CHEST

Forbearance With Bronchoscopy
A Review of Gratuitous Indications

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Advanced technologies such as endobronchial ultrasound and electromagnetic navigation have revolutionized the field of bronchoscopy. Its indications as a diagnostic as well as a therapeutic tool continue to expand at a rapid pace. This growth also has led to the emergence of a new subspecialty of interventional pulmonology and more than 40 fellowship training programs. However, with increasing popularity and accessibility, there is a high impetus for performing the procedure when it may be of limited value. On the basis of a literature review and our own experience, we produced a list of conditions for which bronchoscopy is of limited value yet is being performed frequently. Conditions such as idiopathic pulmonary fibrosis, massive hemoptysis, cystic fibrosis, smear-negative pulmonary TB, and stage I sarcoidosis may be approached best in a more prudent fashion, with the bronchoscopic approach reserved for exceptional cases. We present an overview of conditions for which the expectations for bronchoscopy exceed the evidence in the literature, and we coined the term "forbearance with bronchoscopy" for situations in which this popular tool may not be the most appropriate initial approach.

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The bronchoscope initially was introduced as a foreign body retrieval tool; its indications have since expanded.[1] In current practice, both the rigid and the flexible variants are used.[2] Transbronchial biopsy (TBBx) of the lung parenchyma is a procedure commonly performed for a variety of pulmonary diseases. It can be useful in the diagnosis of malignancy (lung or metastatic), infections (TB, nontubercular *Mycobacterium*, fungal, *Cytomegalovirus*, *Pneumocystis jirovecii* pneumonia), rejection in recipients of lung transplants, infiltrates in patients who are immunocompromised, and certain diffuse lung diseases (sarcoidosis, pulmonary alveolar proteinosis, eosinophilic pneumonia, berylliosis, amyloidosis, pulmonary Langerhans cell histiocytosis, hypersensitivity pneumonitis, lymphocytic interstitial pneumonia, and cryptogenic organizing pneumonia).[3]

The field of bronchoscopy has been revolutionized further by the introduction of

ABBREVIATIONS: CD = cluster of differentiation; CF = cystic fibrosis; EBUS = endobronchial ultrasound; FB = flexible bronchoscopy; FM = fibrosing mediastinitis; HRCT = high-resolution CT; IPF = idiopathic pulmonary fibrosis; MDCT = multidetector CT; PN = pulmonary nodule; SN-PTB = smear-negative pulmonary TB; TBBx = transbronchial biopsy; TBNA = transbronchial needle aspiration; TTNA = transthoracic needle aspiration

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endobronchial ultrasound (EBUS) and newer techniques collectively termed "guided bronchoscopy."[4] An ultrathin bronchoscope has been introduced to sample subcentimeter peripheral nodules, and the therapeutic indications for this tool also continue to expand.[5] With the increasing popularity of bronchoscopy, a whole new subspecialty of interventional pulmonology has emerged, and today there are more than 40 programs in North America providing fellowship training, with a list that is ever growing.[6]

Increasing popularity and accessibility occasionally can become an impetus for performing bronchoscopy when it may have a low diagnostic value or therapeutic impact. On the basis of a literature review and our own experience, we produced a list of conditions for which the procedure is of limited value yet is being performed frequently (Table 1). We coined the term "forbearance with bronchoscopy" for such procedures when performed with high expectations but with poor outcomes. We believe that the indication for the procedure should be based strictly on the risk to benefit ratio to improve the patient's welfare and the cost-effectiveness of the procedure.

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease with an average age expectancy < 40 years. Mucous plugging, bronchiectasis, mediastinal lymphadenopathy, and recurrent lower respiratory tract infections are its common manifestations (Fig 1). Studies have recommended a bronchoscopic evaluation to guide antimicrobial therapy during CF exacerbations, and there is some evidence to support this practice.[7] However, less invasive means such as sputum or throat swab cultures also can predict lung colonization with *Pseudomonas aeroginosa* with reasonable accuracy. Aaron et al[8] found that induced sputum was as good as BAL and reserved brushing to characterize genotype and antibiotic susceptibility in chronic *P aeruginosa* infection in patients with CF.

TABLE 1] Diseases for Which Bronchoscopy Is Not the Optimal Diagnostic or Therapeutic Tool

Disease state
Infections 1. Cystic fibrosis 2. Smear-negative pulmonary TB
Hemoptysis
Radiographic findings
1. Atelectasis in patients receiving mechanical ventilation 2. Fibrosing mediastinitis 3. Pulmonary nodules 4. Pleural effusion
Mediastinal lymphadenopathy
1. Idiopathic pulmonary fibrosis 2. Sarcoidosis: stage I 3. Congestive lymphadenopathy 4. Calcified lymphadenopathy 5. Lymphoma 6. COPD exacerbation and lymphadenopathy

Mediastinal lymphadenopathy occurs in at least 52% of patients with CF because of chronic inflammation and is usually progressive, correlating with the severity of the pulmonary disease.[9] CT scanning of the chest is a reasonable tool to follow up interval development with no role for bronchoscopy unless suspicion for malignancy or lymphoma is high.

Bronchoscopy also is performed frequently for the management of hemoptysis in patients with CF. Guidelines on massive hemoptysis state that bronchoscopy is of little value in source localization and time management in this group of patients.[10] However, bronchoscopy can be useful in patients with CF with lobar collapse because dornase alfa can be instilled precisely into the involved bronchopulmonary segment to improve outcomes.[11,12]

TB

Smear-negative pulmonary TB (SN-PTB) is a diagnostic challenge. As many as 50% of patients with active infection may have sputum-detectable SN-PTB.[13] In such cases, using an appropriate diagnostic algorithm becomes essential, especially in resource-limited environments.

Induced sputum was the preferred diagnostic test for SN-PTB until replaced by bronchoscopy. SN-PTB can be diagnosed by using brushing, washings, or postbronchoscopic sputum studies.[14,15] Shin et al[16] found that flexible bronchoscopy (FB) alone had sensitivity, specificity, positive predictive value, and negative predictive value of 75.9%, 97.2%, 95.3%, and 84.3%, respectively.[16] However, these studies compared bronchoscopy with two or fewer induced sputum specimens. Directly resorting to bronchoscopy possibly could have resulted in demonstrating its higher yield.[17] Several studies have shown the yield of three induced sputum specimens to diagnose SN-PTB to be 91% to 99% (Table 2).[18-22] Thus, obtaining at least three induced sputum specimens in patients suspected of

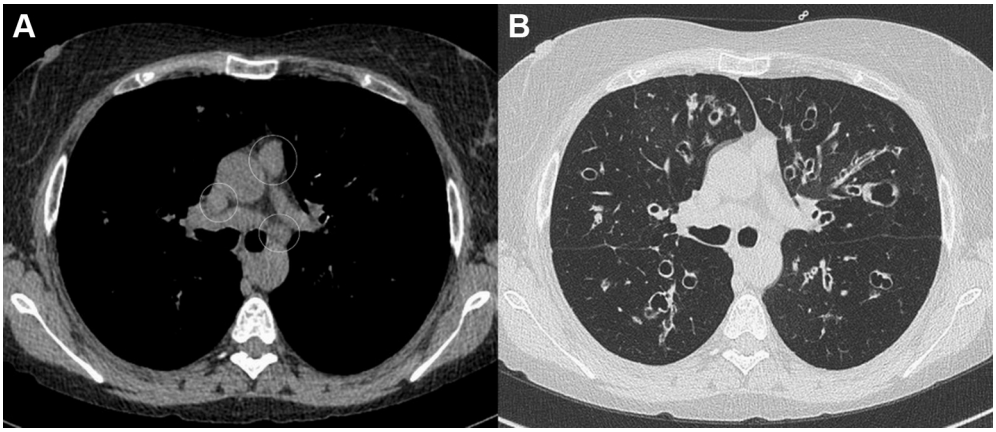

Figure 1 – *A, B, Axial high-resolution CT scans of the chest in a patient with cystic fibrosis revealing mediastinal lymphadenopathy (circled in A).*

having SN-PTB is recommended prior to performing bronchoscopy.

The *Mycobacterium tuberculosis* nucleic acid amplification test has a 95% sensitivity and a 98% positive predictive value in diagnosing TB in patients suspected of having TB.[23] It can reduce the time from specimen collection to treatment (3 vs 14 days, $P < .0001$).[24] The Centers for Disease Control and Prevention recommends carrying out nucleic acid amplification testing in at least one respiratory sample along with an acid-fast bacilli smear to improve diagnostic capabilities.[25]

The Xpert MTB/RIF (*M tuberculosis* DNA and resistance to rifampicin) assay is another highly sensitive and specific test that can detect *M tuberculosis* within 2 hours, making it a good point-of-care testing method. In addition, it has the capability of detecting rifampin (the first-line drug for TB treatment) resistance in respiratory samples.[26] Chakravorty et al[27] developed an Xpert MTB/RIF Ultra assay that has an increased sensitivity and specificity to detect *M tuberculosis* in smear-negative pulmonary samples as well, making it even more accurate. With the increasing utility of these rapid tests, quick and cost-effective decisions to initiate treatment can be made, further bypassing the need for diagnostic bronchoscopy, given that these tests can be performed on respiratory samples from both sputum and BAL with accurate results.

TABLE 2] Studies Comparing Induced Sputum With Bronchoscopy in Smear-Negative Pulmonary TB

Study	Characteristics	Results		
Al Zahrani et al[18]	The combined yield of smear and culture induced sputum was higher with a greater number of samples.	No. of samples	Smear, %	Culture, %
		4	98	100
		3	91	99
		2	81	91
		1	61	74
McWilliams et al[19]	Acid-fast bacilli smears in induced sputum vs BAL	96% (sputum) vs 52% (bronchoscopy)		
Ganguly et al[20]	Acid-fast bacilli smears in induced sputum vs BAL	74% (sputum) vs 58% (BAL)		
Conde et al[21]	Single induced sputum vs bronchoscopy	No significant difference in yield		
Brown et al[22]	Comparison of induced sputum with gastric washing and bronchoscopy in patients who could not induce sputum spontaneously	Induced sputum was more sensitive than was gastric washing. 3 induced sputum vs 3 gastric washing (39% vs 30%; $P = .03$) Use of bronchoscopy and BAL did not increase sensitivity.		

Local anesthesia such as lidocaine can inhibit the growth of *M tuberculosis* organisms.[17,28] A concentration as low as 1 mL of 2% lidocaine is enough to inhibit the growth of *Mycobacterium*.[28] Because administration is operator dependent, an excess of lidocaine may be used during bronchoscopy that could inhibit the organism and lead to a lower yield for bronchoscopy and TBBx. In addition, studies have demonstrated purified protein derivative conversion of up to 11% in pulmonary medicine trainees working in the bronchoscopy unit, suggesting a potential risk of TB transmission to health-care providers in bronchoscopy suites.[29]

In the endemic parts of the world, if the induced sputum specimen remains negative but clinical and imaging suspicion of TB remains high, a trial of anti-TB therapy may be appropriate. The role of bronchoscopy should be limited to patients with consistently negative sputum smears, those not responding to therapy, or those in whom there is a higher suspicion for an alternate diagnosis.[30]

Hemoptysis

The role of rigid bronchoscopy in the management of massive hemoptysis is well established; however, that of either rigid bronchoscopy or FB in diagnosing the source or the cause of mild to moderate hemoptysis is still debatable. The yield of FB in identifying the cause of hemoptysis of any severity with a negative radiograph or CT scan of the chest is only 16% to 21%.[31,32]

In the experience of Hsiao et al[33] with 28 patients with massive hemoptysis localized by means of radiography, bronchoscopy was able to identify the source in 23 patients (82.1%). However, when the radiograph was nonlocalizing, bronchoscopy was able to identify the site in only three patients (10.7%), all of whom had bronchiectasis and none of whom had undergone CT scanning to identify the site.[33]

Multidetector CT (MDCT) scanning has an overall higher sensitivity in localizing the site of hemoptysis than does FB.[34] It can identify the source of hemoptysis in 63% to 100% of patients and is notably superior to bronchoscopy in cases of bronchiectasis, pulmonary infections, and lung cancer.[34] It also has the advantage of visualizing distal airways that may be obscured by bleeding and a sensitivity of 90% in detecting endobronchial lesions (Fig 2).[34]

Poe et al[35] identified that the presence of two of three risk factors for malignancy (Table 3) or hemoptysis of more than 30 mL identified 100% of cases with bronchogenic carcinoma identified with bronchoscopy. This finding suggests that using risk stratification can prevent unnecessary procedures by 28%.[35] Hirshberg et al[36] also found that bronchoscopy was more effective in locating the bleeding site in moderate (64%) and severe (67%) hemoptysis than in mild (49%) hemoptysis. Consequently, the combined use of MDCT scanning and bronchoscopy may increase accuracy in detecting the source of bleeding (93%) compared with CT scanning alone (67%).[36] Nielsen et al[37] found that sensitivity in localizing the source of hemoptysis in patients with lung cancer with

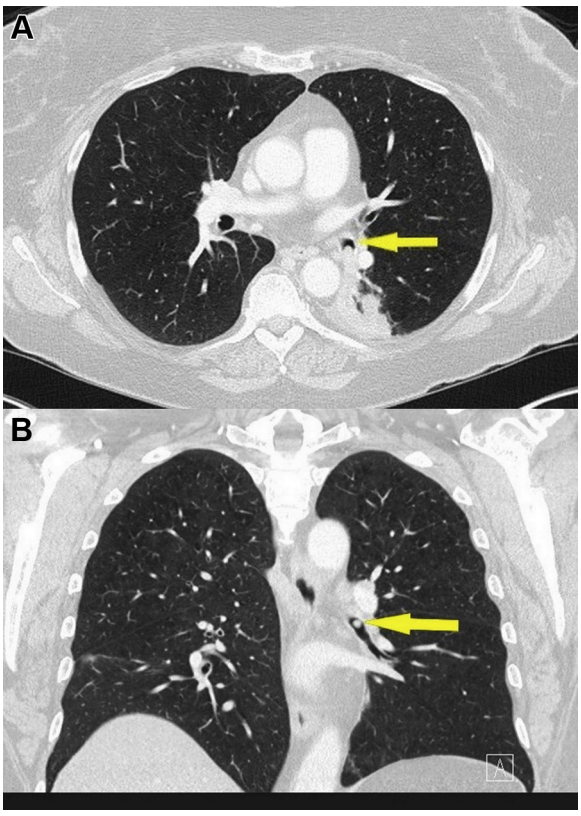

Figure 2 – *Axial (A) and coronal (B) CT scans of the chest revealing left endobronchial lesion (arrows) in a patient with mild, intermittent hemoptysis. Note left lower lobe atelectasis. A carcinoid tumor was diagnosed at the time of curative therapeutic bronchoscopy.*

TABLE 3] Risk Factors Associated With Malignancy and Massive Hemoptysis

High yield of bronchoscopy in hemoptysis if any 2 of the 3 risk factors are present[35]
1. Age > 50 y
2. Male sex
3. Smoking history > 40 pack-years

bronchoscopy was 61%, with CT scanning was 92% ($P < .05$), and with both modalities combined was 97% ($P = .58$); in most cases of hemoptysis from a nonmalignant cause, the diagnosis was established with CT scanning alone.

Thus, the need for bronchoscopy in patients with hemoptysis is based on the severity, preexisting diagnosis, and therapeutic potentials. It should be performed only if MDCT scanning results are unrevealing. Once the source is confirmed, then therapeutic procedures such as the application of cold saline or local vasoconstrictors, balloon tamponade, electrocautery, laser ablation, or stent placement can be considered.

Atelectasis in Patients Receiving Mechanical Ventilation

Atelectasis can be classified based on its pathophysiologic characteristics. It commonly is diagnosed with chest imaging. Its management includes addressing the cause and noninvasive methods such as chest physiotherapy, mechanical percussion therapy, positive end-expiratory pressure support, dornase alfa instillation, and bronchodilators.

The utility of FB as a diagnostic or therapeutic tool for atelectasis in patients receiving mechanical ventilation long has been debated. Radiographic resolution and improvements in oxygenation and static lung compliance can be seen following bronchoscopy.

Bronchoscopy commonly is used to treat atelectasis, most often in the critical care setting. Bronchoscopy is not the cornerstone of therapy for atelectasis; aggressive noninvasive chest physiotherapy can be equally efficacious.[38,39] Prognostically, an air bronchogram portends a delayed response to any therapy for atelectasis.[38,39] Marini et al[38] conducted a randomized study comparing bronchoscopy and noninvasive respiratory therapy among patients with atelectasis receiving mechanical ventilation. Thirty-one subjects were placed into one of two groups, with one group receiving bronchoscopy followed by respiratory therapy and the other group receiving respiratory therapy alone. No difference was observed in the restoration of volume loss between the two groups within first 24 and 48 hours ($P > .20$).[38] Raoof et al[39] also showed that combined kinetic and percussion therapy was a superior modality to conventional treatments and that it obviated the need

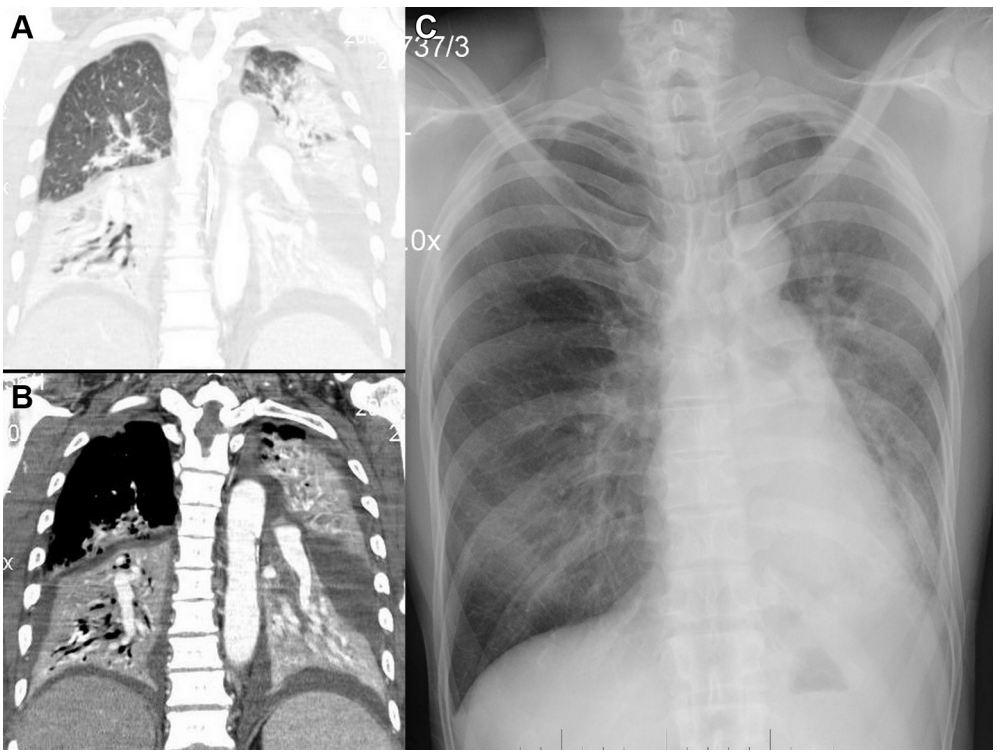

Figure 3 – *Coronal CT scans (A, B) of the chest in a patient in the ICU with bilateral lower lobe and left upper lobe atelectasis with interval resolution of right lower lobe and left upper lobe atelectasis and improvement without resolution of left lower lobe atelectasis shown in a follow-up chest radiograph (C). The patient was treated without bronchoscopy.*

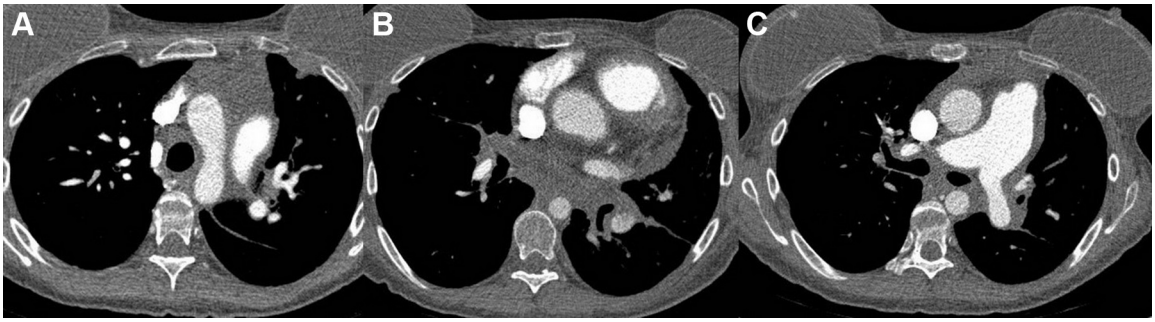

Figure 4 – *A-C, Axial CT scans showing fibrosing mediastinitis with confluent soft tissues in multiple mediastinal and left hilar compartments. Marked narrowing of the left pulmonary artery and complete occlusion of the left inferior pulmonary vein are visible. Flexible bronchoscopy is of little diagnostic value.*

for bronchoscopy in 68% of patients (Fig 3). The current recommendation is to use noninvasive methods to treat atelectasis in patients who are critically ill.[40] FB should be reserved for patients who cannot undergo these treatments because of either chest wall trauma or spinal injury.

Fibrosing Mediastinitis

Fibrosing mediastinitis (FM) is sclerosis of the mediastinum that may occur as an inflammatory sequela of infection such as histoplasmosis or of neoplasms such as lymphoma, sarcoidosis, or an idiopathic process.[41] Exposure to an extrinsic antigen such as fungi may cause a severe inflammatory response and fibrosis.

In severe cases, the fibrotic process may compress mediastinal structures, including the airways, large vessels, and esophagus. Diagnosis is confirmed mainly via CT scanning of the chest. Findings of mediastinal soft-tissue mass, calcification and evidence of collateral vessels from chronic obstruction, peribronchial cuffing, and interlobular septal thickening obviate the need for biopsy (Fig 4).

EBUS transbronchial needle aspiration (TBNA) often is attempted for diagnostic purposes; however, these specimens mostly reveal nonconfirmatory findings of inflammation and fibrosis without organisms.[42] Bronchoscopy also often is used for therapeutic purposes in FM. Airway stent placement and mesh repair have been conducted using a flexible bronchoscope, and it may result temporarily in clinical improvement. However, FM is a metabolically active disease, and self-expanding metallic stents frequently reocclude due to granuloma formation.[43] Destruction of anatomic planes further makes such interventions ineffective, with higher rates of complications such as bleeding due to concomitant collateral vessels and engorgement.[44] The utility of silicone stents in FM also is limited due to a higher incidence of stent migration.[45] Bronchoscopy can be considered cautiously in cases of severe symptomatic disease. However, the operator must be aware of the substantial risk of hemorrhage and should be prepared for it. Spray cryotherapy is a form of noncontact cryotherapy being used for hemoptysis in FM, with a lower rate of recurrent hemoptysis.[46]

Pulmonary Nodules

A large variety of benign and malignant diseases can manifest as pulmonary nodules (PNs) on chest radiographs. A variety of prediction models commonly are used to estimate the risk of a PN's malignancy: Mayo, Brock, Herder, and Veterans Affairs. They all have been validated externally and have some commonalities regarding risk factors for malignancy: older age, current smoking or history of smoking, larger nodule, and history of lung or extrathoracic malignancy.[47]

Biopsy commonly is performed in PNs to establish a diagnosis; however, not all nodules need to be sampled. Besides, there are many sampling modalities to choose from, and the selection depends on the interaction of multiple factors: patient, operator, and institutional specifics. There a variety of bronchoscopic approaches. It is essential to remember that the decision to use a specific diagnostic modality is made on a case-by-case basis. A limited summary of the bronchoscopic modalities, their overall diagnostic accuracy, and factors that may increase diagnostic yield is presented in Table 4.[48-51]

FB often is used to obtain tissue samples from a PN. However, Zhang et al[52] found that the accuracy of

TABLE 4] Bronchoscopic Modalities Used in Assessment of Pulmonary Nodules

Method	Overall Diagnostic Accuracy	Factors That Improve Diagnostic Accuracy (Corresponding Diagnostic Accuracy)
Transbronchial biopsy	28%-80%[49]	- Size > 2 cm[49] - Lesions not located in the periphery - Presence of bronchus sign
Radial probe EBUS (with use of extended working channel or guide sheath)	69%[50]	- Size > 5.1 cm (88%)[50] - Concentric view (84%)[50]
Convex probe EBUS	87%[51]	- Size > 2 cm[51] - Use of rapid on-site cytology[51] - Distal lesions in which the bronchoscope can be wedged into place for stabilization[51] - Neoplastic lesions (95.3%)[51]
Virtual bronchoscopic navigation	72%-74%[49]	- Lesions > 2 cm - Newer technology such as bronchoscopic transparenchymal nodule access system (Archimedes System, Broncus Medical) (100%)[49]
Electromagnetic navigation bronchoscopy	67%[48]	- Bronchus sign - Upper lobe location - Size < 3 cm
Ultrathin bronchoscopy	57%-70%[49]	- Use in combination with radial probe EBUS (69%)

EBUS = endobronchial ultrasound.

conventional bronchoscopy in the preoperative workup for PNs was only 24.3%, with a negative predictive value of only 20.5%. This finding suggests that conventional bronchoscopy should be used carefully in the evaluation of peripheral nodules in the age of high-value and cost-effective care.

The advent of newer technologies, including radial probe EBUS, virtual bronchoscopy, and electromagnetic navigation bronchoscopy, has resulted in increased use of bronchoscopy in the evaluation of PN. Some studies have shown that the procedure guided by these tools has a higher diagnostic yield for PNs.[53-55] A meta-analysis found the pooled diagnostic yield to be 70%.[48] However, most studies looking at electromagnetic navigation bronchoscopy were uncontrolled, and further randomized trials are needed.

Despite the advancement in bronchoscopy, its diagnostic yield remains inferior to that of transthoracic needle aspiration (TTNA). A meta-analysis of 48 studies showed a pooled diagnostic accuracy of 92.1% for CT scanning-guided TTNA and 88.7% for ultrasound-guided TTNA.[56] TTNA remains the diagnostic modality of choice for small peripheral lesions if the patient can sustain the risk of pneumothorax. If the tools for guided bronchoscopy are unavailable, FB should be reserved for large (> 2 cm in diameter), centrally located lesions that have a positive bronchus sign and for which the certainty of the yield would justify the procedure.

Isolated Pleural Effusion

More than 1.5 million people in the United States develop a pleural effusion each year.[57] The list of benign and malignant causes of a pleural effusion is exhaustive. Up to 27% of pleural effusions are due to malignancy.[58] Breast cancer and lung cancer account for more than one-half of all malignant pleural effusions.[59] At times, the initial radiographic manifestation of pleural effusion might be accompanied by lung nodules or masses. In such scenarios, the risk of malignancy is always in question, and the most pragmatic approach would be to analyze the pleural fluid for malignant cells. Pleural cytology test results are positive for malignant cells in 60% of cases.[60] Complete or near complete opacification of a hemithorax could be due to a large degree of atelectasis caused by an endobronchial obstruction or a large pleural effusion. Plain chest radiography (mediastinal shift), point-of-care lung ultrasound, or airway examination via bronchoscopy is useful in determining the cause. In such a scenario, FB may be of great utility for both diagnostic and therapeutic purposes.

In most cases of isolated pleural effusion, there is no role for bronchoscopy. The diagnostic workup

largely is centered on the results of the pleural fluid analysis.

Idiopathic Pulmonary Fibrosis

The condition of idiopathic pulmonary fibrosis (IPF) can be diagnosed by means of either high-resolution CT (HRCT) scanning or open lung biopsy. At HRCT scanning, IPF is diagnosed by exclusion of other diseases and typical findings of usual interstitial pneumonia. According to revised American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association guidelines, lung biopsy is not required in patients with no environmental exposure, connective tissue disease, or drug toxicities and definite usual interstitial pneumonia diagnosed on the basis of HRCT scanning findings.[61-63] In this regard, the value of TBBx performed via FB is limited. To our knowledge, the role of cryobiopsy in establishing the diagnosis of IPF still remains to be studied. BAL also may be performed to help differentiate IPF from other fibrotic lung diseases (sarcoidosis, hypersensitivity pneumonitis, nonspecific interstitial pneumonitis, and interstitial lung disease related to connective tissue disease). BAL demonstrating lymphocytosis (> 30%) is postulated to suggest a non-IPF diagnosis in a patient with radiographically visible fibrotic lung disease.[64] The clinical utility of this finding is still under debate.[64,65]

In patients with IPF, bronchoscopy often is performed to assess mediastinal lymphadenopathy, which is a common finding seen in approximately 60% of cases.[66] The size and the number of enlarged lymph nodes directly correlate with the severity of the IPF.[67] This lymphadenopathy is usually a sequela of chronic inflammation and not a concurrent infection or neoplasm. Bronchoscopy should be avoided under such circumstances unless there is a high suspicion of malignancy (Fig 5).

Bronchoscopy also is performed in patients with IPF presenting with acute respiratory failure. Diffuse alveolar hemorrhage, infections, and acute exacerbation of interstitial lung disease are the common causes of such a presentation. Bronchoscopy is of low diagnostic yield in assessing the cause of respiratory failure under such circumstances. Bronchoscopy is of any therapeutic impact in < 25% of patients, and there is no mortality difference between those with and those without positive findings at bronchoscopy.[68] Besides, the procedure is associated with high rate of complications (25%).[68] BAL also leads to increased risk in patients with acute exacerbation of interstitial lung disease.[69] FB might be

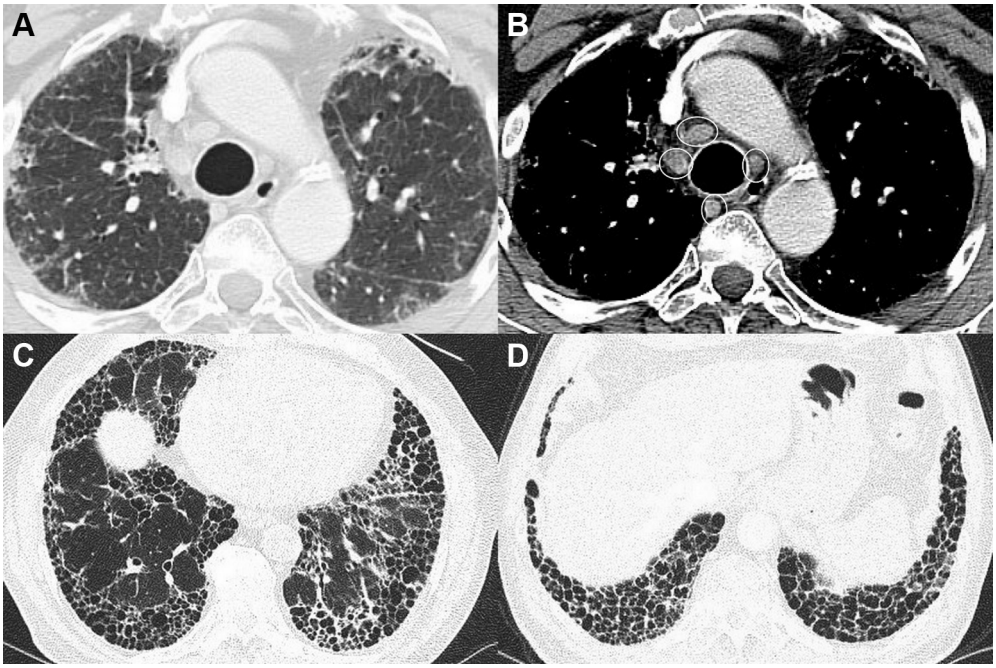

Figure 5 – *A-D, Axial high-resolution CT scans showing typical usual interstitial pneumonia with honeycombing or multilayered cysts with peripheral, subpleural, and basilar predominance (C, D) along with mediastinal lymphadenopathy (circled in B).*

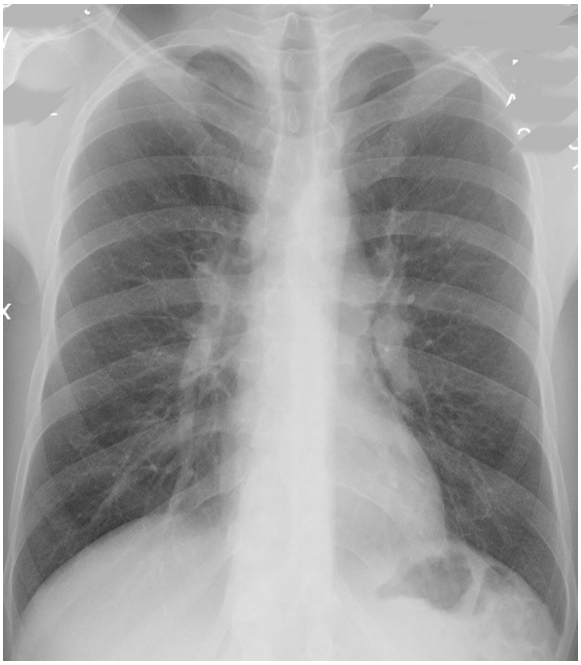

Figure 6 – *Chest radiograph showing bilateral symmetric hilar lymphadenopathy in a patient with stage I sarcoidosis. In most instances, tissue diagnosis is not mandatory.*

of diagnostic value in patients who are receiving immunosuppressive regimens or who have clinical concerns about diffuse alveolar hemorrhage; however, meticulous patient selection is essential.[70]

Stage I Sarcoidosis

Sarcoidosis is a granulomatous disorder that commonly manifests as bilateral hilar adenopathy and pulmonary reticular opacities. More than one-half of all patients with active disease receive the diagnosis at stage I when spontaneous resolution is common.

A tissue diagnosis is not necessary for most patients with stage I sarcoidosis.[71] The risk of missing a more sinister diagnosis such as lymphoma is a common counterargument in favor of tissue sampling. Several studies have proven that the lack of symptoms and clinical findings have a strong negative predictive value against a malignant process in patients with radiographic evidence of bilateral hilar adenopathy.[72] Statistical models that account for the incidence of sarcoidosis estimate that the likelihood of finding an alternative diagnosis via invasive biopsy in a patient with stage I sarcoidosis is 5 in 10,000 (Fig 6).[73]

BAL often is performed to differentiate between sarcoidosis and hypersensitivity pneumonitis, favoring performance of FB. The most frequently assessed parameters in this scenario are the cell counts and proportions of lymphocyte subpopulations; a high ratio of cluster of differentiation (CD)4 to CD8 point toward sarcoidosis. In a study of 562 patients who underwent BAL for the evaluation of interstitial lung disease, both IPF and sarcoidosis had ratios of CD4 to CD8 > 1.0.[74] In another study, the lymphocyte subset ratio was assessed in patients with clinical and histologic evidence of sarcoidosis. The ratio of CD4 to CD8 of < 1 was found in less than 12% of patients.[75] However, the diagnostic value of the BAL lymphocyte subset ratio also is modified by the radiographic stage of sarcoidosis and the patient's smoking status. In summary, BAL with an elevated ratio of CD4 to CD8 should be used in context with the clinicoradiologic picture and should not form the sole basis for diagnosing sarcoidosis.

Although many centers rely on TBNA for diagnosing sarcoidosis, the data behind its use must be analyzed carefully. Early EBUS-TBNA studies used a patient population that was rich with sarcoidosis. More than 90% of patients in these studies received a final diagnosis of sarcoidosis.[76] A majority of sarcoidosis studies also originated from tertiary medical centers flush with highly skilled operators and experienced pathologists. EBUS-TBNA performed in a less experienced center yielded a nondiagnostic rate of 73%.[77] Also, most EBUS-TBNA studies have never defined the entry criteria for patient selection, thereby limiting the generalizability of the results.

The presence of a noncaseating granuloma is an essential piece of information used to diagnose sarcoidosis. However, it is not an all-or-nothing finding. Although conventional and advanced bronchoscopic methods are available for sampling purposes, the priority should be pursuing the least invasive approach. In patients who may have stage I sarcoidosis, this may be as simple as taking a careful history and performing a thorough physical examination. In summary, the clinical acumen of the operator is paramount in estimating any potential benefit of bronchoscopy in this patient population.

Congestive Lymphadenopathy

More than five million people in the United States and an estimated 23 million people worldwide have congestive heart failure.[78,79] Mediastinal lymphadenopathy is not an uncommon finding in patients with congestive heart failure and often is referred to as "congestive adenopathy." To our

knowledge, it was first reported in the literature in 1998 and can be found in 54% to 68% of patients with congestive heart failure.[80,81] Congestive lymphadenopathy is common in patients with acute uncompensated congestive heart failure without diastolic dysfunction and in patients with coronary artery disease without heart failure.[82] It is a maker of volume overload, not of systolic dysfunction. Occasionally, mediastinal lymphadenopathy is found among patients with uncorrected congenital heart disease. Similarly, up to 18% of patients with PAH can have mediastinal lymphadenopathy.[83] This adenopathy often resolves with appropriate treatment. Keeping in mind the clinical context and nonmalignant nature of mediastinal lymphadenopathy, an attempt to obtain tissue in such cases would be of low diagnostic value. If there is a doubt, repeat chest CT scanning should be performed to assess for regression in the size of the lymph nodes once the patient has been deemed euvolemic (Fig 7).

Calcified Lymph Nodes

Calcified mediastinal lymph nodes have a broad differential diagnosis.[84] Often, they are noted as incidental findings at chest imaging. There are limited data regarding the effects of calcification on the yield of EBUS-TBNA. In a study of 236 patients who underwent EBUS-TBNA, lymph node calcification was a factor that contributed to inadequate sampling or a false-negative result.[85] However, Shweihat et al[80] demonstrated that in patients living in a histoplasmosis endemic area, the presence of calcification does not affect the yield of EBUS-TBNA. At present, sampling a calcified mediastinal lymph node via EBUS-TBNA should be caveat emptor for any bronchoscopist (Fig 8, Table 5).

Lymphoma

Mediastinal lymphadenopathy is a common manifestation of all types of lymphoma. EBUS-TBNA is a valuable tool to identify several causes of mediastinal lymphadenopathy. However, its role in diagnosing lymphoma, particularly Hodgkin lymphoma, remains controversial.[86] Small sample size limits confirmation of lymph node architecture, Reed-Sternberg cells, extent of sclerosis, and extent of any granulomatous component, all of which are essential to confirm and plan the therapy for the condition. This difficulty may lead to a high discordance between the cytologic findings at EBUS-TBNA and histopathologic data obtained by more

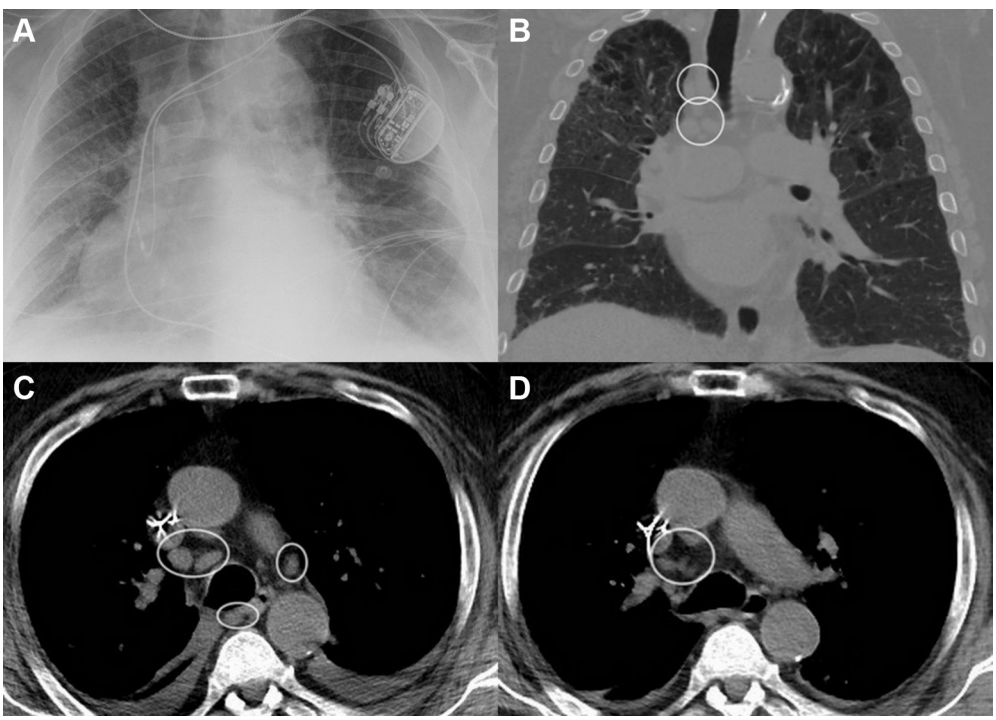

Figure 7 – *A, Chest radiograph of a patient with acute exacerbation of heart failure. Coronal (B) and axial (C, D) CT scans showing congestive lymphadenopathy in a case of acute exacerbation of heart failure (circles in B and C), with resolution after treatment with diuretics (circle in D). Note pacemaker (A).*

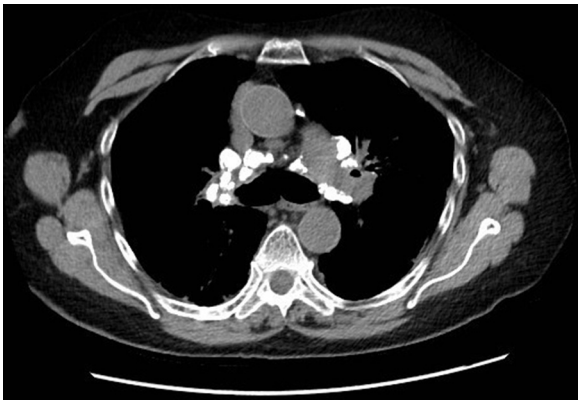

Figure 8 – *Axial CT scan showing dense lymph node calcifications in bilateral, symmetric hilar and multiple mediastinal compartments in a patient with sarcoidosis.*

invasive means. In other words, among patients with a high likelihood of having Hodgkin disease, EBUS-TBNA may not be the ideal diagnostic test.

Several studies have shown high sensitivity and specificity of EBUS-TBNA for lymphomas.[87] However, most of the results have been for recurrent disease or in cases of non-Hodgkin lymphomas and ultimately required confirmation with mediastinoscopy or surgical biopsy.[88] EBUS-TBNA has a sensitivity of only 61% to 78% for newly diagnosed non-Hodgkin lymphoma.[89,90]

Immunohistochemical and flow cytometric assessment of TBBx specimens is important because these assessments determine the type of treatment required for patients with lymphoma. Patients suspected of having lymphoma for the first time ultimately require surgical biopsy to characterize the type of lymphoma further. In addition, the yield of TBBx in diagnosing lymphoma may differ significantly in different studies because of the availability of rapid on-site microscopic examination, which may not be available at all institutions.[91] The utility of 19-guage needle significantly increases the yield in lung malignancy but still falls short for diagnosing Hodgkin lymphoma because subsequent mediastinoscopy is required for further subtyping.[92] Studies also have demonstrated increased blood contamination of the sample with larger needles.[93] EBUS-TBNA could be reserved for recurrent lymphomas or in selected cases of high suspicion for non-Hodgkin lymphomas.[94]

Lymphadenopathy and Acute Exacerbation of COPD

Approximately one-half of the patients with COPD demonstrate mediastinal lymphadenopathy on a CT scan of the chest.[95] It is more frequent with heavy smoking, chronic bronchitis, and bronchial wall thickening. Performing an invasive procedure without suspicion for an alternate diagnosis can be detrimental. There is increased risk of hypoxemia with bronchoscopy in patients with COPD and pulmonary hypertension. Towe et al[96] found that BAL in patients with severe COPD is associated with increased risk of pneumothorax, bleeding, respiratory failure, and pneumonia (OR, 6.49; 95% CI, 1.68-24.3; $P < .006$). BAL may cause airway obstruction and disequilibration of the pressure of intraalveolar gases and, as a result, leakage into the pleural cavity, leading to pneumothorax.[97] Studies have shown that clinical presentation with self-reported sputum purulence and multiple exacerbations (> 4 in a year) and severe airway obstruction correlates well with distal airway bacterial infection.[98] There is no indication for bronchoscopy to document lower respiratory tract infection among patients presenting with acute exacerbation of COPD.

Contraindications for Bronchoscopy

As with any procedure, there are absolute and relative contraindications to FB. Overall, bronchoscopy is a safe

TABLE 5] Causes of Calcified Mediastinal Lymphadenopathy

Cause	Common	Uncommon
Infectious	TB Histoplasmosis	*Pneumocystis jirovecii* pneumonia
Noninfectious	Sarcoidosis Silicosis	Amyloidosis Scleroderma
Neoplastic	Treated lymphoma	Thyroid carcinoma Osteogenic sarcoma Bronchial carcinoid tumors Mucinous ovarian cystadenoma Mucinous colonic adenocarcinoma

procedure, and most contraindications are relative. The most crucial physiologic contraindication is the inability to provide adequate oxygenation to the patient during the procedure. The combination of sedation and partial blockage of the airway with the bronchoscope itself can impede oxygenation. Another major contraindication is either endogenous or iatrogenic coagulopathy.[99] Increased intracranial pressure also is considered a contraindication to the procedure.

A discussion of risk vs benefit always should be considered prior to performing the procedure. It is mandatory that the procedure be performed by an experienced bronchoscopist or under his or her supervision.

Summary

FB is a relatively safe procedure, yet like other invasive procedures, the ability to perform should not translate into the necessity to perform. It can be considered in clinical scenarios in which a high diagnostic yield is anticipated. Alternative modalities of investigation should be sought when the pretest probability of diagnostic yield from bronchoscopy is low. The operator should be well versed with indications, contraindications, diagnostic yield alternatives, and the relative cost of the procedure. Vascular endothelial growth factor D is a biomarker that is emerging as a promising diagnostic tool for lymphangioleiomyomatosis, a destructive lung disease.[100,101] Several biomarkers are currently under study to detect various types of rejection in patients with lung transplants. Cylex Immune Cell Function Assay (ImmuKnow; Cylex, Inc) was approved by the Food and Drug Administration and is being studied for use in lung transplant rejections.[102]

The utility of these biomarkers as a first-line investigation will increase exponentially for better classifying phenotypes and diagnosing several diseases, such as lymphangioleiomyomatosis and acute rejection in lung transplant. However, bronchoscopy and TBBx remain standard practice because of their high yield.

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