

# Adjunctive corticosteroid therapy in patients with pulmonary tuberculosis

Carolina Xavier Lemos<sup>1</sup> , Camila Anton<sup>1</sup> , Felipe Dominguez Machado<sup>1</sup> ,  
Rafaela Manzoni Bernardi<sup>1</sup> , Alana Ambos Freitas<sup>2</sup> , Denise Rossato Silva<sup>1,2,3\*</sup> 

## SUMMARY

**OBJECTIVES:** In tuberculosis treatment, corticosteroids are used as adjuvants, especially in meningeal/pericardial tuberculosis. In other forms of the disease, especially in severe tuberculosis requiring mechanical ventilation, its use is controversial. The aim of the present study is to assess whether the use of corticosteroids in the treatment of pulmonary tuberculosis patients in mechanical ventilation is associated with in-hospital mortality.

**METHODS:** This is a retrospective cohort study. Tuberculosis patients >18 years requiring mechanical ventilation, admitted to the emergency department or intensive care unit, were included. Data on corticosteroid use and mortality were collected.

**RESULTS:** In total, 467 patients were included in the analysis; 399 used corticosteroids and 68 were noncorticosteroid users. The mortality rate was higher among corticosteroid users (59.9%) than in noncorticosteroid users (41.2%) ( $p=0.010$ ). The total dose of corticosteroid in prednisone equivalents was not different between survivors and nonsurvivors (median [interquartile range]: 80 mg [5–56.6 mg] vs. 80 mg [50–135 mg];  $p=0.881$ ).

**CONCLUSIONS:** Tuberculosis patients in mechanical ventilation who used corticosteroids had a higher mortality rate than those who did not use corticosteroids. The role of corticosteroids in pulmonary tuberculosis, especially in critically ill patients, remains unclear and needs further evaluation in prospective studies.

**KEYWORDS:** Tuberculosis. Respiration, artificial. Respiratory insufficiency. Glucocorticoid. Critical care.

## INTRODUCTION

A significant portion of tuberculosis (TB) patients, especially severe cases, are still being hospitalized, with estimates ranging from 2 to 12%. In addition, patients required mechanical ventilation (MV) in many cases<sup>1,2</sup>. In a study conducted in Brazil, ICU admission was necessary in 8.5% of cases<sup>3</sup>. In another study at a university hospital, 16.7% of the 311 cases of TB were admitted to the ICU and 15.4% required MV<sup>4</sup>. Besides, in-hospital mortality of patients with TB remains high, particularly among patients requiring MV. TB associated with acute respiratory failure has been associated with mortality rates of up to 81.0%<sup>5-9</sup>.

Several factors have been identified as predictive of mortality among TB patients, such as delay in diagnosis, irregular treatment, human immunodeficiency virus infection, malnutrition, and multidrug-resistant TB<sup>4,10-13</sup>. In a study<sup>10</sup> that evaluated 311 patients with TB, MV and negative sputum

smear were predictors of in-hospital death in multivariate analysis. In another retrospective cohort study<sup>4</sup> with 67 patients requiring intensive care, ventilator-associated pneumonia and early intensive care unit admission were risk factors for in-hospital mortality. In addition, serum levels of albumin, reflecting the nutritional status, were associated with higher mortality in ICU patients with TB and respiratory failure<sup>14,15</sup>.

In the treatment of TB, corticosteroids are used as adjuvants, especially in meningeal and pericardial TB. Corticosteroids can allow anti-TB drugs to penetrate granulomas, undoing their formation. Moreover, they inhibit the release of cytokines and lymphokines<sup>16,17</sup>. In other forms of the disease, especially in severe TB, its use is controversial<sup>16,18-22</sup>. Therefore, the aim of the present study is to assess whether the use of corticosteroids in the treatment of pulmonary TB patients in MV is associated with in-hospital mortality.

<sup>1</sup>Universidade Federal do Rio Grande do Sul, Graduate Program in Pulmonology Sciences – Porto Alegre (RS), Brazil.

<sup>2</sup>Universidade Federal do Rio Grande do Sul, School of Medicine – Porto Alegre (RS), Brazil.

<sup>3</sup>Hospital de Clínicas de Porto Alegre, Department of Pulmonology – Porto Alegre (RS), Brazil.

\*Corresponding author: [denise.rossato@terra.com.br](mailto:denise.rossato@terra.com.br)

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## METHODS

### Study design and location

The study was conducted at the Hospital de Clínicas de Porto Alegre (HCPA). This was a retrospective cohort study, with data collection from January 2010 to December 2019. The study was approved by the HCPA's Ethics Committee (2013-0024), and all research was performed in accordance with relevant guidelines/regulations. Informed consent has been waived by the Ethics Committee of HCPA, but patient confidentiality has been maintained.

### Patients and data collection

Tuberculosis (TB) patients >18 years, requiring MV, admitted to the intensive care unit, were included in the study. The TB diagnosis was based on consensus criteria<sup>23</sup>. There is no protocol to guide the administration of corticosteroids in our hospital; it is at the discretion of the attending physician. The following information was collected: demographic data, alcoholism, smoking status, prior anti-TB therapy, comorbidities, Acute Physiologic and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment scores, vasopressor use, and hospitalization outcome (death or discharge).

### Statistical analysis

Data analysis was performed using IBM SPSS 22.0 (Statistical Package for the Social Sciences, Armonk, NY). Chi-square test using Yates's correction if indicated or Fisher's exact test was

used for categorical comparisons. The t-test or Wilcoxon test was used to compare continuous variables. A multivariate logistic regression analysis was performed to evaluate if the use of corticosteroids is independently associated with mortality. The Hosmer-Lemeshow test was used to assess the goodness of fit of the multiple logistic regression models. Odds ratios (ORs) and nominal 95% confidence intervals (CIs) were presented, and a p-value <0.05 was considered significant<sup>24</sup>.

A previous study<sup>18</sup> was used for the calculation of the sample size, in which the percentage of use of corticosteroids in the nonsurviving group was 37.8% and in the surviving group, it was 61.9%. Thus, it would be necessary to include at least 128 patients (at least 64 per group), with an alpha error of 0.05 and a beta error of 0.20.

## RESULTS

In total, 467 patients were included in the analysis; 399 used corticosteroids and 68 were noncorticosteroid users (Table 1). Patients using corticosteroids were younger ( $46.5 \pm 14.9$  years) than those not using corticosteroids ( $51.3 \pm 16.4$  years) ( $p=0.017$ ). HIV infection was more frequent in corticosteroid users (53.6%) compared to noncorticosteroid users (36.8%) ( $p=0.010$ ). Vasopressor use was also more common among corticosteroid users. On the other hand, diabetes was more frequent in noncorticosteroid users (25.0%) as compared to corticosteroid users (14.5%) ( $p=0.030$ ). There were no drug-resistant TB cases included in the study.

**Table 1.** Characteristics of patients according to the use of corticosteroids.

Characteristic	Corticosteroid users (n=399)	Noncorticosteroid users (n=68)	p-value
Age	46.5±14.9	51.3±16.4	0.017
Male sex	252 (63.2)	46 (67.6)	0.476
BMI	22.3±4.8	21.1±4.4	0.073
Smoking	186 (46.6)	37 (54.4)	0.234
Alcohol abuse	111 (27.8)	23 (33.8)	0.312
HIV	214 (53.6)	25 (36.8)	0.010
Diabetes	58 (14.5)	17 (25.0)	0.030
Neoplasia	29 (7.3)	3 (4.4)	0.547
Liver failure	113 (28.3)	13 (19.1)	0.114
Smear-positive TB	114 (28.6)	19 (27.9)	0.915
Prior anti-TB therapy	123 (30.8)	23 (33.8)	0.622
Vasopressor use	318 (79.7)	44 (64.7)	0.006
APACHE II score	22.3±8.1	22.1±8.2	0.864
SOFA score	6.8±3.6	6.3±3.5	0.270
Death	231 (57.9)	28 (41.2)	0.010

Data are presented as mean ±SD, or n/N (%): number of cases with characteristic/total number of cases (percentage).

The mortality was higher among corticosteroid users (59.9%) than in noncorticosteroid users (41.2%) ( $p=0.010$ ). In a multivariate analysis, the best model included the variables: age, diabetes, HIV, vasopressor use, and death. Only death was independently associated with corticosteroid use (Table 2). The total dose of corticosteroid in prednisone equivalents was not different between survivors and nonsurvivors (median [interquartile range]: 80 mg [56.6–146.7 mg] vs. 80 mg [50–135 mg];  $p=0.881$ ). In addition, the total time of corticosteroid use was shorter in nonsurvivors than that in survivors (median [interquartile range]: 12 days [5–25 days] vs. 21 days [8.8–36.2 days];  $p<0.0001$ ), but the length of hospital stay was also shorter in nonsurvivors as compared to that in survivors (median [interquartile range]: 23 days [11–43 days] vs. 42 days [28–58 days];  $p<0.0001$ ).

## DISCUSSION

In this retrospective study, we demonstrated, in TB patients in MV, higher mortality rate among corticosteroid users (59.9%) as compared to noncorticosteroid users (41.2%). In addition, the total dose of corticosteroids in prednisone equivalents was not different between survivors and nonsurvivors.

The use of corticosteroids is recommended in the meningeal TB treatment with a moderate degree of evidence and is considered in the treatment of pericardial TB, with a low degree of evidence<sup>25</sup>. In pleural TB, the use of corticosteroids would be associated with a faster recovery of symptoms, although it has no impact on the outcome<sup>26</sup>. However, the role of corticosteroids in the pulmonary TB treatment is still uncertain and, although it has been evaluated in several studies, some of them were conducted more than 20 years ago, before the introduction of therapies with rifampicin and combinations of drugs.

One of the first studies<sup>16</sup> that described the adjunctive use of corticosteroids in pulmonary TB, 12 cases were reported in which 20–60 mg of prednisone was used daily, for an average of  $20.1\pm 9$  days. During this period, the patients' appetites, weight, and serum albumin were increased, and no deaths were reported. Kim et al.<sup>18</sup> demonstrated that among TB pneumonia

patients, the use of corticosteroids was associated with a lower mean mortality rate, but in the miliary TB group, those receiving corticosteroids did not have a better survival rate. In both studies<sup>16,18</sup> the mean daily dosage of prednisone equivalents was lower than that used in our study, which may explain some of the different results.

Several studies have shown no benefit in reducing mortality with the use of corticosteroids in pulmonary TB patients. A meta-analysis<sup>20</sup> that evaluated the use of corticosteroids in patients with pulmonary TB showed that after excluding studies with a high risk of bias, there was no difference in mortality between the groups that used and that did not use corticosteroids. Another meta-analysis<sup>21</sup>, which included 18 studies, also demonstrated that the use of corticosteroids did not show a reduction in all-cause mortality when compared to placebo or no steroid. Also, Yang et al.<sup>22</sup> investigated the 90-day mortality rate in patients with pulmonary TB requiring intensive care and using corticosteroids. They studied retrospectively 124 patients and found that the corticosteroid used had no effect on the 90-day mortality rate. In addition, in a more recent meta-analysis<sup>19</sup>, from 2018, 35 studies were included to assess the outcomes of patients with TB who required ICU admission. The most common indications for the use of corticosteroids were miliary TB, respiratory failure, acute respiratory discomfort syndrome, and shock. The use of corticosteroids in this group of patients did not demonstrate a reduction in mortality.

This study has some methodological limitations. First, we recruited patients from a single tertiary care hospital. However, we believe the results may apply to other settings. Second, retrospective analysis is also a limitation, since the data collected are dependent on medical records, often incomplete or insufficient, and some information is not widely accessible, such as adherence to TB and HIV treatment or duration of illness (HIV). Third, we cannot exclude a selection bias once that is quite probably that the most severe cases (of lung involvement) were candidates who receive the corticosteroids; nevertheless, we performed a multivariate analysis to evaluate if the use of corticosteroids was independently associated with mortality, minimizing the possible selection bias. Despite these concerns,

**Table 2.** Multivariate analysis of factors associated with corticosteroid use.

Characteristic	$\beta$	SE	Wald	OR (95%CI)	p-value
Age	-0.016	0.010	2.532	0.984 (0.965–1.004)	0.112
Diabetes	-0.271	0.352	0.591	0.763 (0.382–1.522)	0.442
HIV infection	0.370	0.314	1.389	1.448 (0.782–2.680)	0.238
Vasopressor use	0.553	0.308	3.221	1.738 (0.950–3.179)	0.073
Death	0.589	0.291	4.104	1.803 (1.019–3.188)	0.043

we showed that the use of corticosteroids in patients with pulmonary TB is associated with higher mortality.

## CONCLUSIONS

In this study, we identified that TB patients in MV who used corticosteroids had a higher mortality rate than those who did not use corticosteroids. The role of corticosteroids in pulmonary TB, especially in critically ill patients, remains unclear and needs further evaluation in prospective studies.

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## AUTHORS' CONTRIBUTIONS

**CXL:** Conceptualization, Methodology, Investigation, Data curation, Project administration, Writing – original draft. **CA:** Conceptualization, Methodology, Investigation, Writing – review & editing. **FDM:** Conceptualization, Methodology, Investigation, Writing – review & editing. **RMB:** Conceptualization, Methodology, Investigation, Writing – review & editing. **AAF:** Conceptualization, Methodology, Investigation, Writing – review & editing. **DRS:** Conceptualization, Methodology, Investigation, Data curation, Project administration, Supervision, Writing – original draft.

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