Bacteriological analysis of induced sputum for the diagnosis of pulmonary tuberculosis in the clinical practice of a general tertiary hospital*, **

Análise bacteriológica do escarro induzido para o diagnóstico de tuberculose pulmonar na prática clínica de um hospital geral terciário

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Abstract

Objective: To determine the diagnostic sensitivity of bacteriological analyses in induced sputum (IS) for the diagnosis of pulmonary tuberculosis (TB) and to identify the clinical characteristics associated with the confirmed diagnosis, as well as to determine the diagnostic yield of bronchoscopy carried out when IS tests negative for AFB in smear microscopy. **Methods:** A retrospective, cross-sectional study of patients suspected of having active pulmonary TB and referred to our clinic for sputum induction. We consecutively reviewed the laboratory data of all patients submitted to sputum induction between June of 2003 and January of 2006, as well as their electronic medical records. In addition, the results of the bacteriological analysis of bronchoscopic specimens collected from the patients whose AFB tests were negative in IS were reviewed. **Results:** Of the 417 patients included in the study, 83 (19.9%) presented IS samples that tested positive for TB (smear microscopy or culture). In the logistic regression analysis, radiological findings of cavitation (OR = 3.8; 95% CI: 1.9-7.6) and of miliary infiltrate (OR = 3.7; 95% CI: 1.6-8.6) showed the strongest association with the diagnosis of pulmonary TB. In 134 patients, bronchoscopy was carried out after negative AFB results in IS and added 25 (64.1%) confirmed diagnoses of pulmonary TB. **Conclusions:** In our clinical practice, the frequency of confirmed diagnosis of pulmonary TB using IS (19.9%) was lower than that previously reported in controlled trials. Cavitation and miliary infiltrate increase the diagnostic probability of pulmonary TB using IS. The use of bronchoscopy when IS tests negative for AFB significantly increases sensitivity in the diagnosis of pulmonary TB.

Keywords: Tuberculosis, pulmonary; Diagnosis; Sputum.

Resumo

Objetivo: Verificar a sensibilidade diagnóstica da análise bacteriológica do escarro induzido (EI) para o diagnóstico de tuberculose (TB) pulmonar e identificar as variáveis clínicas associadas com o diagnóstico confirmado. Além disso, avaliar o rendimento diagnóstico da broncoscopia realizada se a pesquisa de BAAR for negativa no EI. **Métodos:** Estudo transversal e retrospectivo de pacientes com suspeita de TB pulmonar ativa, encaminhados ao serviço para a indução de escarro. Foram revisados consecutivamente os registros laboratoriais de todos os pacientes submetidos à indução de escarro entre junho de 2003 e janeiro de 2006, assim como o prontuário eletrônico de cada caso. Também foram revisados os resultados bacteriológicos das amostras broncoscópicas coletadas dos pacientes cujos resultados de BAAR em EI foram negativos. **Resultados:** Dos 417 pacientes estudados, 83 (19,9%) tiveram resultados positivos (BAAR e/ou cultura) no EI. Na análise de regressão logística, os achados radiológicos de cavitação pulmonar (OR = 3,8; IC95%: 1,9-7,6) e de infiltrado de padrão miliar (OR = 3,7; IC95%: 1,6-8,6) associaram-se mais significativamente com o diagnóstico de TB pulmonar. A broncoscopia foi realizada, após resultado de BAAR negativo no EI, em 134 pacientes e acrescentou 25 (64,1%) diagnósticos confirmados de TB pulmonar. **Conclusões:** Na prática clínica, a frequência de diagnósticos confirmados de TB pulmonar por EI (19,9%) foi menor do que aquela previamente relatada em ensaios controlados. Cavitação e infiltrado miliar aumentam a probabilidade diagnóstica de TB pulmonar no EI. O uso de broncoscopia quando EI é negativo para BAAR melhora significativamente a sensibilidade para o diagnóstico de TB.

Descritores: Tuberculose pulmonar; Diagnóstico; Escarro.

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Introduction

Tuberculosis (TB) is a leading health problem worldwide, with an estimated eight million new cases and almost two million deaths occurring every year.[1] Although the control of TB has improved dramatically in most industrialized countries during the last century, the disease continues to be a major cause of morbidity and mortality in developing countries.[2] The World Health Organization (WHO) estimates that 22 countries account for 80% of all new cases and 98% of all deaths from TB, a situation that is exacerbated in countries with high rates of HIV infection.[3]

The investigation of pulmonary TB differs among countries, depending on the prevalence of the disease and on economic status. The WHO recommends the examination of respiratory specimens for the detection of AFB as the initial approach to the diagnosis of pulmonary TB.[4] However, this method has low sensitivity and is of little value in patients who cannot produce sputum spontaneously.[5]

Sputum induction was first reported in the 1960s,[6] and virtually no reports of its use were published during the 1980s, when bronchoscopy became widely available. However, the invasive nature of bronchoscopy, together with its higher cost, has motivated researchers to assess its yield in the diagnosis of pulmonary TB.[7-14]

The objective of our study was to assess the diagnostic sensitivity of the bacteriologic analysis of induced sputum (IS) for the diagnosis of pulmonary TB in a tertiary referral hospital in a region with a high prevalence of TB, as well as to identify the clinical characteristics associated with the confirmed diagnosis. In addition, we evaluated the diagnostic yield of bronchoscopy performed after IS samples have tested negative for AFB.

Methods

This cross-sectional study was conducted at the *Hospital de Clínicas de Porto Alegre* (HCPA), a general, tertiary care, university-affiliated hospital with 750 beds, in southern Brazil. We retrospectively included all inpatients and outpatients submitted to sputum induction at the Pulmonology Clinic of the HCPA between June 3, 2003 and January 13, 2006. There were no exclusion criteria.

The protocol was approved by the Research Ethics Committee of the HCPA, and the investigators signed a confidentiality agreement.

The technique of collecting IS has been standardized at the HCPA since 1999. The patients were placed into a negative-pressure isolation chamber, and sputum was induced through delivery of 5% hypertonic saline solution by an ultrasonic nebulizer (RespiraMax®; NS, São Paulo, Brazil). Inhalation was continued until the subject had produced an adequate sample of sputum or 30 min had elapsed. Three samples were obtained and then processed within 1 h using a standardized technique (Ziehl-Neelsen staining for AFB in smears and *Mycobacterium tuberculosis* culture on Löwenstein-Jensen medium).[15,16] Staff TB protection measures included wearing a respiratory protection mask and following standard hospital procedures.[17,18]

If the sputum smear microscopy was negative or the specimen was deemed unacceptable, the need for fiberoptic bronchoscopy with BAL and transbronchial biopsy was determined by the attending physician in each case. The fiberoptic bronchoscopy was performed by a pulmonologist at the HCPA. The local anesthetic agent employed was lignocaine. Bronchial segments thought to be sites of active TB, based on chest X-ray findings, were washed with saline solution. The fluid was collected and processed using standardized methodology.[19] Smear positivity was confirmed by Ziehl-Neelsen staining. Specimens were cultured on Löwenstein-Jensen medium. For the transbronchial biopsy, the bronchoscope was introduced into the desired segment, and a biopsy forceps was extended to the lung periphery; as the patient exhaled, the forceps was advanced 1-2 cm in the open position, closed, and then retracted in order to obtain the specimen. This procedure was repeated 3-5 times to obtain an adequate number of samples, which were then sent to a pathologist for interpretation.

To select the patient sample, we reviewed all laboratory data and electronic medical records from the study period. We compiled the data related to following variables: age; gender; race; respiratory symptoms; presence of spontaneous sputum; tuberculin skin test (TST); HIV testing (ELISA); radiological findings; history of TB; and treatment. In addition, we reviewed the results of tests performed on IS samples (AFB staining

and *M. tuberculosis* culture), BAL samples (AFB staining and *M. tuberculosis* culture) and transbronchial biopsy samples.

All of the patients were submitted to chest X-rays, and a board-certified radiologist interpreted the images in the clinical routine of the HCPA. These results were categorized as follows: normal; cavitary disease; pattern of infiltration; consolidation; fibrosis/atelectasis pattern; non-calcified opacities; mediastinal lymphadenopathy; pleural effusion; or miliary pattern.

A confirmed diagnosis of pulmonary TB was defined as a positive culture for *M. tuberculosis* in IS, BAL or transbronchial biopsy; a probable diagnosis of pulmonary TB was defined as a positive AFB smear in IS, BAL or transbronchial biopsy without positive culture for *M. tuberculosis*. To assess the relationships between IS and the clinical variables, we defined IS positivity as positive AFB staining and positive *M. tuberculosis* culture, whereas we defined negativity as an AFB-negative smear or a negative *M. tuberculosis* culture. To compare the diagnostic yield of IS and bronchoscopy, cases of pulmonary TB were defined as those meeting the criteria for either a confirmed or a probable diagnosis.

The collected data were stored in a Microsoft Excel XP spreadsheet. Data were analyzed using the Statistical Package for the Social Sciences, version 14.0 (SPSS Inc., Chicago, IL, USA).

Data were expressed as number (percentage) or as mean ± standard deviation. Univariate analysis was used in order to compare the IS-positivity group and the IS-negativity group. Categorical comparisons were performed by chi-square test using Yates' correction or Fisher's exact test, if indicated. In addition, ORs and 95% CIs were calculated. Student's t-test was used in order to compare continuous variables between the two groups.

Statistical analysis

All statistical tests were two-tailed, and values of $p < 0.10$ were required for inclusion in the univariate analysis. All statistically significant variables were evaluated for inclusion in a binary logistic regression analysis. The dependent variable was the IS sample status (positive or negative). An adjusted OR and 95% CI, for each factor in the model, were calculated in this analysis. We ran univariate and logistic regression analyses by excluding the subjects whose selected variables were missing. The level of statistical significance was set at $p < 0.05$.

Results

During the period of the study, 417 patients were referred to the HCPA for the collection of IS and were included in the analysis. Of the 417 patients, 83 (19.9%) had positive results—positive AFB smear or positive culture for *M. tuberculosis.* The samples of 348 patients (83.5%) were considered adequate, with 82 (23.6%) confirmed diagnoses of pulmonary TB. Among the 69 samples considered inadequate, only 1 (1.4%) tested positive. None of the specimens testing positive through AFB staining or mycobacterial culture also tested positive for nontuberculous mycobacteria.

Table 1 - Clinical characteristics of the subjects.

Characteristic	Results (n = 417)
Age, years	49.9 ± 16.3
Gender	
Male	213 (51.1)
Female	204 (48.9)
Race	
White	315 (75.5)
Non-white	91 (21.8)
Unknown	11 (2.6)
Respiratory symptoms	
Yes	299 (71.7)
No	105 (25.2)
Unknown	13 (3.1)
Tuberculin skin test induration	
0-4 mm	143 (34.3)
5-9 mm	11 (2.6)
≥ 10 mm	86 (20.6)
Unknown	177 (42.2)
Spontaneous sputum production	
Yes	144 (34.5)
No	241 (57.8)
Unknown	32 (7.7)
HIV serology	
Positive	183 (43.9)
Negative	186 (44.6)
Unknown	47 (11.3)
History of tuberculosis	
Yes	68 (16.3)
No	310 (74.3)
Unknown	39 (9.4)

Data presented as mean ± SD or n (%).

Table 2 - Comparison between the groups with confirmed and unconfirmed diagnosis of pulmonary tuberculosis using the induced sputum method.

Variable	Confirmed	Unconfirmed	OR (95% CI)	p
Age, years[a]	39.8 ± 14.8	46.2 ± 16.9		0.002
Gender, n (%)				
Male	51 (23.9)	162 (76.1)	1.7 (1.0-2.8)	0.047
Female	32 (15.7)	172 (84.3)		
Respiratory symptoms, n (%)				
Yes	68 (22.7)	231 (77.3)	2.1 (1.1-4.0)	0.032
No	13 (12.4)	92 (87.6)		
History of tuberculosis, n (%)				
Yes	18 (26.5)	50 (73.5)	1.6 (0.9-2.9)	0.201
No	58 (18.7)	252 (81.3)		
Tuberculin skin test induration, n (%)				
≥ 10 mm	21 (24.4)	65 (75.6)	1.4 (0.8-2.5)	0.305
0-9 mm	62 (18.7)	269 (81.3)		
Spontaneous sputum, n (%)				
Yes	33 (22.9)	111 (77.1)	1.3 (0.8-2.2)	0.383
No	45 (18.7)	196 (81.3)		
HIV, n (%)				
Positive	47 (25.7)	136 (74.3)	1.7 (1.0-2.9)	0.046
Negative	31 (16.7)	155 (83.3)		
Radiological findings				
Cavitation, n (%)				
Yes	22 (36.7)	38 (63.3)	2.8 (1.6-5.1)	0.001
No	61 (17.1)	296 (82.9)		
Fibrosis/atelectasis, n (%)				
Yes	16 (15.7)	86 (84.3)	0.7 (0.4-1.3)	0.278
No	67 (21.3)	248 (78.7)		
Nodule, n (%)				
Yes	13 (16.9)	64 (83.1)	0.8 (0.4-1.5)	0.564
No	70 (20.6)	270 (79.4)		
Consolidation, n (%)				
Yes	29 (22.1)	102 (77.9)	1.2 (0.7-2.0)	0.522
No	54 (18.9)	232 (81.1)		
Miliary infiltrate, n (%)				
Yes	13 (43.3)	17 (56.7)	3.5 (1.6-7.5)	0.002
No	70 (18.1)	317 (81.9)	2.9 (1.3-6.8)	
Yes, without associated findings	10 (40.0)	15 (60.0)		0.017
Interstitial infiltrate, n (%)				
Yes	27 (22.9)	91 (77.1)	1.3 (0.8-2.2)	0.412
No	56 (18.7)	243 (81.3)		
Pleural effusion, n (%)				
Yes	23 (28.4)	58 (71.6)	1.8 (1.0-3.2)	0.048
No	60 (17.9)	276 (82.1)	2.0 (1.1-3.7)	
Yes, with associated findings	20 (30.8)	45 (69.2)	0.9 (0.3-2.7)	0.026
Yes, without associated findings	3 (18.8)	13 (81.3)		1.000
Mediastinal lymphadenopathy, n (%)				
Yes	15 (26.8)	41 (73.2)	1.6 (0.8-3.0)	0.228
No	68 (18.8)	293 (81.2)		
Normal, n (%)				
Yes	2 (4.8)	40 (95.2)	0.2 (0.1-0.8)	0.017
No	81 (21.6)	294 (78.4)		

Data were analyzed using the chi-square test. Yates' correction or Fisher's exact test was used if indicated. [a]Data presented as mean ± SD.

Table 3 - Binary logistic regression for the confirmed diagnosis of pulmonary tuberculosis using the sputum induction method.

Variable	b	Adjusted OR	95% CI for OR	p
Cavitation	1.3	3.8	1.9-7.6	< 0.001
Miliary infiltrate	1.3	3.7	1.6-8.6	0.002
Pleural effusion	0.6	1.8	0.9-3.3	0.086
Gender, male/female	0.5	1.6	0.9-2.9	0.087
HIV	0.39	1.5	0.8-2.7	0.207
Respiratory symptoms	0.34	1.4	0.7-2.8	0.345
Age	0.03	1.0	1.0-1.1	0.004
Normal chest X-ray	−1.5	0.2	0.1-1.0	0.051

The clinical characteristics of the patients are shown in Table 1. Of the 417 patients studied, 213 (51.1%) were male. The mean age was 49.9 ± 16.3 years. The majority of the patients were White (75.5%) and had respiratory symptoms (71.7%). On the TST, the induration was 0-4 mm in 143 patients (34.3%), 5-9 mm in 11 (2.6%) and ≥ 10 mm in 86 (20.6%). Spontaneous sputum samples were collected from 144 patients with previously negative AFB results (34.5%). In our sample, 183 patients (43.9%) were HIV-positive, and 68 (16.3%) had a history of TB.

The comparison between the two groups (confirmed and unconfirmed diagnosis of pulmonary TB through IS sample testing) is shown in Table 2. Patients in the confirmed group were significantly younger than were those in the unconfirmed group (p = 0.002). Males predominated significantly in the confirmed group (p = 0.047). Positive IS results were significantly associated with the presence of respiratory symptoms (p = 0.032) and HIV positivity (p = 0.046). In addition, the following radiological findings were significantly associated with the diagnosis of pulmonary TB: cavitation (p = 0.001); miliary infiltrate (p = 0.0002); and pleural effusion (p = 0.048). The rate of confirmed diagnosis of pulmonary TB was significantly higher among the patients with the miliary infiltrate pattern, with or without other radiological findings, than among those without (p = 0,017). However, among those with pleural effusion in isolation, no significant association was found (p = 1.000).

After sputum induction, 134 patients were submitted to bronchoscopy; 8 had positive results for AFB, 24 had positive cultures for *M. tuberculosis*, and 10 presented with granuloma in the transbronchial biopsy, resulting in a total of 34 confirmed diagnosis of pulmonary TB using this method.

Among the 39 patients diagnosed with pulmonary TB after undergoing sputum induction and bronchoscopy, the diagnosis was made based on IS findings in 14 (35.9%) and on bronchoscopy findings in 34 (87.2%; p < 0.001). In this specific population (bronchoscopy after IS with negative AFB results), bronchoscopy added 25 (64.1%) diagnoses of pulmonary TB, and IS added 5 (12.8%) diagnoses.

Table 3 displays the binary logistic regression for the confirmed diagnosis of pulmonary TB using IS. A diagnosis of pulmonary TB was significantly associated with the radiological findings of cavitation (OR = 3.8; 95% CI: 1.9-7.6) and miliary infiltrate (OR = 3.7; 95% CI: 1.6-8.6).

Discussion

This study demonstrated the yield of IS testing for the diagnosis of pulmonary TB in the clinical practice of a large tertiary hospital in a region with a high prevalence of TB. We demonstrated that 19.9% of all patients referred due to clinical suspicion of pulmonary TB tested positive in IS samples. The radiological findings of cavitation and miliary infiltrate were significantly associated with the diagnosis of pulmonary TB. In addition, we showed that performing bronchoscopy after sputum induction when AFB results are negative increased the diagnostic yield by 64.1%.

As previously demonstrated, sputum induction is a safe[9,20-22] and an effective method of obtaining specimens for AFB smear and culture in patients who cannot produce sputum spontaneously or who have presented negative AFI results.[7,8,10-12,14,23] In our study, nebulization

with 5% hypertonic saline solution induced the production of an adequate sample of sputum in 83.5% of patients, a rate lower than that demonstrated in another study,[7] in which an adequate sample was obtained in 99.8% of the 1,115 cases. The results of the present study underscore the importance of evaluating the adequacy of IS samples. The rate of positivity was higher in samples considered adequate than in those considered inadequate (23.6% *vs.* 1.4%).

The sensitivity of the AFB smear tests and cultures was much lower in our study than in the literature, for IS and bronchoscopy specimens.[7,8,10-14,23,24] Anderson et al.[8] compared a single IS sample with BAL specimens in HIV-negative patients and also reported low sensitivity for AFB smear testing using both techniques (19% and 12%, respectively), although the sensitivity of culture was 73% in IS and 87% in BAL fluid. Another group of authors[11] demonstrated higher sensitivity for AFB smear testing, comparing 3 IS samples with BAL specimens, and found no difference between HIV-negative and HIV-positive patients (34% and 36% for IS, and 38% and 40% for BAL fluid, respectively). The authors reported culture sensitivity similar to that demonstrated by Anderson et al.[8] for HIV-negative patients (67% for IS and 74.5% for BAL fluid); for HIV-positive patients, the sensitivity was slightly lower but not statistically different (60% for IS and BAL fluid). One explanation for the lower diagnostic sensitivity in the present study is the degree of clinical suspicion of pulmonary TB of patients who were excluded from the study. Our study took a sample of patients who were referred to the clinic by different physicians to perform sputum induction, and we did not check the clinical pretest probability. In other words, we did not know how many patients had a high clinical suspicion of pulmonary TB before the procedure, and many of these patients were probably referred to our clinic with a lower diagnostic probability in order to have the diagnosis of pulmonary TB ruled out.

In accordance with the findings of previous studies,[10,11] we demonstrated that the yield of the culture is almost twice as high as the yield of AFB smear testing and confirmed the importance of culture in the diagnosis of pulmonary TB.

To our knowledge, no previous study has demonstrated high rates of pulmonary TB diagnosis using IS in patients who present a miliary pattern on chest X-rays. A study carried out in India showed that 45% of HIV-positive patients with miliary TB had positive AFB smear sputum microscopy results and 61% had positive cultures; however, neither the number of samples, the type of sample (spontaneous or IS) nor the radiological findings were described.[25] This finding has a practical issue, if we consider these patients at a potential risk of transmitting the disease and therefore requiring isolation.

In our study, only 134 patients (32%) were submitted to bronchoscopy for the confirmation of the diagnosis. This might reflect the clinical characteristics of the patients and the judgment of the attending physicians, who decided to proceed with the investigation based on the clinical status of the patients prior to performing an invasive procedure. Therefore, in this specific population (bronchoscopy after IS with negative AFB smear results), we observed a low degree of concordance between the IS and BAL fluid findings for the diagnosis of pulmonary TB, which is in contrast with the findings of previous studies.[8,11,12] Bronchoscopy samples accounted for 25 (64.1%) of the 39 confirmed diagnoses of pulmonary TB.

Our study has several limitations. It was retrospective in nature, using data from available records, and the variables under study lacked uniformity. Therefore, the results are susceptible to biases related to missing data. In addition, we did not perform long-term follow-up of the patients in order to determine the definitive diagnosis of cases with negative IS results. Furthermore, we did not perform the sputum induction on consecutive days. One group of authors[12] demonstrated that, in subjects investigated for possible active or inactive TB who produced no sputum or had negative smear sputum results, the most cost-effective strategy is to perform three sputum induction sessions on consecutive days without bronchoscopy. Despite these limitations, we believe that the study provides relevant information on the yield of IS for clinical practice in the real world.

We conclude that sputum induction is an effective method for the initial approach to patients with suspected pulmonary TB who are not able to produce sputum or have tested

negative on a previous AFB smear test. However, we demonstrated that, in clinical practice, the frequency of positive TB results in IS (19.9%) is lower than that previously reported. The radiological findings of cavitation and miliary infiltrate increase the diagnostic probability of pulmonary TB in IS samples. The low sensitivity of AFB smear testing of IS samples and the need for a prompt diagnosis, if pulmonary TB is highly suspected, demand further investigation. Bronchoscopy samples, when IS samples are AFB-negative, significantly increase the yield in the diagnosis of pulmonary TB.

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