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Diagnostic yield of induced sputum and Bronchoalveolar lavage in suspected pulmonary tuberculosis

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Abstract

Aim of this study was to compare the diagnostic yield of induced sputum (IS) and bronchoalveolar lavage (BAL) in patients with suspected pulmonary tuberculosis (PTB) and negative sputum smears. We enrolled 215 patients who underwent both IS and BAL after two negative spontaneous sputum samples. PTB was confirmed by culture or molecular test in 26 patients (12.1%). IS detected 10 cases (38.5%) of all PTB, while BAL detected 22 cases (84.6%) of all PTB. IS had a sensitivity of 38.46% and a specificity of 100%, while BAL had a sensitivity of 84.62% and a specificity of 100%. BAL had a higher diagnostic yield than IS and was useful for ruling out alternative diagnoses. According to our experience FBS execution is mandatory in case of strong TB suspicion and sputum smear negative patients, especially in a low TB prevalence country. Moreover, it consents testing microorganism sensitivity and assessing possible alternative diagnosis with similar clinical presentation. The choice of the best diagnostic method may depend on the clinical context and the availability of resources.

Highlights

- The study compared IS and BAL in suspected PTB patients with negative sputum smears.
- BAL had a higher diagnostic yield than IS and detected 84.6% of all PTB cases.
- BAL was also useful for ruling out alternative diagnoses.
- FBS execution is mandatory in case of strong TB suspicion and sputum smear negative patients, especially in a low TB prevalence country.
- The choice of the best diagnostic method may depend on the clinical context and the availability of resources.

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Background

Despite tuberculosis (TB) is a preventable and curable disease, an estimated 10.6 million people fell ill with TB in 2022, and 1.3 million people died from TB (including 167 000 among HIV positive people), according to the World Health Organization 2023 Global TB report [1].

1. In Italy in 2021 TB incidence was 4.2/100.000, with 2,480 total cases notified [2]. Pulmonary tuberculosis (PTB) suspicion is based on a combination of clinical, radiological and epidemiological features. Initial work-up in patients with clinical suspicion of PTB (S-PTB) includes a radiological examination, then acid-fast bacilli (AFB) smear microscopy and molecular in spontaneous sputum samples (SS) must be performed [3]. Unfortunately, sputum microscopy has only approximately 50–70% sensitivity for diagnosis [4]. ATS guidelines suggest induced sputum (IS) sampling in adults with suspected PTB who are either unable to expectorate sputum or whose spontaneously expectorated sputum is AFB smear microscopy negative and then performing flexible bronchoscopy (FBS) with bronchoalveolar lavage (BAL) when spontaneous or induced sputum fails or if the latter are negative [3].

Literature data regarding the comparative diagnostic yield of IS and BAL in TB patients with negative sputum smears are inconclusive [5]. The objective of the present study is to analyze the diagnostic yield of these two procedures in patients with clinical suspicion of pulmonary tuberculosis, who produced two consecutive negative spontaneous sputum smears and underwent both IS and BAL.

Methods

This retrospective observational study was carried out at the National Institute of Infectious Diseases "L. Spallanzani" in Rome, Italy, a tertiary referral hospital for respiratory infectious diseases. The study included all adult patients hospitalized from November 2017 to February 2020 for S-PTB who had tested negative on microscopic examination for acid-fast alcohol bacilli on at least two samples. S-PTB patients were defined as having all of the following: [1] clinical suspicion by the treating physician, (reflected by patient isolation during admission in a negative pressure room) [2], one or more PTB-related symptoms or imaging finding (pulmonary upper lobe consolidation or cavitation, miliary pattern), and one or more risk factor for PTB (such as household contact, immigrants from high-burden countries, intravenous drug users and immunosuppression) (3). Symptoms related to TB included hemoptysis, night sweats (more than two episodes of heavy sweating during sleep in the month prior to hospitalization), a cough for at least two weeks, unintentional weight loss (more than 5 kg in the past six months, 10% of ideal body weight), pleuritic chest pain, or recurrent fevers (more than 38 °C, at least once a week for more than two weeks).

(3) Microbiological diagnostic procedures, according to the institutional protocol of the National Institute for Infectious Diseases L. Spallanzani, include the detection of *Mycobacterium tuberculosis* complex (MTBC) in a clinical specimen by either AFB, culture or a WHO-endorsed rapid diagnostic test (acid amplification tests (NAATs), such as GeneXpert MTB/RIF (Cepheid, USA) or PCR (BD MAX™ System, BD, Sparks, MD 21152-0999 USA) after examination of at least two sputum spontaneous sputum samples [3].

In agreement with ATS guidelines, if a patient is not able to produce valid sputum or in case of sputum negativity and S-PTB, IS and successively BAL are performed [4]. IS is a procedure used to collect a valid sample from the lower respiratory tract [5]; it has numerous advantages compared to BAL, because is non-invasive, carries few risks, and is more cost effective [6].

According to the study protocol, patients were included in the retrospective analysis if they had undergone either two IS and BAL procedures after two consecutive spontaneous sputum smear and rapid test negative.

All samples are sent to Microbiological Laboratory and processed by *Ziehl-Neelsen* Stain, PCR multiplex, and GeneXpert MTB/RIF. Cultures are performed in solid media [*Lowenstein-Jensen* (LJ)] and liquid media (BACTEC MGIT 960 systems; Becton Dickinson, Sparks, MD, USA) Drug-susceptibility testing procedures included testing on solid media (proportion method in Lowenstein-Jensen medium) and on liquid media (MGIT 960 systems; Becton Dickinson, Sparks, MD, USA).

Baseline variables (age, sex, comorbidities, demographic and risk factors for PTB) and clinical variables (symptoms, prior and current cultures, sputum samples, imaging, and BAL results) were extracted from electronic hospital records.

Frequencies and percentages (%) were obtained for qualitative variables, whereas quantitative variables were presented as means ± standard deviations. All statistical analyses were performed using SPSS 28.0 (SPSS, Inc., Chicago, Illinois).

Induced sputum

Hypertonic saline solution (saline concentration 2%) is administered with an ultrasonic nebulizer at high flows with 5-minute intervals for a total of 20 min.

We adopted a sequential technique starting from isotonic to 2% saline concentration to minimize risks of bronchospasm in high-risk patients.

Table 1 Characteristics of the 215 study subjects

Characteristics	*n*	%
Age, median (IQR)	52 (39–66)	
Sex		
Male	116	54.0
Female	99	46.0
Positive QTF or TST (n = 196)	89	45.4
Risk factors		
Highly endemic TB country of origin (n = 212)	67	31.6
Immunodeficiency (n = 213)	52	24.4
Previous TB (n = 212)	23	10.8
High risk community (n = 212)	11	5.2
Alcoholism (n = 212)	9	4.3
Chronic renal failure (n = 213)	7	3.3
Not treated latent TB infection (n = 214)	6	2.8
Recent TB exposure (n = 212)	6	2.8
Symptoms (n = 212)		
Cough	98	46.2
Fever	69	32.5
Dyspnea	55	25.9
Weight loss	32	15.1
Hemoptysis	32	15.1
Night sweats	15	7.1
Main abnormalities on CT scan		
Cavitations	55	25.6
Miliary involvement/nodules	83	38.6
Hilar adenopathy	5	2.3
Upper lobes infiltrates	89	41.4

The operator macroscopically assesses the quality of the sample before sending it to the microbiology unit.

Fibrobronchoscopy

A flexible FBS is performed with introduction of the bronchoscopy preferably nasally. Operators in the endoscopy room wear water-repellent gowns, FP3 protective masks, plasticized face visors and double-fitted gloves. Dressing and undressing of operators are carried out in different rooms to avoid contamination. BAL samples (minimum 15 ml) are promptly sent to microbiology and analyzed within two hours of collection. Both IS and FBS are performed in a negative pressure endoscopy room with 12 air exchanges per hour.

Statistical analysis

Descriptive analysis was conducted to characterize subjects enrolled in the study. Categorical variables were expressed as numbers and percentages and differences between groups were assessed by χ^2 or Fisher's exact test, as appropriate. Age (in years) was reported as continuous variable, expressed as median and interquartile range (IQR), and compared by the non-parametric Mann–Whitney U test.

The diagnostic yield and the diagnostic performance parameters, sensitivity, specificity, positive and negative predictive values, of IS and BAL were calculated. Kappa statistics was used to measure the agreement between IS and BAL.

Data were analyzed using Stata 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX, USA: StataCorp LLC).

Table 2 Microbiological results from IS and BAL

Type of respiratory specimen	Smear positive patients (%)	PCR/Xpert positive patients (%)	Culture positive patients (%)
Induced sputum, 2 samples set	1/215 (0.5%)	5/206 (2.4%)	9/209 (4.3%)
BAL	3/215 (1.4%)	20/204 (9.8%)	15/215 (7.0%)

Ethical statement

The study was approved by Ethics Committee of National Institute for Infectious Diseases "L: Spallanzani" IRCCS, with the decision n.12 (17th of February 2015) about data collection. All enrolled patients provided written informed consent to the utilization of anonymized clinical data.

Results

During the study period, 215 patients with S-PTB who underwent to at least two consecutive negative spontaneous sputum, two induced sputum and a FBS were enrolled. The main characteristics of the study population are reported in Table 1. The mean age was 52 ± 17 years; 53% males. At admission 21,9% of patients were asymptomatic. Cough was the most frequent symptom (45,6%). Eighty-nine patients out of 196 (45.4%) had positive tuberculin skin test (TST) or QuantiFERON Gold in-tube test. All patients except 5 had abnormal chest CT scan, the most common finding was upper lobes infiltrates in 89/215 (41.4%).

PTB was confirmed with at least one positive specimen (molecular or culture positivity) in 26 of the 215 patients of the study.

Socio-demographic factors associated with the likelihood of receiving TB diagnosis were origin from countries with high incidence of TB (OR 0.97; $p = 0.04$) and young age (OR 3.9; $p = 0.095$). Clinical factors associated with a diagnosis of TB were positivity of Quantiferon test ($p = 0.003$) and upper lobes involvement ($p = 0.008$). Diagnostic yield of microbiological tests performed on IS and BAL (smear, molecular assays and culture) is provided in Table 2. IS procedure achieved 5 rapid diagnoses of TB (1 smear positive, 0.5%; and 5 molecular tests, 2.4%) and 9 positive cultures (4.3%). FBS promptly identified PTB by rapid molecular tests in 20 patients (9.8%), with 15 culture positivity (7.0%). Furthermore, BAL enabled identification of other diagnosis, excluding PTB in 58 patients (26,9%) and diagnosis of lung cancer in 16

(7,4%). A diagnosis of pulmonary disease caused by non-tuberculous mycobacteria (NTM-PD) was established in 6 patients, accounting for 2.7% of cases.

Considering the positivity for MTB culture and/or molecular test of respiratory samples in the clinical setting, IS had a sensitivity of 10/26 cases, 38,46% (IC 95%, 20.2%, 59.4%), with a specificity of 100% (IC 98%, 100%, 100%), a positive predictive value of 100% (IC 69.2%, 100%), a negative predictive value of 92,2% (95% CI, 87.6–95.7) for the microbiological diagnosis of PTB in patients with negative sputum smear (Tables 2 and 3). BAL had a sensitivity of 22/26 samples, 84,62% (IC 95%, 65.1- 95.6%), a specificity of 100% (IC 98- 100%), a positive predictive value of 100% (IC 95%, 84.6-100%), a negative predictive value of 97,93% (IC 95%, 94-8- 99.4%) for the microbiological diagnosis of PTB in patients with negative sputum smear. (Table 4). There was a moderate agreement between IS and BAL procedures (kappa coefficient is 0.326).

Table 3 Diagnostic yield of IS and BAL

Diagnosis	IS (n = 215)	BAL (n = 215)
Pulmonary AFB + TB	10 (4.6%)	22 (10.2%)
NTM PD	3 (1.3%)	6 (2.7%)
Bacterial Pneumonia	0	58 (26.9%)
Malignancies	0	16 (7.4%)

Table 4 Comparison of sensitivity, specificity, and predictive values between IS and BAL

Diagnostic performance parameters	IS	BAL
Sensitivity (95% CI)	38.5 (20.2–59.4)	84.6 (65.1–95.6)
Specificity (95% CI)	100 (98.1–100)	100 (98.1–100)
Positive predictive value (95% CI)	100 (69.2–100)	100 (84.6–100)
Negative predictive value (95% CI)	92.2 (87.6–95.5)	97.9 (94.8–99.4)

CI: confidence interval

Discussion

The aim of this retrospective study was to assess the additional diagnostic value of either IS and BAL in patients with negative spontaneous sputum samples and clinical suspicion of PTB in a real-world setting, determining the contribution of different diagnostic steps to the diagnosis of Tuberculosis.

The protocol adopted at our Institution for patients with suspected pulmonary tuberculosis who are smear-negative for acid-fast bacilli on spontaneous sputum, is execution of two sputum induction first and then bronchoscopy, in accordance with the ATS guidelines [3].

As shown in Table 3, Induced sputum allowed the diagnosis of TB in 10 cases out of 215 (4.6% of the total patients and 38.5% of the PTB diagnosis) (Table 3).

Our data confirm that IS through hypertonic saline inhalation improves the diagnostic yield of PTB in patients with sputum smear negative or no reliable sputum production.

IS has performed well both in resource-poor and resource-rich countries [7–9].

While in other studies IS provided adequate samples for diagnosis and was positive in about 25–42%, in our study IS samples tested positive in 4.6% of patients unable to spontaneously expectorate sputum [10]. Sensitivity of IS in our study was 38.46%, different from previous reports, where it ranged from 42 to 96% [11].

Data published showed that factors affecting the quality and quantity of sputum samples were the bacillary load, the clinical presentation and prevalence of TB in the study setting [12].

In the context of low-incidence countries, the yield of IS can be particularly influenced by low prevalence of TB, which reduces the likelihood of detecting TB in sputum samples because of the need to rule out TB even in atypical clinical pictures. In our population, the low percentage of positive results can be explained by the pre-selection of the patients, who had already delivered two negative spontaneous sputum samples or who were unable to spontaneously expectorate, and by the low prevalence of TB in the study setting.

However, we found that performing IS enabled a rapid diagnosis of PTB with molecular test in 5 patients (2.4%) whose sputum smear was negative, and an overall identification of 10 cases of microbiologically confirmed TB. Moreover, IS additionally detected bacillary TB in 4/26 cases where FBS was negative (15%).

Data in this study reconfirmed that IS is useful for the diagnosis of PTB in clinical practice. Since the Stop-TB Strategy emphasizes the timely diagnosis and treatment of all cases of TB, including smear-negative PTB (12), IS can be an effective alternative to invasive procedures, offering a cost-effective and accessible option for TB diagnosis in resource-limited settings [13]. Unfortunately, 62% (16/26) of total cases of TB diagnosed in our patient population were missed by IS alone.

Fiberoptic bronchoscopy is a relatively safe procedure. Since its introduction in the 1960s, published rates of complication have ranged from < 0.1 to 11% [14].

Among the many advantages of fiberoptic bronchoscopy in TB diagnosis are visualizing endobronchial abnormalities, lower respiratory tract sampling and tissue sampling [15]. On the other hand, FBS can directly access the alveolar space and collect specimens from the site of infection, increasing the chances of detecting TB bacilli [16].

It can also provide additional information helping in differentiating TB from other pulmonary diseases [17]

However, FBS also has some drawbacks, such as being more invasive, costly, and requiring specialized equipment and personnel and may not be readily available or feasible in some settings, especially those with limited resources or high TB burden. Therefore, the choice of the best diagnostic method may depend on the location and extent of the pulmonary TB lesions, which may vary according to the immune status and risk factors of the patients and availability of equipment [18]. As a routine practice in our medical center, patients with S-PTB undergo FBS with BAL in cases of negative spontaneous and IS samples. We found that using FBS led to a diagnosis of PTB in 22 (10.2%) of the cohort of 215 patients, i.e. 84,6% of the 26 TB diagnosis. Sensitivity of microbiological assessments in our study was 84,62% confirming literature data (70% and 95%).

Smear-negative PTB poses many challenges, as it can transmit the infection, delay the diagnosis of PTB with a significant mortality rate, and cause irreversible lung damage [12]. In 62% of our negative IS patients (16/26) diagnosis of TB was possible exclusively thanks to bronchoscopy, highlighting the important added value of FBS in subjects with negative sputum smear and molecular tests and clinical suspicion of PTB [19]. WHO recommends using the most accurate and rapid diagnostic tests available to confirm TB cases, such as Xpert MTB/RIF assay or culture methods [12]. However, these tests require adequate biological specimens from the respiratory tract, which can be challenging to obtain in some patients. Data from our study confirm that FBS and IS are useful procedures to enhance the quality and quantity of the samples for TB diagnosis [20] In our study, the diagnostic yield of FBS is superior to that of IS [20]. The existing literature on the diagnostic effectiveness of FBS and IS for cases with negative sputum is limited and diverse [21; 22]. The optimal timing and frequency of using these procedures, as well as their cost-effectiveness, remain unclear [23].

There is a lack of data on the performance of FBS and IS in different populations, such as children, elderly, immunocompromised, or patients with extrapulmonary TB [24]. Therefore, more studies are needed to evaluate the role of FBS and IS in TB diagnosis in various settings and scenarios [25]. Literature evidence suggests that bronchoalveolar lavage (BAL) is more sensitive compared to sputum induction (SI) for the diagnosis of pulmonary tuberculosis (PTB), especially in patients lacking sputum and HIV/AIDS patients with lower bacterial loads and miliary form of lung disease [18] A recent meta-analysis showed that IS and FBS had a similar diagnostic yield in sputum smear-negative pulmonary tuberculosis, but it included a very limited number of studies [26]. In our study IS had a sensitivity of 38,46% (IC 95%, 20.2%, 59.4%), while BAL had a sensitivity of 84,62% with a positive predictive value of 100% (IC 95%, 84.6%-100. (Table 4). One possible explanation for the different sensitivities of IS and FBS in our study is that they were applied to different types of TB lesions. This hypothesis is supported by previous studies that found a correlation between radiological findings and diagnostic yield of IS or FBS [27]. Therefore, the choice of the best diagnostic method may depend on the location and extent of the pulmonary TB lesions, which may vary according to the immune status and risk factors of the patients.

TB poses a significant health challenge worldwide, with high-burden countries often receiving the most attention [28]. Deciding which patients with S-PTB and negative sputum samples should undergo bronchoscopy is of high importance [29].

While both IS and BAL are effective in diagnosing TB, their use depends on the clinical context and available resources [30]. IS is non-invasive, more cost-effective and suitable for outpatient settings, making it an ideal first-line diagnostic tool in many cases. The invasiveness and higher cost of BAL, however, limit its use to more severe cases or when other diagnostic methods are inconclusive [31].

Our study highlights the need for a tailored approach to TB diagnosis, taking in consideration factors such as the prevalence of TB in the clinical setting and the available resources.

This is particularly relevant in settings where TB incidence is low, and the likelihood of smear negative pulmonary TB is higher.

The most important limitation of our study is the retrospective design that certainly caused a selecting bias regarding evaluation of IS diagnostic yield.

Second limit regards the small sample size. Third, even though patients were studied because of TB suspect, sometimes FBS was performed to rule out alternative diagnosis as neoplasm.

Conclusion

According to our experience FBS execution is mandatory in case of strong TB suspicion and sputum smear negative patients, especially in a low TB prevalence country. Moreover, it consents testing microorganism sensitivity and assessing possible alternative diagnosis with similar clinical presentation.

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Author contributions

Conceptualization, P.C., A.M. and M.M.; methodology, P.M.; software, A.N.; validation, D.G.; formal analysis and revision, P.M.; investigation, C.P; R.L.; resources, F.P.; data curation, M.M., A.C.; writing—original draft preparation, G.G., M.M. and P.M.; writing—review and editing, F.P. and C.N.; visualization,

V.DB, D.G.; supervision, S.M, F.P.; funding acquisition, F.P. All authors have read and agreed to the published version of the manuscript.

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Data availability
Data Availability StatementAll relevant data are within the manuscript. Raw data are accessible, if requested, from National Institute for Infectious Diseases "L. Spallanzani" Library to E-mail address: biblioteca@inmi.it.

Declarations

Institutional review board statement
This study was approved by the Ethics Committee of the National Institute for Infectious Diseases, "L. Spallanzani" IRCCS, with decision n.12 (17 February 2015). All enrolled patients provided written informed consent to the utilization of their anonymized clinical data. Our study adhered to ethical principles of the Declaration of Helsinki.

Informed consent
Informed consent was obtained from all subjects involved in the study.

Competing interests
The authors declare no competing interests.

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