Role of bronchoscopy in diagnosis of smear-negative pulmonary tuberculosis

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Tuberculosis (TB) remains an important cause of morbidity and mortality in many developing countries including India. Prompt and accurate establishment of diagnosis is one of the essential basic principles of care for persons with TB. Sputum smear microscopy and culture remain the cornerstone of diagnosis but can be negative in a substantial proportion of pulmonary TB patients (multiple smear-negative status or scanty sputum). Bronchoscopy has been proven to be a safe and effective method for those patients with varying diagnostic yields ranging from 30 to 90%. Various specimens are obtained from a fiber-optic bronchoscope such as smear and culture for mycobacteria from the bronchial aspirate or wash, bronchoalveolar lavage fluid, bronchial brushing, postbronchoscopy sputum, transbronchial needle aspiration, and transbronchial biopsy. The diagnostic yield is significantly enhanced when nucleic acid amplification testing is applied to bronchoscopic specimens. The role of bronchoscopy in TB diagnosis is likely to be limited because of availability, cost, and logistical challenges. Future studies are needed to better define the role of the newer diagnostic modalities to improve early TB diagnosis.

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Introduction

Tuberculosis (TB) is considered to be a public health problem worldwide and remains an important cause of morbidity and mortality in many developing countries including India. There were an estimated 2.8 million new cases in India, and 0.32 million people died in India because of TB in 2016 [1]. It is a cause for major concern as India stands first in terms of the absolute number of cases. Prompt and accurate establishment of diagnosis is one of the essential basic principles of care for persons with TB. A majority of pulmonary TB cases relies on bacteriological examination to establish diagnosis that includes sputum smear microscopy and cultures of various specimens, including a regular sputum, induced sputum, gastric washings, and bronchoscopic sampling. There is a wide variation in the sensitivity, specificity, and diagnostic yield of each of these tests, as reported from various studies [2,3]. Sputum smear microscopy and culture remain the cornerstone of diagnosis and are relatively easy to perform, but can be negative in a substantial proportion of pulmonary TB patients with reported sensitivities ranging from 25 to 45% [1,2,4]. The diagnostic yield of sputum examination has been improved by inducing with hypertonic saline, as reported in several studies but requires additional resource allocation and manpower training [2,5,6]. The diagnostic yield of bronchoscopy has also proven to be higher, as compared with sputum examination in the diagnosis of pulmonary TB with a probability of higher microscopy and culture positivity results [2,7].

However, the diagnosis is really challenging for physicians when a patient encounters with multiple negative sputum results even after induction, although there is high suspicion of active disease. Therefore, the choice remains whether to proceed with empiric treatment for pulmonary TB without any further delay or to perform an invasive test such as bronchoscopy to confirm the diagnosis in such patients. The issue remains whether bronchoscopy offers any additional diagnostic yield in patients suspected to have active pulmonary TB, presenting with multiple negative sputum results.

Diagnostic yield of bronchoscopy in smear-negative pulmonary TB

Bronchoscopy has been proven to be a safe and effective method for the diagnosis of pulmonary TB, especially in those patients in whom diagnosis by sputum smear microscopy is difficult. The existing literature on this subject reports varying diagnostic yields ranging from 30 to 90% for bronchoscopy, depending on the study design and demographic profile of the population being studied [2]. The higher diagnostic yields were reported in the

majority of studies. These studies have either included those patients with smear-negative status or also included those unable to expectorate sputum in addition to smear-negative ones. Other studies have not used sputum induction as the next step in patients having negative or scanty expectoration but proceeded directly to bronchoscopy. It is also a matter of concern whether bronchoscopy provides any additional diagnostic yield over induced sputum with conflicting evidence. A study comparing the diagnostic yield between a regular sputum, induced sputum, and bronchoscopy in the diagnosis of TB observed that bronchoscopy had a significantly higher diagnostic yield when compared with multiple sputum samples after induction. It was also observed that the diagnostic yield of each modality was low, varying from 36 to 63% and yield was enhanced when used in combination [8]. However, few studies have shown no additional or lower yield of bronchoscopy over sputum induction [2]. The lower yields from bronchoscopy might have resulted from lack of technical expertise of the operators performing procedures and also from the use of 2% lidocaine for local anesthesia having well-described antibacterial properties with potent specific inhibitory effects on growth of *Mycobacterium tuberculosis* and nontuberculous mycobacteria, thereby reducing the culture positivity rate [2]. A study also reported that bronchoscopy provides an additional 10% diagnostic yield [bronchioalveolar lavage (BAL) culture positive] in smear-negative pulmonary TB even after multiple sputum induction (at least two samples) and also nucleic acid amplification testing (NAAT) performed before the procedure, although the overall diagnostic yield was low [2]. These cases would have been otherwise missed by smear and NAAT testing of multiple samples after sputum induction.

Diagnostic accuracy of various bronchoscopic specimens for diagnosis of pulmonary TB

Various specimens are obtained from a fiber-optic bronchoscope such as smear and culture for mycobacteria from the bronchial aspirate or wash, BAL fluid, bronchial brushing, postbronchoscopy sputum, cytopathological assessment by transbronchial needle aspiration (TBNA), and histopathological assessment by transbronchial biopsy (TBB). All these techniques have been used for diagnosing pulmonary TB. The initial bronchoscopic approach for diagnosis relies on bronchial wash (BW) or BAL acid-fast bacillus (AFB) smear microscopy and conventional cultures for *M. tuberculosis* complex (MTBC). Smear microscopy shows a sensitivity ranging between 4.7 and 58.0% on BAL and BW [9]. It has the advantage that diagnosis can be established within 1–2 days at a minimal cost. An issue

of diagnostic delay is associated with conventional cultures, as results are turning positive after 2–6 weeks. Despite this limitation, a positive culture is considered the gold standard with the highest diagnostic accuracy and having an additional advantage of providing further information on drug sensitivity. There is no convincing evidence when diagnostic yield for pulmonary TB was compared between BW and BAL. A study reported that BW had the same culture yield as BAL (95%) but a higher frequency of positive AFB smears (26 vs. 4%) [10]. Another study reported BAL to be superior as culture for *M. tuberculosis* in BAL, and BW specimens were positive in 15 (88%) of 17 patients and nine (53%) of the 17 patients, respectively [11]. BAL was the only source of positive culture in seven of 17 patients. Out of nine BW culture positive patients, eight patients also had positive cultures from BAL. BW of one patient was the only source of a positive culture. BAL could possibly result in s better diagnostic yield than BW but is not frequently performed in resource-constrained settings. A good-quality BAL sample also requires technical expertise. The diagnostic yield was enhanced further when NAAT was applied to BW and BAL with a better yield for the latter. Various studies have reported that when NAAT was applied on BW and BAL, the sensitivities were 51.9–97.2% and the sensitivities for BAL were 31.3–83.8%, whereas the specificities were 73.2–100.0 and 92.4–98.2%, respectively [9]. The variability in diagnostic yield was related to different methodological approaches used by researchers. Bronchial brushing, postbronchoscopy sputum, TBNA, and TBB may support the diagnosis in addition to BAL or BW by detection of cytologic and histopathological TB findings (i.e. caseating or noncaseating granulomatous inflammation) [9,12]. These techniques were indicated, depending on the site of involvement such as lung parenchyma, including nodules, airway, mediastinal lymph nodes, or in combination. All of them have been observed to increase the sensitivity of bronchoscopy, unless there are no contraindications. Several studies have reported a sensitivity of 16–77% for TBB in association with a good safety profile for patients with TB with smear negative or scanty sputum, especially peripheral pulmonary nodules or masses [9]. Pneumothorax and bleeding are the most frequently reported complications. The wide interstudy variability of the diagnostic accuracy might be explained by the heterogeneous TB diagnostic criteria (i.e., histology, bacteriology, or their combination), lesion size, and radiologic features of the parenchymal lesions. The highest sensitivity of TBB has been reported with lesion size of more than 2 cm, miliary TB, and use of a radial probe endobronchial

ultrasound (EBUS). The sensitivity of AFB smear and cultures of BAL were also increased if collected from the lesions detected with EBUS. BAL has been considered to be superior over BW in diagnosing both interstitial lung diseases and pulmonary cancers, that is, in cases showing clinical and radiologic features that can closely resemble pulmonary TB [9–11]. Further, TBLB and EBB have an additional higher yield than BAL and BW for such diseases other than pulmonary TB. Use of ultra-thin bronchoscopes and cryoprobes may further enhance the diagnostic performance but evidence is limited.

Role of bronchoscopy in diagnosis of endobronchial TB

Bronchoscopy can be relevant for bacteriological and histopathological diagnosis of endobronchial tuberculosis (EBTB), as sputum smear examinations reveal a low diagnostic yield in the majority of cases. Various subtypes of EBTB have been recognized by bronchoscopic techniques, such as nonspecific bronchitic, edematous-hyperemic, actively caseating, granular, tumorous, ulcerative, and fibrostenotic. All these subtypes have presented with diverse clinical presentations. The radiologic imaging, such as chest computed tomography, is indicated before bronchoscopy as it provides details regarding the extent of bronchial involvement length, peribronchial thickness, luminal patency, and signs of bronchial stenosis. EBB is the most reliable sampling method for EBTB diagnosis, with a sensitivity of 72.2–100.0% in the detection of granulomas, as compared with endobronchial needle aspiration [9]. Smear and culture of bioptic tissues show a wide sensitivity (8.0–100.0%), but few studies are available on their diagnostic performance [9]. Real-time PCR can help in rapid diagnosis, thereby minimizing the complication of stenosis. Studies based on traditional bacteriology on BW and BAL revealed a diagnostic yield of 10.0–37.0 and 12.5–62.5% for smear microscopy and culture, respectively [9]. The yield was the highest for a granular subtype, as compared with the fibrostenotic EBTB.

Role of bronchoscopy in treatment of endobronchial TB

Bronchoscopy can also be used for therapeutic purpose to treat fibrostenotic and tumorous varieties of EBTB. The bronchoscopic procedures include either dilation (a rigid bronchoscope barrel, a metal bougie, balloon bronchoplasty, silicon or metallic stenting, and application of mitomycin-C) or ablation techniques (Nd-YAG laser therapy, electrocautery, argon plasma coagulation, and cryotherapy). Dilation techniques are used to restore airway dilation with EBTB-related stenosis, whereas ablation techniques remove excessive growth occluding the airway lumen, thereby restoring endoluminal patency. Both of these techniques can be performed through rigid or flexible bronchoscopes. Therapeutic bronchoscopy represents an alternative and less-invasive strategy than conventional surgery, particularly when the latter is contraindicated or technically not feasible as in the case of multilevel stenosis. It has also been reported that endobronchial one-way valves could be effective in achieving cavity collapse, emphysema-related hyperinflation, and sputum conversion in these fibro-cavitary TB patients who were considered ineligible for surgery.

Role of bronchoscopy in diagnosis of tubercular mediastinal lymphadenopathy

The diagnosis of extrapulmonary TB, such as hilar and mediastinal lymphadenopathy, can be challenging, especially when occurring in isolation without any parenchymal involvement and specific clinico-radiological features. The bronchoscopic approaches such as conventional TBNA and recently standardized linear EBUS-TBNA can be useful to collect samples for smear microscopy and culture in association with specific cytopathology. Conventional TBNA and EBUS-TBNA has shown sensitivities of 65.0–100.0 and 70–80%, respectively, whereas the specificity is 100.0% for both, with a good safety profile [9]. A definite diagnosis is essential to rule out sarcoidosis or malignancies (i.e. lymphoma and lung cancer). These procedures have avoided more invasive procedures such as video-assisted thoracic surgery and mediastinoscopy. A transesophageal approach known as endoscopic ultrasound (with a bronchoscope) fine needle aspiration or endoscopic ultrasound bronchoscope-guided fine needle aspiration, has been successfully used recently for TB diagnosis, particularly involving left paratracheal, subcarinal, aortopulmonary mediastinal, or inferior mediastinal lymph nodes, and also when EBUS is not technically feasible or unsuitable for a transbronchial approach. Rapid on-site evaluation of conventional and EBUS transbronchial needle aspirates has facilitated rapid diagnosis of TB by detecting granulomas. It has reported to predict a better yield in hilar/mediastinal lymphadenopathies, parenchymal, endobronchial, and peripheral pulmonary lesions sampling. A further advantage is that alternate diagnosis of malignancy or sarcoidosis can also be ruled out on a preliminary basis. It may reduce the procedure time and cost by allowing the operator to interrupt the sampling procedure by avoiding needle passes and useless transbronchial biopsies or brushings when sufficient material has been collected.

Role of nucleic acid amplification test in bronchoscopic specimens for diagnosis of pulmonary TB

Nucleic acid amplification testing is a rapid diagnostic test for detection of MTBC rRNA, providing good diagnostic yield from respiratory specimens. The Xpert MTB/RIF (Cepheid Inc., Sunnyvale, California, USA) assay is an automated cartridge-based nucleic acid amplification test that can rapidly detect MTBC and rifampicin resistance simultaneously within 2–3 days. The reported sensitivity of this assay for the detection of MTBC in the sputum was more than 98% among smear-positive and more than 70% among smear-negative pulmonary TB patients [13]. It has been utilized for various clinical specimens from extrapulmonary sites other than the sputum with promising results. The sensitivity for AFB smear microscopy based on bronchoscopic specimens such as BW, BAL, and TBNA remains low and highly affected by bacillary load. The diagnostic accuracy of Xpert MTB/RIF has enhanced the sensitivity for such samples in patients with suspected pulmonary TB who had a smear negative for AFB even after induction or who could not produce a sputum. A study has been reported to have a higher sensitivity than smear microscopy (92.3 vs. 41%) and almost similar specificity (87.7 vs. 98.6%) for confirmation of TB in specimens obtained by bronchoscopy considering culture as the gold standard. It has shown a positive predictive value of 80% and a negative predictive value of 95.5% [14]. Further, diagnostic accuracy of Xpert MTB/RIF was not affected with HIV coinfection. Various studies have reported that Xpert MTB/RIF detected MTBC in BW, BAL, and EBUS-TBNA with overall sensitivity and specificity of 31–100 and 72–100%, respectively [9]. The authors have adopted a heterogeneous methodological approach across these studies that might be responsible for a mismatch between sensitivity and specificity. The evidence regarding its diagnostic accuracy in EBUS-TBNA samples is limited but seems to be convincing. The yield is enhanced when combined with conventional bacteriology and histopathology. Several studies also demonstrated a high sensitivity (83.3–100.0%) and specificity (97.7–100.0%) of Xpert MTB/RIF in diagnosing rifampicin resistance on both BAL and BW [9]. Therefore, it should be utilized routinely in patients with a high suspicion of pulmonary TB. However, the results should be interpreted cautiously among discordant (positive Xpert MTB/RIF; culture negative) cases based on the clinical context, and ideally be confirmed with additional tests and/or follow-up. It cannot be assumed solely that a positive test result corresponds to active disease because of the inability of the PCR test to distinguish between alive or dead bacilli.

Very-low positive test results in patients with latent infection or recent exposure could be possible because of reduced bacterial load in bronchoscopy samples.

Conclusion

Bronchoscopy can be considered to be a safe and highly reliable technique for management of difficult-to-treat or complicated TB patients where sputum collection is challenging (sputum smear negative or scanty). However, the major concern is that rigorous decontamination procedures and strict protocols should be implemented to avoid nosocomial transmission of TB and other infectious agents by contaminated bronchoscopes. The majority of TB burden occurs in developing countries where resources are severely limited. The role of bronchoscopy in TB diagnosis is likely to be limited because of availability, cost, and logistical challenges. Further studies are needed to better define the role of the newer diagnostic and therapeutic bronchoscopic modalities to improve early TB diagnosis and avoid more invasive surgical procedures. The availability of bronchoscopic techniques in reference centers might improve the overall treatment success rate by enhancing the case-detection rate of both drug-sensitive and more complicated drug-resistant TB patients.

Conflicts of interest
There are no conflicts of interest.

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