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# Bronchoscopic Strategies to Improve Diagnostic Yield in Pulmonary Tuberculosis Patients

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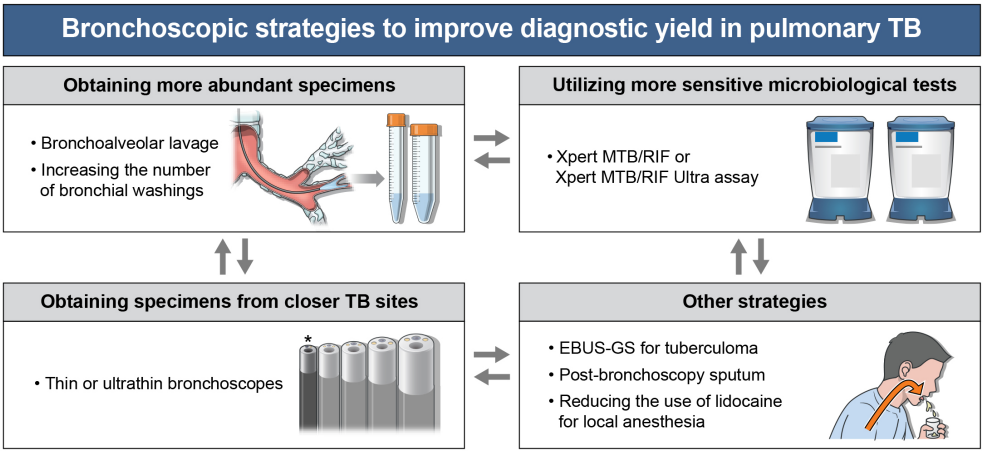




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## Abstract

In cases where pulmonary tuberculosis (PTB) is not microbiologically diagnosed via sputum specimens, bronchoscopy has been the conventional method to enhance diagnostic rates. Although the additional benefit of bronchoscopy in diagnosing PTB is well-known, its overall effectiveness remains suboptimal. This review introduces several strategies for improving PTB diagnosis via bronchoscopy. First, it discusses how bronchoalveolar lavage or an increased number of bronchial washings can increase specimen abundance. Second, it explores how thin or ultrathin bronchoscopes can achieve specimen acquisition closer to tuberculosis (TB) lesions. Third, it highlights the importance of conducting more sensitive TB-polymerase chain reaction tests on bronchoscopic specimens, including the Xpert MTB/RIF assay and the Xpert MTB/RIF Ultra assay. Finally, it surveys the implementation of endobronchial ultrasound with a guide sheath for tuberculomas, collection of post-bronchoscopy sputum, and reduced use of lidocaine for local anesthesia. A strategic combination of these approaches may enhance the diagnostic rates in PTB patients undergoing bronchoscopy.

**Keywords:** Bronchoscopy; Diagnosis; Pulmonary; Tuberculosis

## Introduction

Tuberculosis (TB) is a prevalent respiratory infectious disease that has affected humanity for thousands of years and continues to pose a serious threat to global public health. During the onset of coronavirus disease 2019 (COVID-19) pandemic, there was a global decline in the number of reported TB cases. This decline has been attributed to missed or delayed diagnoses, rather than an actual reduction in TB incidence[1]. However, increasing numbers of TB cases were reported beginning in 2021, and pre-COVID-19 levels were reached in 2022. Approximately 7.5 million new TB cases were reported globally in 2022; this was the highest total since the World Health Organization (WHO) initiated global TB monitoring in 1995[1]. Additionally, TB was responsible for an estimated 1.3 million deaths worldwide in 2022. Globally, TB was the 13th most common cause of death and the main infectious disease associated with mortality in 2019[1]. These high incidence and mortality rates substantially deviated from the targets outlined in the WHO's End TB Strategy, which aimed to achieve a 50% reduction in TB incidence rates and 75% reduction in TB-related deaths by 2025 relative to 2015 levels.

Accurate pulmonary tuberculosis (PTB) diagnosis relies on the identification of *Mycobacterium tuberculosis* through high-quality sputum samples subjected to microbiological tests, including acid-fast bacillus (AFB) smear, *M. tuberculosis* culture, and TB-polymerase chain reaction (PCR). However, the sensitivities of these sputum-based diagnostic methods are suboptimal, particularly in settings with a low disease burden and patients who exhibit minimal symptoms. Additionally, a substantial proportion of PTB patients fail to produce sputum samples, hindering the diagnostic process[2-5]. Globally, only 63% of PTB patients have bacteriologically confirmed disease[1]. In a recent study based on nationwide data from South Korea, up to 70% and 40% of PTB patients had smear-negative and culture-negative results, respectively[6].

When TB cannot be bacteriologically confirmed, clinicians often initiate empirical TB treatment based on clinical symptoms and radiological findings. Although empirical treatment is an inevitable aspect of real-world TB diagnosis and management, it carries the inherent risk of misdiagnosis and the inconvenience of unnecessary receipt of anti-TB drugs, often associated with severe adverse events. Efforts to address these challenges include augmenting the diagnostic yield of PTB through bronchoscopy. Although bronchoscopy has a recognized diagnostic benefit, its diagnostic yield remains suboptimal[7,8]. This review summarizes potential methods to enhance the rate of PTB diagnosis via bronchoscopy.

## Improving Specimen Abundance

Bronchoscopy procedures that yield abundant specimens increase the likelihood of TB bacillus detection, thereby improving diagnostic accuracy. Bronchial washing (BW) has been the conventional method for PTB diagnosis via bronchoscopy. A single specimen collected using 10 to 20 mL of sterile saline during BW is the standard practice in many centers. However, there is no consensus regarding the optimal number of BW procedures for TB diagnosis. In cases involving sputum, collecting multiple samples can enhance the detection rates of TB[9,10]. Consequently, guidelines often recommend obtaining sputum two to three times for PTB diagnosis[11-13]. Similarly, an increased number of BW procedures might enhance the diagnostic yield for PTB. A retrospective study in South Korea compared outcomes when performing BW once versus twice in PTB patients during a single bronchoscopy session, using 10 mL of sterile saline in each procedure. The study revealed that two BW procedures increased the AFB smear positivity rate by 8% and the *M. tuberculosis* culture positivity rate by 13%, compared with one BW procedure[14].

Another method for obtaining abundant specimens is bronchoalveolar lavage (BAL). In the diagnosis of respiratory diseases other than TB, such as pneumonia or lung malignancy, BAL has demonstrated superiority over BW[15,16]. A randomized controlled trial in South Korea compared the diagnostic yields of BW and BAL in PTB patients. The study showed that BAL fluid had significantly higher sensitivity for TB diagnosis (positive *M. tuberculosis* culture or TB-PCR) at 85.7%, compared with 50.0% for BW fluid[17]. Furthermore, the incidences of complications, including hypoxemia, post-bronchoscopy fever, and pneumonia, did not significantly differ between the two groups[17].

## Improving Specimen Proximity to TB Lesion Sites

The acquisition of BW or BAL fluid at sites with close proximity to the PTB lesion can enhance diagnostic accuracy by yielding bacillus-rich specimens. However, conventional bronchoscopes typically have larger diameters, which limits access to PTB lesions (especially in peripheral lung areas)[18]. In recent years, the widespread adoption of thin or ultrathin bronchoscopes,

particularly for diagnoses of peripherally located lung cancers, has demonstrated advantages because their smaller diameters enable closer access to target lung lesions. The use of thin or ultrathin bronchoscopes for PTB diagnosis can potentially improve diagnostic rates.

A randomized controlled trial of PTB patients in South Korea compared TB diagnosis via BW between conventional thick bronchoscopes (outer diameter: 5.9 mm) and thin bronchoscopes (outer diameter: 4.0 mm). The study revealed a significantly higher sensitivity of 72.4% for TB diagnosis (positive Xpert MTB/RIF assay) using the thin bronchoscope, compared with 43.5% when using the thick bronchoscope[19]. The thin bronchoscope facilitated access to two additional bronchial branches, leading to the discovery of more endobronchial TB cases. This resulted in a more rapid and accurate TB diagnosis, while reducing the time to treatment initiation for PTB patients[19]. However, accurate selection of a bronchial route to the target TB lesion using a thin bronchoscope, particularly in cases involving peripheral lung lesions, remains challenging[20]. In such cases, virtual bronchoscopic navigation can be used for guidance[21,22]. Similar to virtual bronchoscopic navigation, manual mapping through computed tomography images may also be beneficial, especially for experienced bronchoscopists[23].

Although research concerning the diagnostic utility of ultrathin bronchoscopes (e.g., bronchoscopes with a 3.0-mm outer diameter) is limited, the significantly thinner diameters can theoretically enable closer and more precise sampling near TB lesions, thereby improving diagnostic rates. However, the use of thin or ultrathin bronchoscopes for BAL (rather than BW) may have limitations. Specifically, the smaller diameters and lower elasticity of peripherally located higher-branch bronchi make them susceptible to collapse during BAL and can hinder the retrieval of BAL fluid.

## Utilizing More Sensitive Microbiological Tests

*M. tuberculosis* culture remains the gold standard for TB diagnosis, but TB-PCR is beneficial for rapid identification of TB bacilli and differentiation from non-tuberculous mycobacteria (NTM). However, conventional TB-PCR involves complex testing procedures, specialized infrastructure and skilled personnel, and long turnaround times. To overcome these limitations, the Xpert MTB/RIF assay, endorsed by the WHO in 2010, offers a fully automated, cartridge-based real-time PCR test capable of detecting TB within 2 hours[24]. It has been extensively adopted in clinical settings for PTB diagnosis via sputum specimens and is recommended by the WHO guidelines as the initial diagnostic test for PTB; thus, it is prioritized over AFB smear and *M. tuberculosis* culture tests[25]. Although conventional TB-PCR and the Xpert MTB/RIF assay theoretically have similar diagnostic accuracies, the Xpert MTB/RIF assay often has higher sensitivity in clinical settings. This difference is based on the Xpert MTB/RIF assay's direct utilization of sputum specimens without preprocessing; conventional TB-PCR may lose TB bacilli during preprocessing steps, such as decontamination or concentration, especially in patients with a low-TB burden[26]. Similarly, the use of the Xpert MTB/RIF assay for bronchoscopic specimens may be able to overcome the limitations of conventional TB-PCR, potentially enhancing diagnostic accuracy.

In two retrospective studies of PTB patients from South Korea, comparing the Xpert MTB/RIF assay and conventional TB-PCR (AdvanSure TB/NTM real-time PCR, LG Life Sciences, Seoul, Korea) in assessments of BW and BAL fluid, the Xpert MTB/RIF assay demonstrated significantly higher sensitivity for TB diagnosis, especially in analyses of AFB smear-negative patients[26,27]. A study in Hong Kong revealed similar findings, based on a comparison of the Xpert MTB/RIF assay and conventional TB-PCR (Cobas TaqMan TB-PCR, Roche Diagnostics, Basel, Switzerland) for assessment of BAL fluid[28]. Therefore, the use of bronchoscopic specimens in the Xpert MTB/RIF assay enhances TB diagnosis rates, while offering the advantages of rapid turnaround time and simultaneous detection of rifampin resistance.

The Xpert MTB/RIF Ultra assay is another testing method that enhances sensitivity by expanding amplification targets and increasing the reaction chamber size[29]. Although this assay is not fully validated for specimens other than sputum, its use with bronchoscopic specimens is expected to improve diagnostic rates. In a prospective study from Taiwan, the Xpert MTB/RIF Ultra assay using BW fluid exhibited a >30% increase in sensitivity compared with conventional TB-PCR[30]. Similarly, a prospective study from China demonstrated an approximately 14% increase in sensitivity when the Xpert MTB/RIF Ultra assay was utilized to evaluate specimens obtained through endobronchial ultrasound with a guide sheath (EBUS-GS) or endobronchial ultrasound-guided transbronchial needle aspiration[31].

Despite these advantages, caution is required when interpreting results from the Xpert MTB/RIF and Xpert MTB/RIF Ultra assays, as their accuracy can be affected by a patient's previous TB treatment. For example,

compared to the microbiological reference standard, the specificity for detecting TB in adult PTB patients using the Xpert MTB/RIF assay is around 98%, but it decreases to 95% for previously treated patients. The difference is even more significant with the Xpert MTB/RIF Ultra assay, in which the specificity is reduced from 96% to 86%[25]. Thus, the possibility of false positives should always be considered, especially when using the Xpert MTB/RIF Ultra assay in patients who have recently completed TB treatment.

## Other Strategies

Recent advancements in bronchoscopy techniques for lung cancer diagnosis include the use of EBUS-GS for tissue sampling, which may be a valuable method for PTB diagnosis. A retrospective study from China assessed the efficacy of EBUS-GS in tuberculoma diagnosis. Tissue obtained through EBUS-GS, subjected to both pathologic evaluation and the Xpert MTB/RIF assay, demonstrated the highest diagnostic accuracy compared with the use of BAL fluid for *M. tuberculosis* culture and the Xpert MTB/RIF assay[32]. Accurate diagnosis of tuberculomas may prevent unnecessary surgeries.

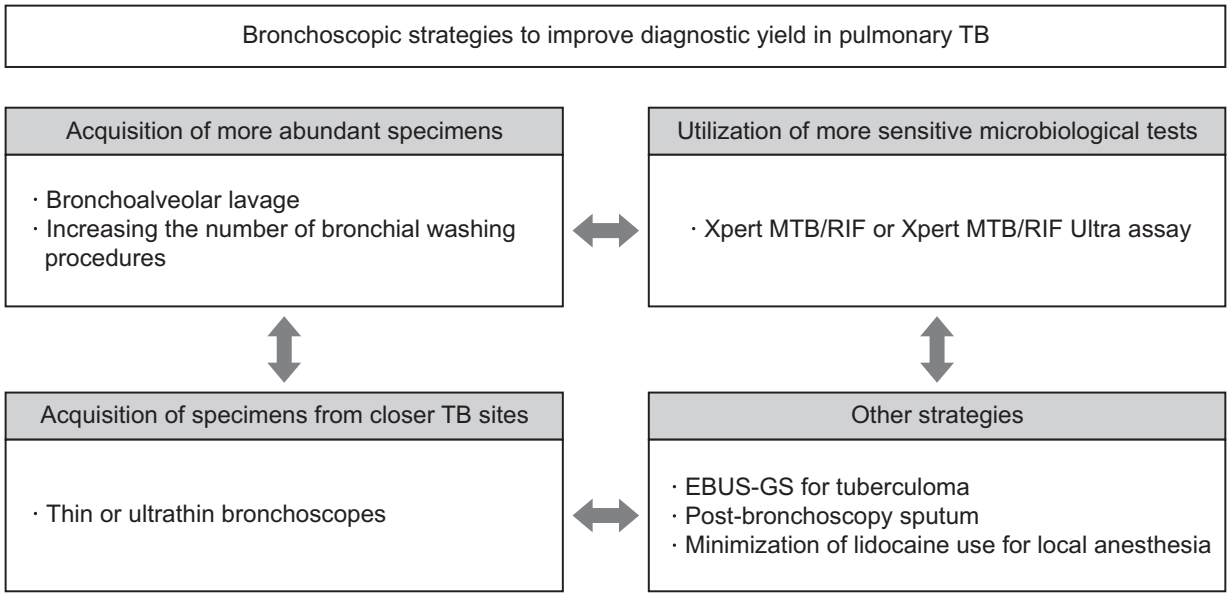
The collection of post-bronchoscopy sputum can also facilitate PTB diagnosis. Bronchoscopy procedures may irritate the airway mucosa, facilitating the expectoration of sputum containing bacteria from deep-seated lesions. This expectoration increases the likelihood of detecting TB bacilli in post-bronchoscopy sputum, which is particularly important for patients with limited sputum[33]. A prospective study from Qatar demonstrated that post-bronchoscopy sputum contributed to an additional diagnostic yield of 2.6%[34]. In some instances, TB may not be identified in bronchoscopic specimens but may be present in post-bronchoscopy sputum. Moreover, because post-bronchoscopy sputum collection is a convenient, non-invasive, and easy test, it is a viable option for patients undergoing bronchoscopy.

Research findings from the 1960s and 1970s suggest that lidocaine, used for local anesthesia in bronchoscopy, could interfere with *M. tuberculosis* culture[35,36]. However, subsequent research on this topic has been limited and the findings are inconclusive. It may be prudent to consider this potential effect when performing bronchoscopy.

## Healthcare Worker Protection during Bronchoscopy

Bronchoscopy is a procedure known to generate large amounts of aerosols; when this procedure is conducted on PTB patients, the bronchoscopist can experience a substantial risk of TB infection. In South Korea, a study of nosocomial exposure to TB demonstrated that 29% of patients with unrecognized active TB had undergone bronchoscopy before the initiation of TB treatment[37]. A study from South Korea showed

**Figure 1.** Bronchoscopic strategies to improve diagnostic yield in pulmonary tuberculosis (TB) patients. EBUS-GS: endobronchial ultrasound with a guide sheath.



that 4.6% of patients who underwent bronchoscopy with a preliminary diagnosis of non-TB respiratory disease were eventually diagnosed with TB[38]. In another study conducted in South Korea, BW was performed through bronchoscopy on patients suspected of having NTM pulmonary diseases. Of these patients, 5.7% were ultimately diagnosed with PTB[39]. These findings demonstrate the potential challenge in differentiating PTB from other respiratory diseases based solely on clinical symptoms or imaging studies. Therefore, all patients undergoing bronchoscopy should be regarded as potential TB patients, particularly in countries with a high TB burden. The prevention of TB infection during bronchoscopy requires the use of personal protective equipment, including N95 respirators, and appropriate ventilation systems. For patients scheduled to undergo bronchoscopy, pre-procedural TB screening using the sputum Xpert MTB/RIF assay may be considered.

## Conclusion

Several strategies can be implemented to enhance PTB diagnosis via bronchoscopy. First, more abundant specimens can be obtained by utilizing BAL or increasing the number of BW procedures. Second, the acquisition of specimens closer to TB lesion sites can be facilitated by thin or ultrathin bronchoscopes. Third, diagnostic accuracy can be enhanced by using more sensitive TB-PCR tests, including the Xpert MTB/RIF assay and the Xpert MTB/RIF Ultra assay, on bronchoscopic specimens. Finally, it is important to conduct pathologic evaluation and use the Xpert MTB/RIF assay for tuberculoma through EBUS-GS, consider the collection of post-bronchoscopy sputum, and minimize the use of lidocaine for local anesthesia (Figure 1). An appropriate combination of these methods based on the TB lesion characteristics, clinical situation, and available resources may improve diagnostic rates for PTB patients. Additionally, there is a need to establish approaches that reduce the bronchoscopist's risk of TB infection during bronchoscopy, including the use of personal protective equipment, effective ventilation systems, and TB pre-screening among patients scheduled for bronchoscopy.

## Authors' Contributions

Conceptualization: Eom JS, Mok J. Data curation: all authors. Writing - original draft preparation: all authors. Writing - review and editing: all authors. Approval of final manuscript: all authors.

## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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