 95% confidence interval
HIV – Human immunodeficiency virus
HUPE – *Hospital Universitário Pedro Ernesto* (Pedro Ernesto University Hospital)
INH – Isoniazid
Mtb – *Mycobacterium tuberculosis*
OR– Odds ratio
RIF – Rifampin
SINAN – *Sistema de Informações de Agravos de Notificação* (Case-registry database)
TB – Tuberculosis

With the deconstruction of the treatment of patients diagnosed with TB – caused by the dismantling of TB control programs in various cities and the presence of a considerable number of public hospitals in the city of Rio de Janeiro – patients usually go to hospitals for diagnosis and treatment of TB instead of visiting primary health units.[17] In addition to this, some complex cases, such as those with acquired immunodeficiency syndrome (AIDS) or other comorbidities, are referred to hospitals. Since there are no TB control programs in hospitals, there are no data on treatment outcomes (noncompliance, cure, mortality, side effects) or strain resistance to anti-TB drugs. Only two hospitals in the city of Rio de Janeiro have been currently submitting patients to mycobacteria culture as a routine procedure, but none have been performing anti-TB drug susceptibility tests.[18] Recent studies have shown high primary multidrug-resistant rates (15% in HIV-positive patients and 3% in HIV-negative patients) at a reference center general hospital in the city of Rio de Janeiro, and a great number of positive tuberculin test results (8.7%) among health care professionals.[20]

The objective of the present study was to evaluate prevalence of primary and acquired drug resistance and to identify associated risk factors. In order to do so, we studied resistance to anti-TB drugs in Mtb strains isolated from patients at another reference center general hospital over an 18-month period.

METHOD

A transversal study was carried out from August 1996 to February 1998. Cultures for mycobacteria were requested by attending physicians and analyzed in the microbiology laboratory at the *Hospital Universitário Pedro Ernesto* (HUPE, Pedro Ernesto University Hospital) of the *Universidade do Estado do Rio de Janeiro* (Rio de Janeiro State University). All cultures testing positive within this period were selected. All samples were submitted to susceptibility tests and, when possible, patients were interviewed. Medical records of all cases selected were analyzed using a standardized form. These procedures allowed demographic, clinical, and laboratory analysis data to be collected. The HUPE is a tertiary-care general hospital, treating inpatients and outpatients. The complex incorporates clinics, infirmaries, and intensive care units, and activities targeted at the education of health care professionals are also developed. It is also a reference center for patients with HIV/AIDS, and is located in the Vila Izabel district, in the metropolitan area of the city of Rio de Janeiro. Nevertheless, this hospital receives patients from other districts, other cities (especially from the *baixada fluminense*, or "lower Rio" region) and even from other states. The annual number of patients diagnosed with TB has been approximately 350 for the past few years. At the time of the study, there were 604 patient beds in the HUPE, yet there were no beds designated for respiratory isolation or TB control activities.

All positive cultures of strains isolated during the study period and confirmed as Mtb through biochemical tests were included in the study. Exclusion criteria included contamination of culture material and technical problems that affected susceptibility test results.

Direct examination of mycobacteria was performed using the Ziehl-Neelsen method, and the culture medium used for mycobacteria was Löwenstein-Jensen, in accordance with the guidelines recommended in the *Manual de Bacteriologia da Tuberculose do Ministério da Saúde* (Health Ministry Guidebook for Tuberculosis Bacteriology)[21]. At the *Laboratório Noel Nuttels*, a state reference laboratory for the bacteriological diagnosis of TB, Mtb was identified (through the verification of growth in the presence of the inhibitors TCH and PNB) and susceptibility tests were performed (Canetti and Grosset proportion method), both in accordance with the guidelines recommended in the Health Ministry Guidebook.[21]

Data were analyzed using Epi Info 6.0 and STATA 6.0 software programs. We obtained p values using the chi-square test and Yates correction, except for those cases in which Fisher's exact test or chi-square test for trend was indicated. Bivariate analysis adjusted for potentially confounding variables was performed according to the plausibility of their occurrence and the outcome: occurrence of resistant TB. In this initial phase, the level of significance was set at $p \leq 0.10$. After the

identification of the variables significantly correlated with the outcome, multivariate analysis was performed.

The Research Ethics Committee of the *Hospital Universitário Pedro Ernesto* approved the project, and all participating patients gave written informed consent.

RESULTS

During the study period, 380 cases of TB were reported at HUPE. A total of 165 strains (isolated from 165 patients) met the inclusion criteria. Two samples characterized as nontuberculous mycobacteria were excluded. There were no exclusions due to contamination or technical problems. The medical records of all participating patients were reviewed in order to gather clinical and epidemiological data, which were included in the analysis. In addition, 110 of the 165 patients were interviewed. There were no statistically significant differences in sociodemographic characteristics, clinical presentation of TB, gender, age, HIV positivity or hospitalization between interviewed patients and those for whom data was obtained solely from medical records.

Twenty-five patients (15%) were less than 20 years of age, 77 (46%) were between 20 and 40, 46 (29%) were between 40 and 60, and 17 (10%) were older than 60. One hundred and eleven patients (67%) were male. There were 77 Caucasians (47%) and 58 non-whites (35%). Fifty-six patients (34%) reported having had less than 8 years of schooling, and 103 (63%) reported having completed at least 8 years. One hundred and forty-seven patients (89%) were employed and 17 (10%) were unemployed. Twenty-four patients (14.5%) reported previous anti-TB treatment (data were consistent between medical records and interview notes). Of the 113 patients submitted to HIV testing, 52 (46%) tested positive. Thirty-six (22%) patients reported having contact with a TB patient in the home. Seven patients (4%) were health care professionals. Seventy-two patients (44%) were hospitalized at the time of diagnosis and 86 (52%) were diagnosed as outpatients. The most common clinical presentation was typical pulmonary TB (95 patients – 56%). Of the patients studied, 59 (48%) presented with a positive sputum smears were seen in 59 (48%), 14 of whom presented with strains resistant to some of the drugs tested, and 4 of whom were diagnosed during hospitalization.

Thirty-three of the strains isolated (20%) presented resistance to at least one drug: 21 (12.72%) were resistant to one drug, 10 (6.67%) to two drugs, 1 (0.61%) to three drugs, and 1 (0.61%) to four drugs. Twenty-two (13.3%) strains were resistant to INH, 17 (10.3%) to streptomycin, 6 (3.6%) to RIF, 3 (1.8%) to ethambutol, and 6 (3.6%) to the RIF+INH combination. Of the 52 HIV/AIDS patients, 15 (28.85%) presented strains resistant to at least one drug. Primary resistance was detected in 26 of 141 patients (18.4%) and acquired resistance in 3 of 24 (12.5%). We reviewed data from the *Sistema de Informações de Agravos de Notificação* (SINAN, Case-registry database) for the state of Rio de Janeiro in order to confirm whether the patients included as never previously submitted to anti-TB treatment had ever been registered in the database. None of the patients participating in the present study had been previously registered in the SINAN.

In the univariate analysis, general resistance to antimicrobial drugs was significantly correlated with being a health care professional (p = 0.0007). Distribution of the main variables under study in relation to the occurrence of general resistance is found in Table 1. Among patients with previous anti-TB treatment, only cavitation-free chest X-rays showed a statistically significant correlation with drug resistance, with an odds ratio (OR) of 0.15 and a 95% confidence interval (95% CI) of 0 to 1.66 (p = 0.05). Among patients who were treatment naive, bivariate analysis showed statistically significant correlations between drug resistance and the following variables: being a health care professional (OR = 18.16; 95% CI = 1.80 to 870.66; p = 0.004), diarrhea at the time of diagnosis (OR = 4.06; 95% CI = 1.19 to 13.94; p = 0.01) and unemployment (OR = 4.76; 95% CI = 0.92 to 25.77; p = 0.03).

Based on findings reported in the literature, bivariate analysis was performed using potentially confounding variables in drawing correlations between certain risk factors (being a health care professional, co-infection with HIV, previous treatment) and resistance to anti-TB drugs. Sociodemographic, clinical, and laboratory test variables were used in the analysis. We noticed that being a health care professional strongly

TABLE 1
Distribution of principal sociodemographic, epidemiological, radiographic and clinical characteristics, in accordance with the finding of general resistance

Characteristic	Resistant	Susceptible	OR	95% CI	*p*	Total
Gender						
Female	8	38	0.72	0.26 – 1.85	0.61	46
Male	25	86	—	—	—	111
No data	0	8	0.00	0.00 – 2.18	0.20	8
Age						
0-19 years	3	22	—	—	—	25
20-39 years	15	62	1.77	0.44 – 10.41	0.55	77
40-59 years	11	35	2.30	0.52 – 14.14	0.35	46
60-79 years	3	11	2.00	0.22 – 17.22	0.65	14
80-99 years	1	2	3.67	0.05 – 88.35	0.38	3
Race						
Non-white	14	44	1.32	0.53 – 3.25	0.66	58
Caucasian	15	62	—	—	—	77
No data	4	26	0.64	0.14 – 2.27	0.64	30
Schooling						
≤8 years	10	46	0.85	0.33 – 2.08	0.86	56
>8 years	21	82	—	—	—	103
No data	2	4	1.95	0.16 – 14.61	0.60	6
Occupation						
Unemployed	6	11	2.42	0.67 – 7.88	0.11	17
Employed	27	120	—	—	—	147
No data	0	1	0.00	0.00 – 174.78	1.00	1
Health care professional						
Yes	6	1	24.27	2.64 – 1128.37	0.0007	7
No	22	89	—	—	—	111
No data	5	42	0.48	0.13 – 1.43	0.24	47
Hospital status						
Inpatient	14	58	0.91	0.38 – 2.14	0.97	72
Outpatient	18	68	—	—	—	86
No data	1	6	0.63	0.01 – 5.75	1.00	7
Smoking						
Yes	20	59	1.77	0.69 – 4.83	0.28	79
No	9	47	—	—	—	56
No data	4	26	0.80	0.16 – 3.25	1.00	30
Alcoolismo						
Yes	9	45	0.61	0.22 – 1.57	0.37	54
No	20	61	—	—	—	81
No data	4	26	0.47	0.11 – 1.61	0.30	30
Clinical presentation						
Pulmonary	18	77	0.66	0.27 – 1.69	0.45	95
Other	12	34	—	—	—	46
No data	3	21	0.40	0.07 – 1.77	0.31	24
Chest X-ray						
Other forms	14	42	1.20	0.34 – 4.90	0.99	56
Cavitation	5	18	—	—	—	23
No data	14	72	0.70	0.20 – 2.82	0.54	86
HIV serology						
HIV-positive	13	39	1.23	0.46 - 3.25	0.81	52
HIV-negative	13	48	—	—	—	61
Not tested	2	7	1.05	0.10 - 6.51	1.00	9
No data	5	38	0.49	0.13 - 1.63	0.31	43
Previous anti-TB treatment						
Yes (retreatment)	3	21	0.46	0.08 – 1.75	0.35	24
No	26	84	—	—	—	110
No data	4	27	0.48	0.11 – 1.57	0.30	31

OR: odds ratio; 95% CI: 95% confidence interval; HIV: human immunodeficiency virus; TB: tuberculosis

correlated with resistance to one or more drugs (OR = 48.44; 95% CI = 4.37 to 536.68; $p = 0.002$), as well as with resistance to the RIF+INH combination (OR = 90.89; 95% CI = 1.05 to 7878.99; $p = 0.05$).

DISCUSSION

The findings of the present study underscore the importance of giving increased attention to TB in hospitals. We noticed a sociodemographic, clinical, and laboratory test result distribution that rarely differed from SINAN data. The great number of patients with typical pulmonary TB (95%) and positive sputum smear results (58%), as well as the proportion diagnosed during hospitalization (72%), indicates that the potential for nosocomial transmission is very high. This is even more worrisome if we consider the fact that, in the hospital under study, procedures recommended for decreasing TB transmission risk were not being followed at the time of the study.[22]

Our finding that primary resistance was 18.4% differs significantly from the rate reported (8.5%) in the most recent national survey carried out in primary care units.[7] Particularities in the population treated in hospitals may increase the incidence of resistant strains. Co-morbidities, including HIV co-infection, and diseases that are difficult to diagnose or treat may be examples of such factors.

The anti-TB drug resistance rate that commanded the most attention was that related to INH (13.3%). This is the drug most commonly employed in TB treatment and prophylaxis regimens. Resistance to the RIF+INH combination was 3.6% in our study, approximately three times higher than that found in the national survey and similar to that described in another general hospital in the city of Rio de Janeiro.[19] This type of resistance must be closely monitored because of the serious consequences for control of the disease.

The only variable that correlated significantly with acquired resistance was cavitation-free chest X-ray. It is important to highlight that, in the sample studied, the number of patients presenting secondary resistance was very low (only 3 patients). This finding differs greatly from that of other studies in the literature, in which the incidence of patients presenting with acquired resistance is usually much higher than that of those presenting primary resistance.[7] This is likely to be a sample bias, and the small number of cases affected the analysis of this subgroup.

In general, there was significant correlation between anti-TB drug resistance and being a health care professional. In the treatment naive population, this correlation was also found in the bivariate analysis, and appeared again in the multivariate analysis. This is highly relevant. Although the odds ratios were high and statistically significant, similar studies in other hospitals should be carried out. If these findings are confirmed, they will lead us to re-evaluate the well-known risks of infection that health care professionals have to face and to reconsider the findings on nosocomial transmission of resistant strains reported in the literature.[25-27] We can conclude that health professionals are more likely to be infected by Mtb than the population in general, and that there are more resistant strains circulating in hospitals such as that of the present study, where control measures are poor. Therefore, health care professionals are definitely exposed to significant risks, and specific guidelines for protecting these professionals must be established by those responsible for setting public health care policy.

In the bivariate analysis, we found a correlation between primary resistance and diarrhea, as well as between primary resistance and unemployment, but these correlations were not found in the multivariate analysis. These may be confounding variables. Therefore, these findings would be better characterized in studies with larger samples.

Another aspect that must be highlighted is that there was no significant correlation between resistance and HIV infection, although 28.85% of the patients with HIV/AIDS presented resistant strains. This finding corroborates that of a study performed in another Rio de Janeiro hospital with a profile similar to that of HUPE.[8-10] The authors of that study reported results that also deviated from the trend described in the international literature. Nevertheless, this may be due to the smaller number of patients presenting with HIV co-infection when compared to those who are not in follow-up treatment for multidrug-resistant TB in the state of Rio de Janeiro.[16] The possibility that this correlation exists merits further study since this was not investigated in the most recent national survey.[7] There are few data on TB/HIV

co-infection and susceptibility profile, as shown in a recent study on mortality caused by TB in hospitals in the state of Rio de Janeiro (very few mycobacteria cultures, susceptibility tests and anti-HIV tests had been requested for patients who subsequently died).[26]

Another aspect that deserves attention was highlighted in a study by Salles et al., who reported a high rate of noncompliance (26%) in patients treated in a general hospital that had no TB control program in place.[27] This finding provides evidence that patients with resistant strains are more likely to be found in such environments.

In a review of the literature, McGowan Jr [28] demonstrated that the attention given to nosocomial TB is a reaction to the increased number of cases in the community. Therefore, the problem with hospitals cannot be dissociated from the epidemiological reality of TB in the community. Assessing the impact of TB and implementing control measures in hospitals should be considered priorities, especially in areas where the total number of cases is increasing and there are high rates of noncompliance with treatment and high incidence of resistant strains. Moreover, we must bear in mind that this increase is clearly more pronounced within population subgroups of those who are more likely to be hospitalized, such as patients with AIDS or other debilitating diseases.[28]

The lack of appropriate biosafety measures to reduce the risk of TB infection in hospitals, as well as the presence of resistant strains, make hospitals an environment in which resistant strains are more likely to be identified and disseminated. Therefore, health care professionals and patients are exposed not only to Mtb but also to resistant strains of Mtb.

The recommendations for TB control in hospitals include: the establishment of a special committee responsible for control; an action plan that is periodically revised; identification, evaluation, and early treatment of patients diagnosed with active TB; environmental control; respiratory protection; continuing education; and integration with public health organizations.[22]

Blumberg et al. studied the effectiveness of introducing such measures in a hospital in Atlanta, Georgia (USA) and reported a decrease in the number of new cases among individuals exposed to the disease and in the number of positive PPD tests among health care professionals.[29] The authors also suggested that changes in administrative policies played the most important role in achieving success, indicating that these should be the first modifications implemented in such an attempt to improve control measures.

In 1996, Muzzy de Souza et al. reported that general hospitals were the most likely places for TB transmission to occur.[29] According to the authors, hospitals presenting the highest risk would be those which: treat more than 50 TB cases/year; are reference centers for the treatment of immunosuppressed patients (HIV-positive or not); have a high number of health care professionals younger than 29; are also university hospitals (with undergraduate and graduate students); make use of certain diagnostic and therapeutic procedures (such as bronchoscopy, orotracheal intubation and sputum induction); have adopted no TB control programs or biosafety measures.

In conclusion, we must take into consideration the limitations of studies such as the present one. Our study was restricted to a single health care entity, having its own particularities, some of them transitive. However, our results highlight a potentially serious situation that should also be investigated in other hospitals with similar profiles. In addition, the distribution of cases in hospitals located in large urban centers with profiles similar to that of Rio de Janeiro should be evaluated through surveys in order to determine the incidence and prevalence of anti-TB drug resistance.

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