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Delayed culture conversion due to cigarette smoking in active pulmonary tuberculosis patients

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SUMMARY

Although many studies have assessed factors affecting culture conversion during tuberculosis treatment, few have looked into the effect of tobacco smoking. This study included 89 active pulmonary tuberculosis patients with positive sputum culture upon presentation and collected information regarding smoking history and culture conversion after 60 days of therapy. Current smokers had a higher risk (OR 5.6; 95%CI 1.7–18.7) of non-conversion after two months of therapy when compared to never and ex-smokers. Cavities on chest X-ray and alcohol abuse were shown to confound this association. After adjustment for cavities on the chest X-ray and alcohol abuse current smoking compared to current non-smoking remained significantly associated with culture non-conversion at 60 days of treatment (adjusted OR 6.9; 95%CI 1.8–26.7, $p = 0.002$) with a significant ($p = 0.004$) trend in adjusted OR with the number of cigarettes smoked daily to 11.6 (1.8–73.4) among those smoking more than 20 cigarettes per day. In conclusion tobacco smoking was found to delay culture conversion during treatment for pulmonary tuberculosis in a dose-dependent manner. More research is needed to elucidate the effects of smoking on tuberculosis treatment response, and of smoking cessation during tuberculosis treatment.

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1. Introduction

Tuberculosis (TB) is one of the world's leading infectious diseases. In 2010 there was an estimated 8.7 million incident cases and 1.4 million deaths from TB [1]. Tobacco use is a major public health problem and an important preventable risk for premature deaths. Extensive research has shown associations between tobacco smoking and TB [2–5], and identified an increased risk of mortality among smokers due to TB [6]. Smoking causes numerous pathophysiological changes within the respiratory system, including immunological effects, decreased clearance and altered adherence of inhaled pathogens [7]. Tobacco smoking also impedes the pulmonary expression of anti-TB T-helper type 1 (Th-1) immunity via inhibiting innate immune activation and lung T-cell recruitment [8].

Adequate treatment of TB is essential to reduce morbidity and mortality, and to prevent the spread of the disease [9,10]. Smoking has been suggested to affect treatment outcome expressed as mortality or as sputum smear conversion during treatment [11,12]. Few studies have assessed the effect of smoking on culture conversion during treatment, and those that did yielded discordant results [13–18]. An effect of smoking on the time to culture conversion would be important since a delay in conversion may translate into prolonged infectiousness and increased risk of transmission to others. Furthermore persistent non-conversion after 2 months of treatment can predict relapse after successful treatment [19].

We therefore studied the effects of tobacco smoking on culture conversion in a prospective cohort of patients on first-line treatment for pulmonary tuberculosis.

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2. Methods

This study was part of a larger cohort study of TB treatment. Eligible for enrollment were all patients consecutively diagnosed with smear- and/or culture-positive pulmonary tuberculosis at two specialized hospitals in Brazil (Santa Maria Hospital and the State Institute of Chest Diseases Ary Parreiras) during the period March 2007 to September 2009. Included for the current analyses were all patients who provided informed consent and for whom sputum culture results were available before starting treatment and after 60 days of standardized first-line TB treatment consisting of isoniazid, rifampicin, pyrazinamide and ethambutol. Patients for whom the pretreatment isolate showed resistance to isoniazid and rifampicin (i.e. multidrug resistance) were excluded as these were likely to be non-responsive to first-line treatment. All were treated as in-patients until they were no longer infectious.

Clinical and socio-demographic data were collected before treatment and sputum samples were assessed at day 0 and after 60 days of TB treatment. Sputum samples were submitted to microscopic examination of Ziehl-Neelsen stained smears. Samples were then processed using the Kubica method and inoculated onto Löwenstein-Jensen medium. Smears were graded in accordance to the WHO guideline as 1+, 2+, 3+, scanty and negative [20]. Patients were classified as previously treated (i.e. with a history of use of anti-tuberculosis drugs for more than one month) or new (i.e. otherwise).

History of tobacco smoking was ascertained at entry by standardized, staff administered questionnaire as current smoking and smoking in the past. Patients were grouped in two ways: as current smokers versus current non-smokers (to reflect effects of smoking during the months preceding the TB treatment on culture conversion), and as ever smokers, i.e. current smokers or ex-smokers, versus never smokers (to reflect cumulative effects of tobacco smoke exposure on culture conversion). In addition, possible dose–response effects were examined based on the number of cigarettes currently smoked per day and the number of pack-years smoked cumulatively.

Since patients with substance abuse may be less compliant to therapy, drug and alcohol abuse were identified as potential confounders of the association between smoking and culture conversion. For the classification of alcoholism the CAGE criteria were used [21]. Other potential confounders considered in the analysis were HIV infection, sex, ethnicity, malnutrition, illiteracy, the number of pulmonary cavities on chest X-ray, and pretreatment smear microscopy results. Malnutrition was defined as a body mass index (BMI) score below 18.5 kg/m^2 [22]. Because there were only two patients with diabetes mellitus, this potential confounder was not included in the analysis.

Data were stored electronically and analyzed using Statistical Package for Social Science 13.0 (IBM Corp, Armonk NY, USA). Odds ratios (ORs) with their 95% confidence interval (95%CI) were calculated for the association with culture conversion, and *p*-values were obtained using the two-sided Fisher's exact test. We checked all covariates for potential confounding of the association between smoking history and culture conversion by bivariate logistic regression. Included in the final multivariable logistic regression model were those covariates that changed the OR for this association (i.e. displayed confounding) by more than 10%. All tests were done at the 5% significance level.

3. Results

The study enrolled 164 patients, of whom 104 (63.4%) had non-MDR TB and follow-up data at day 60 available. Pretreatment culture results were missing for another 12 (11.5%) patients, and day-60 culture results were missing for 1 (0.9%) patient. In addition, 2 (1.9%) patients were excluded because of missing smoking information (Figure 1).

The remaining 89 patients were included in the analysis (Table 1). Of these 76 (85.4%) were males; 23 (25.8%) were never-smokers, 43 (48.3%) current smokers and 23 (25.8%) ex-smokers. All current and ex-smokers smoked cigarettes.

At 60 days of treatment, 19 patients (21.3%) remained culture positive and 70 (78.7%) had culture conversion.

The odds for culture non-conversion at 60 days of treatment were significantly increased for current smokers compared to current non-smokers (odds ratio (OR) 5.63; 95% confidence interval (95%CI) 1.69–18.72): 15 of 43 (34.9%) current smokers had no culture conversion versus 4 of 46 (8.7%) current non-smokers ($p = 0.004$). Similarly, the odds for culture non-conversion at 60 days of treatment were significantly increased for current smokers compared to ex-smokers (OR 11.79, 95%CI 1.44–96.23, $p = 0.002$, Figure 1), but not for ever-smokers compared to never-smokers (OR 2.13, 95%CI 0.56–8.13, $p = 0.378$). There was a significant trend in probability of culture non-conversion with the number of cigarettes smoked daily among current smokers from 27.3% for 1–19 cigarettes (less than one package) and 35.0% for 20 cigarettes (one package) to 41.7% for >20 cigarettes (more than one package; $p = 0.003$). No clear trend was observed for the number of pack-years smoked (Figure 2).

The only other significant predictor of culture non-conversion at 60 days of treatment was the smear result at baseline (Supplement). In addition to smear test result, the number of cavities, alcohol abuse, malnutrition, and illicit drug use confounded the association between smoking and culture conversion in the bivariate analyses (Supplement). In the multivariable model, only the number of cavities and alcohol abuse remained as confounders. After adjustment for alcohol abuse and number of cavities, current smoking compared to current non-smoking remained significantly associated with culture non-conversion at 60 days of treatment (adjusted OR 6.85; 95%CI 1.76–26.70, $p = 0.002$). Compared to current non-smokers, the adjusted OR for non-conversion increased significantly with the number of cigarettes smoked daily from 4.2 for 0–19 cigarettes to 7.9 for 20 cigarettes and 11.6 for >20 cigarettes ($p = 0.015$; trend across categories $p = 0.004$; Table 2). There were no significant interactions. Adding the number of pack years (>10 years versus ≤10 years) to this model did not result in significantly improved prediction of culture conversion (adjusted OR 0.76, $p = 0.743$).

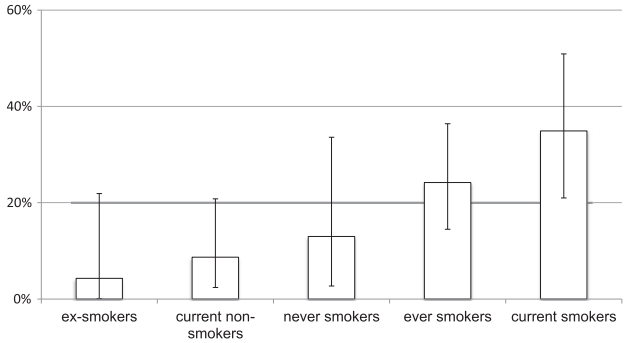

Figure 1. Proportion of patients with positive culture (non-conversion) after 2 months of treatment, by smoking status. Vertical lines denote 95% confidence intervals. Unadjusted odds ratios (95% confidence intervals): ever smokers vs. never smokers 2.13 (0.56–8.13), $p = 0.378$; current smokers vs. current non-smokers 5.63 (1.69–18.72), $p = 0.004$; current smokers vs. ex-smokers 11.79 (1.44–96.23), $p = 0.002$.

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