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## Original article

# Tuberculin skin testing in inflammatory bowel disease patients from an endemic area of Brazil

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## ABSTRACT

**Objective:** Inflammatory bowel disease (IBD) is a chronic disorder involving the gastrointestinal tract. Immunosuppressive drugs are usually prescribed to treat IBD patients, and this treatment can lead to tuberculosis reactivation. This paper aimed to analyze tuberculin skin test (TST) results in IBD patients at a reference center in Brazil.

**Methods:** We evaluated TST results in IBD patients using a cross-sectional study. We also analyzed the medical records of patients treated at a reference IBD outpatient unit where TST is routinely performed.

**Results:** We reviewed 119 medical records of 57 (47.9%) Crohn's disease (CD), 57 (47.9%) ulcerative colitis (UC) and 5 (4.2%) indeterminate colitis (IC) patients. The mean (SD) age was 43.5 (13.7) years old. TST was positive in 24 (20.2%) of the patients. TST was positive in 16/57 (28.1%) UC and 6/57 (10.5%) CD patients (prevalence ratio [PR] 2.7). Forty-one patients (34.5%) were taking immunosuppressive drugs (azathioprine or prednisone) at the time of the TST, and six of these patients (14.6%) had positive test results. Two patients using infliximab had negative TST results. Thirty-five of the 41 patients (85.4%) on immunosuppressive treatment were anergic compared with 73.1% (57/78) of the untreated patients (PR 1.2).

**Conclusions:** Patients with IBD have TST results similar to the general Brazilian population. Within the IBD population, CD patients have a lower frequency of TST positivity than UC patients.

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## Introduction

Inflammatory bowel disease (IBD) is a chronic disorder with three subtypes, namely Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis (IC). All three diseases

occur throughout the world and represent a serious health problem. IBD patients have a compromised quality of life and may develop complications.<sup>1</sup> To control IBD, medicines such as aminosalicylates, corticosteroids, immunosuppressive agents and biological therapies are prescribed during

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treatment. These drugs are provided free-of-charge by the Brazilian Health Department.<sup>2</sup> In Brazil, the Ministry of Health did not routinely release anti-tumor necrosis factor (anti-TNF) for treating patients with UC at the time of this study.

There are nearly 70,000 new cases of tuberculosis (TB) in Brazil per year. In the state of Bahia more than 4000 annual cases of the disease have been reported. Despite the slow and constant decline in the incidence of TB in recent years, there have been approximately 4600 deaths in the state of Bahia, which is a very high number, considering that TB is relatively simple to diagnose, is curable, and the treatment is provided for free by the public health system.<sup>3</sup> Infected patients form granulomas that prevent the bacillus from multiplying and disseminating, leading to the development of latent tuberculosis (LTBI). The reactivation of LTBI may occur with the use of immunosuppressive therapy and presence of diseases that cause immune deficiencies.<sup>4,5</sup> The tuberculin skin test (TST) is widely used as a screening tool for LTBI. Treatment is recommended for LTBI in patients who have a TST result equal to or greater than 5 mm in addition to having a concurrent risk factor, such as HIV infection, immunosuppression, contact with pulmonary TB within the last two years by patients who had received the bacille Calmette-Guérin (BCG) vaccine more than two years previously, untreated TB with sequelae of lesions visible on a chest X-ray or organ transplantation. Treatment is also recommended for patients with a TST result equal to or greater than 10 mm with the following risk factors: contact with pulmonary TB within the last two years by patients who had received the BCG vaccine more than two years previously, intravenous drug use, immunocompromise, or having indigenous ancestry.<sup>6</sup>

Drugs such as corticosteroids, azathioprine and monoclonal anti-TNF can cause reactivation of LTBI.<sup>7,8</sup> The Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) reported that LTBI must tracked not only in patients taking anti-TNF- $\alpha$  but rather in all patients on immunosuppressive medication.<sup>9</sup> Prednisone reduces activation and proliferation of lymphocytes, inhibits the production of certain cytokines, such as IL-1, IL-2, IL-6, IL-11 and TNF  $\alpha$ , causes lymphopenia and monocytopenia, and inhibits the differentiation of monocytes into macrophages. Azathioprine can cause leukopenia, inhibit NK and CD8+ cytotoxic T cells and stimulate T cell apoptosis. Both drugs can cause anergy in patients and lead to false-negative TST.<sup>10</sup> A one-month steroid treatment at doses greater than 15 mg/day may lead to anergic states and false-negative TST results. Similar results have been observed with an azathioprine dosage greater than 2 mg/kg/day.<sup>10</sup>

This study aimed to analyze TST results in IBD patients at a reference center in Brazil.

## Methods

### Study design

This study was conducted in the Inflammatory Bowel Disease Unit of Roberto Santos General Hospital in Salvador city. This clinic is a reference center in the state of Bahia for IBD diagnosis and treatment. The study was approved by the Ethics

Committee of Bahia School of Medicine and Public Health, protocol number 139/2008. This was a cross-sectional study carried on by analyzing patient records under regular follow-up care. A total of 119 patients from January to March of 2009 were analyzed. We evaluated the following variables: age, gender, length of time experiencing symptoms, and length of time of IBD diagnosis when the TST was performed, IBD Montreal classification, IBD treatment and TST and chest X-ray results.

### Patients

Patients with a clinical, radiological, endoscopic and histological diagnosis of IBD on regular follow-up (last visit within the last six months) were included in this study. We see approximately 30 patients per week in this outpatient clinic. Patients were excluded from the study if they had cancer, HIV infection, or other clinical conditions that could alter the TST results. All of the TST values were analyzed and classified as follows: negative (TST less than 5 mm), weakly positive (TST equal to or greater than 5 mm but less than 10 mm), or strongly reactive (TST equal to or greater than 10 mm). Patients were classified as positive or negative after reviewing their TST scores and considering the following risk factors: use of immunosuppressive drugs, use of prednisone greater than 15 mg/day for at least one month, use of azathioprine greater than 2 mg/kg/day, use of anti-TNF- $\alpha$ , chest X-ray consistent with past TB, and diabetes mellitus. Patients had a positive TST if the TST result was  $\geq 10$  mm alone or  $\geq 5$  mm with at least one of the risk factors listed above.<sup>11</sup> The CD and UC patients were classified according to the Montreal classification.<sup>12</sup>

### Statistical analysis

Data collected were entered into a database in SPSS version 16.0. Initially, a descriptive analysis was performed on the sample. Given the characteristics of the study design, it was not possible to estimate the appropriate standard error, therefore, no inferential statistics were calculated (*p*-values and confidence intervals).<sup>13</sup> Proportions were used for categorical variables, and means with their standard deviations were used for continuous variables. A comparison between the proportions was performed using the prevalence ratio (PR).

## Results

Demographic and clinical characteristics are summarized in [Table 1](#). The characterization of the TST according to CD and UC diagnosis is shown in [Table 2](#). Three patients with penetrating disease (50%), two patients with stricturing disease (33.3%) and one patient with non-stricturing and non-penetrating disease (16.7%) were TST positive.

Overall, 24 patients (20.2%) were TST positive. The TST induration was less than 5 mm in 92 patients (77.3%), equal to or more than 5 mm but less than 10 mm in six patients (5%) and equal to or greater than 10 mm in 21 patients (17.6%). Of the 119 patients, 41 (34.5%) were taking immunosuppressive drugs (azathioprine or prednisone) at the time of the TST, and 14.6% (6/41) of these patients were TST positive. The two

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