Flexible Bronchoscopy

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KEYWORDS

• Flexible bronchoscopy • Bronchoalveolar lavage • Transbronchial lung biopsy
• Transbronchial needle aspiration • Bronchial brush

KEY POINTS

- Despite rapid advancements in technology and applications in flexible bronchoscopy, core procedures remain a critical role in the diagnosis of bronchopulmonary diseases.
- Core procedures include as bronchoalveolar lavage, transbronchial lung biopsy, and transbronchial needle aspiration.
- It is essential that pulmonary trainees continue to train and gain proficiency in the core bronchoscopic procedures.
- All bronchoscopists should be fully aware of the indications, contraindications, risks, and diagnostic value of the procedures they perform.
- The indications for both diagnostic and therapeutic flexible bronchoscopy are continually expanding in parallel with technological advances.

INTRODUCTION

As we approach the 50th anniversary of the first commercially available flexible bronchoscope, it is difficult to imagine diagnosing and treating diseases of the lungs and bronchi without this valuable tool. In addition to allowing complete visualization of the airways to the subsegmental level, various biopsy and therapeutic instruments have been developed for the diagnosis and treatment of pulmonary diseases, often with only moderate sedation. This article briefly discusses the development and history of the flexible bronchoscope and its accessory instruments, as well as the technical aspects of conventional biopsy tools, and concludes with discussion of the indications, contraindications, and complications associated with the flexible bronchoscopic procedures. Although we reference some of the more advanced tools used in flexible bronchoscopy, these are covered in detail in other articles in this issue; this article focuses exclusively on conventional flexible bronchoscopy.

HISTORY OF FLEXIBLE BRONCHOSCOPY

The Japanese thoracic surgeon Shigeto Ikeda developed the first flexible fiberoptic bronchoscope in the 1960s, revolutionizing pulmonary medicine.[1–3] However, years of previous scientific advancements were necessary to reach this point. The concept of total internal reflection or "bending light" was first described in 1854 by John Tyndall, who demonstrated that, by shining a light into a

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tank of water attached to an open-ended pipe, the light would follow the arc of water as it fell from the pipe. In 1888, a team of physicians in Austria were the first to incorporate this concept into medical care when they developed bent glass rods for illuminating body cavities. In the 1920s and 1930s, multiple separate groups independently realized that, in addition to simple light transmission, images could also be transmitted through glass fiber bundles.[4] In 1954, physicists Hopkins and Kapany developed the first prototype flexible endoscope using fiberoptic bundles.[5] In 1958, Hirscowitz patented a flexible gastroscope to visualize the stomach.[6,7] In the early 1960s, Dr Ikeda, who was already experimenting with fiberoptic rigid telescopes, approached the Machida Endoscope CO, and the Olympus Optical Company with his vision for the first flexible fiberoptic bronchoscope. In 1964, Dr Ikeda presented the first prototype flexible bronchoscope at the "IX International Congress of Diseases of the Chest" in Copenhagen, Denmark.[1] Although this early rendering had major limitations, including an inability to bend or direct the distal tip, and did not include a working channel, the clinical importance of the flexible bronchoscope was readily apparent to the society; his presentation was published in *The New York Times* shortly after the conference concluded. The first commercially available flexible bronchoscope, which allowed angulation of the distal tip, manufactured by Machida Company, was commercialized in 1968. This development was quickly followed by an Olympus bronchoscope that included a working channel for suction or passage of instruments.[1–3] Over the next few years, rapid improvements in image quality, flexibility, and angulation followed, and by the mid-1970s the flexible fiberoptic bronchoscope was being commonly used worldwide. A major advance occurred when Asahi Optical Company (later renamed Pentax Corporation), using the technology from video camcorders, could replace the flexible fiberoptic bundle system with a miniaturized charge-coupled device integrated into the distal tip of a bronchoscope, creating high-quality video images that could be viewed on a large screen rather than just through an eyepiece.[1,8,9] As charge-coupled device technology progressed, newer generations of bronchoscopes with improved image quality and smaller footprints continue to be developed. Despite the advancements in video technology the fiberoptic technology used by Dr Ikeda has maintained its relevance in the form of hybrid bronchoscopes, which combine the minimal space requirements of the fiberoptic bundles with the superior video quality of the charge-coupled device chip allowing the development of a new generation of "ultrathin" bronchoscopes.

The flexible bronchoscope opened a new era in bronchoscopy and, in the decades since its initial commercial release, there have been numerous innovations that have expanded the field of pulmonary medicine. Some of these innovations were originally used in rigid bronchoscopy, but were not widely adopted because of the limitations of reach and flexibility intrinsic to rigid instruments. One of the most important innovations in flexible bronchoscopy was in 1974 when Reynolds and Newball[10] first introduced bronchoalveolar lavage (BAL). This innovation allowed bronchoscopists to obtain material from the lower respiratory tract to aid in the diagnosis of infectious, inflammatory, and malignant disease, while additionally influencing the understanding of the cellular response to diseases of the lung. Although transbronchial lung biopsy (TBLB) using a rigid bronchoscope had been used at selected centers for several years before the invention of the flexible bronchoscope, the inability to reach lesions with precision, particularly in the upper lobes, limited its clinical usefulness.[11,12] Dr Ikeda recognized the potential of the flexible bronchoscope in the diagnosis of malignancy and specifically designed the original commercially available bronchoscope with this in mind. The original forceps were rudimentary; however, as the design of the flexible forceps evolved, TBLB became a standard procedure easily learned and performed by the general pulmonologist.[13–15] Transbronchial needle aspiration (TBNA), also originally developed for rigid bronchoscopy by Schiepatti in 1948, had the same limitations as rigid TBLB and was uncommonly performed.[16,17] Kato Oho first developed a needle that could be used through the flexible bronchoscope for the aspiration of paratracheal pathology in 1979, 1 year after Ko-Pen Wang first demonstrated the technique of mediastinal TBNA with the use of the rigid bronchoscope. These monumental achievements forever expanded the role of the bronchoscopist beyond disease of the airways, and were an essential step in the development of modern linear endobronchial ultrasound (EBUS) imaging.[18–20]

Numerous advanced modalities have been developed, expanding the role of the bronchoscopist for both diagnosing and treating diseases of the airways and lungs. In 1979, 2 independent discoveries proved that the flexible bronchoscope could be used for more than just biopsying suspect malignancy. Doiron and colleagues[21,22] expanded the role of bronchoscopy in the detection of early airway malignancies by introducing fluorescence bronchoscopy, and Toty

and colleagues[23] first published their experience using Nd:YAG laser fibers inserted through the working channel of the fiberoptic bronchoscope to treat tracheobronchial obstruction. Future diagnostic developments have included, among others, narrow band imaging, confocal microscopy, optical coherence tomography, EBUS imaging, and electromagnetic navigation.[24–29] Important therapeutic developments that followed include photodynamic therapy, endobronchial brachytherapy, cryotherapy, endobronchial valve insertion, bronchial thermoplasty, and contact and noncontact electrocautery.[30–35] Although these and other advanced bronchoscopic techniques are beyond the scope of this topic and are reviewed elsewhere in this issue, they must be mentioned as further evidence of the ongoing evolution in pulmonary practice that began with the development of flexible bronchoscopy.

CONVENTIONAL DIAGNOSTIC TOOLS AND TECHNIQUES IN FLEXIBLE BRONCHOSCOPY

There are multiple modalities available via flexible bronchoscopy for specimen acquisition in suspected infection, as well as benign and malignant disorders of the bronchi and lungs. We discuss the most commonly used modalities in further detail. Bronchial washings, BAL, brushing, and TBNA can provide cytologic material, whereas forceps biopsies, core needles, and cryobiopsy can provide histologic samples, and microbiological testing can be obtained from any of these sampling techniques. Although certain instruments are more likely to obtain diagnostic material in particular scenarios, the use of multiple modalities has been shown to improve overall diagnostic yield and is recommended whenever possible.[36–39]

Bronchial Washings, Bronchial Brushing, and Endobronchial Biopsy

Visually identified abnormalities within the airways concerning for malignancy, infection, or inflammatory disorders are typically evaluated with endobronchial brushings, biopsies, and/or bronchial washings.[36,38] Bronchial washings are obtained by instillation and subsequent recapture of saline into a specimen trap via suction and are most commonly used for microbiological evaluation of central airway secretions suggestive of infection. Although central airway lavage can provide useful information when a dominant pathogen or resistant organism is identified, one must recognize that this is not equivalent to a true BAL and contamination with nonpathologic organisms is expected and not necessarily indicative of a true pathogen.[37,39]

Bronchial brushing is an effective tool for obtaining exfoliative cytologic specimens, especially in infiltrative mucosal disease. Sheathed and unsheathed brushes are available, although the sheathed instrument is more commonly used.[40,41] The protected specimen brush is a sheathed brush with a biodegradable plug at the distal tip that protects from brush contamination when evaluating for infectious diseases.[42] For endobronchial brushing, the sheathed brush is typically introduced through the working channel within the protective sheath and directed toward the patent portion of the target airway, at which point the assistant extends the brush outside of the sheath. The brush is then vigorously moved back and forth across the area of interest while simultaneously spinning the brush. Once brushing is completed, it is retracted into the sheath before withdrawing the device into the working channel to prevent scope damage. In a recent prospective study, brushing performed before endobronchial forceps biopsy significantly increased the diagnostic yield compared with brushing after biopsy.[43] The overall diagnostic yield of brushing for malignancy in visible endobronchial lesions is around 60% to 90%.[36,38,39]

Endobronchial forceps biopsy is performed by advancing the closed forceps' through the working channel and aiming the tip near the target site. The assistant then opens the forceps and the bronchoscopist advances the open jaws onto the lesion before the assistant closes the forceps. The bronchoscopist then retracts the sample. It is important to not extend the forceps too far out of the bronchoscope, because this reduces leverage, and therefore reduces the size of the sample. When a lesion is tangential to the airway, sampling can be challenging because the forceps can easily slip off the lesion while attempting to close the jaws. It is often more effective to place the open forceps within the lumen, parallel to the lesion, and then flex the tip into the lesion rather than pushing distally toward the lesion. The needle forceps can also be useful in these tangential lesions, because the needle can anchor into the lesion to prevent the forceps from slipping when the jaws are closed. In multiple studies, the diagnostic yield of endobronchial biopsy for visible endobronchial tumors is at least 70%.[37,38,44,45]

Bronchoalveolar Lavage

BAL, occasionally referred to as "liquid lung biopsy," is used to obtain cytologic material from distal airways and alveoli. In BAL, the bronchoscope

is wedged into a selected bronchus in the fourth- or fifth-generation airways, at which point serial aliquots of 30 to 60 mL of sterile saline are instilled via the working channel of the bronchoscope into the distal lung segments and subsequent suction is applied to recapture the instilled fluid along with contents from the lower respiratory tract.[46] The method and sequence of performing a BAL is not standardized and multiple protocols exist.[46] Suction can be performed with an inline specimen trap or with hand suctioning from the same syringe used to instill the saline. Although the optimal volume of infused saline is unknown, previous work demonstrated that instilled volume of less than 120 mL, yield inconsistent results.[47,48] In addition to the volume instilled, the volume returned also effects the adequacy of the sample and at least 30% of instilled volume is necessary to obtain adequate alveolar sampling.[46,49] The indication for BAL often dictates the sequence of procedures performed. For diagnosis of diffuse lung disease, BAL should be the first procedure performed, before other biopsy techniques to minimize blood contamination. In suspected malignancy, the primary goal is to obtain as much diagnostic material as possible, performing lavage after biopsy to increase capture of residual tumor elements. That being said, there is really a paucity of data with regard to the effect of sequence. In diffuse lung disease many recommend disposing of initial 20 to 30 mL of aspirated fluid to avoid contamination because this has been shown to contain mostly cells and proteins from the bronchial surfaces and not alveolar contents.[50] Again, this would be of less importance and potentially decrease diagnostic yield in malignancy. For diffuse lung disease, lavage is most commonly performed in the gravity-dependent areas such as the right middle lobe or lingula to maximize return, whereas in suspected localized infection of malignancy the target segment depends on the radiographic area of concern.[10] Risks of BAL are extremely low, with hypoxemia being the most common.[51] Low-grade fevers within the first 24 hours after lavage can occur in up to one-third of patients, likely related to induced cytokine activity, and typically do not represent actual infection.[52] Additionally, emergency department and hospital providers might be unaware that transient radiographic abnormalities are expected because of retained saline. Counseling the patient before bronchoscopy is suggested.

BAL is most commonly performed for suspected pulmonary infections. The diagnostic yield of BAL for bacterial infection is typically greater than 70%, although it is slightly higher in ventilator-associated infections.[53] Bronchoscopy is especially useful in the care of the immunocompromised host and has been shown to identify organisms or resistance patterns not covered by current therapy and hence altering management in 40% of patients.[54] In immunocompromised patients, BAL detection rates of infectious agents varies widely between studies with quoted rates ranging between 20% and 60%. With the addition of newer microbiological methods such as galactomannan antigen, beta-D-glucan, and polymerase chain reaction testing for opportunistic organisms such as *Pneumocystis jirovecii*, *Aspergillus*, and viral pathogens, BAL has become an even more effective tool in the evaluation of pulmonary infections.[55,56] For the diagnosis of *Mycobacterium tuberculosis*, BAL smear and culture detects approximately 75% of cases; however, the addition of *M tuberculosis*–specific nucleic acid amplification tests has resulted in even higher detection rates.[57]

BAL is also commonly used in the evaluation of patients with diffuse parenchymal lung disease. In slowly progressive disorders, it is primarily used to exclude infectious etiologies that might mimic interstitial lung disease. It is far more useful in the assessment of patients with acute or subacute development of diffuse lung disease, such as in acute and chronic eosinophilic pneumonias, and alveolar proteinosis.[58,59] An elevated T-lymphocyte $CD4^+/CD8^+$ ratio in BAL fluid has historically been considered suggestive of sarcoidosis and a reduced ratio suggestive of hypersensitivity pneumonitis. More recent investigations however have shown that $CD4^+/CD8^+$ ratio can be quite variable and current recommendations are that testing should not be routinely performed. However, a very high ratio—greater than 4:1—with BAL lymphocytosis is still considered to be suggestive of sarcoidosis.[46]

BAL is commonly used as an adjunct to other bronchoscopic sampling modalities for the diagnosis of malignancy. As an independent test, the diagnostic yield for peripheral cancers is less than 50% in most studies.[60,61] The diagnostic yield, however, is greater than 80% in lymphangitic carcinomatosis.[62] The additive usefulness of BAL to standard biopsy techniques in the diagnosis of solid malignancies is modest at best. Two recent studies, each containing more than 200 patients with suspected thoracic malignancy, found that when other conventional biopsy tools were used, only a single case of cancer would have been missed in the absence of BAL.[63,64]

Transbronchial Lung Biopsy

TBLB is a commonly used tool for obtaining histologic tissue in the diagnosis of malignancy, diffuse lung diseases, and infection. In TBLB, flexible

forceps are advanced into the lung parenchyma or a localized lesion outside of the visual field of the bronchoscope to obtain histologic material. The most common complications associated with TBLB include pneumothorax and bleeding.[65] The incidence of pneumothorax depends on multiple factors to include with TBLB is type of forceps, use of mechanical ventilation, presence of surrounding emphysema, location of the lesion, operator experience, type of forceps, number of samples taken, and fluoroscopic guidance.[66] The rate of pneumothorax ranges between 1% and 5% in the general population, but is higher in the presence of the risk factors discussed.[67,68] TBLB can generally be performed under moderate sedation in a standard bronchoscopy suite with or without a fluoroscopy. The typical technique for TBLB is to advance the bronchoscope into a wedged position within the target airway and to advance the closed forceps into the target segment. If fluoroscopy is used, it should be activated when the tip of the forceps exits the working channel. The closed forceps are then advanced until gentle resistance is met and then pulled back 1 to 2 cm, at which point the forceps are opened and then advanced until resistance is reencountered, at which point the forceps are closed and retracted. If using fluoroscopy, one should watch the visceral pleural line closely while retracting the closed forceps. If the visceral pleura "tents," retraction should be stopped, while simultaneously opening the forceps, to avoid development of pneumothorax. If fluoroscopy is not used, the development of acute chest pain by the patient should be used as a marker of possible pleural retraction and the same steps applied. The general indications for the use of fluoroscopy are to localize a biopsy target in focal disease, for the prevention and detection of pneumothorax, and in localized disease processes. After biopsy, the bronchoscope is kept wedged with several biopsies performed in rapid succession. After biopsies are completed, the bronchoscope should remain in the wedged position for at least 1 minute before it is slowly retracted.[69] If continued bleeding is encountered, the bronchoscope should be rewedged to allow clot to for an additional 4 to 5 minutes. Fluoroscopy is recommended in the evaluation of focal lung disease and has been shown to improved diagnostic yield.[70] The need for fluoroscopy in the setting of diffuse interstitial lung disease is more controversial. In a 2002 survey of bronchoscopists in the UK, 57% of respondents never used fluoroscopy for transbronchial biopsy and 24% only use it occasionally.[71] In contrast a survey from Canada published in 2011, 68% of respondents reported using fluoroscopy at least some of the time for TBLB in diffuse lung disease.[72] The literature, however, has not found a significant difference in either diagnostic yield or complication rate improved safety with the use of fluoroscopy in the diagnosis of diffuse lung disease.[73–75]

TBLB in the examination of infectious etiologies of the lung provided significant increase in diagnostic yield compared with BAL alone.[76,77] However, in immunosuppressed patients who are often coagulopathic and thrombocytopenic, because of the underlying disease and treatments, the additive benefit of TBLB is negated by the risk. In a recent metaanalysis of patients with cancer who underwent hematopoietic stem cell transplantation, lung biopsy resulted in a 4-fold increase in procedure-related mortality, which was mostly related to bleeding.[78]

Although TBLB is frequently used in the evaluation of diffuse parenchymal lung disease, biopsy specimens are relatively small, compared with other tissue acquisition techniques, and crush artifact is common, limiting the diagnostic usefulness.[79] As such, when atypical radiologic features are present, surgical biopsy or lung cryobiopsy are necessary to maintain architectural integrity for pathologic diagnosis. The exceptions are disease processes, which follow a bronchocentric or centrilobular distribution, in which a diagnosis can often be made with relatively small samples such as sarcoidosis, hypersensitivity pneumonitis, eosinophilic pneumonias, and lymphangitic spread of malignancy.[80] Given that most interstitial lung diseases with atypical radiologic features require surgical lung biopsy (or at a minimum bronchoscopic cryobiopsy) for diagnosis, most experts recommend obtaining a TBLB before advancing to the more high-risk procedures to exclude mimickers, which can often be confirmed on TBLB, such as sarcoidosis, hypersensitivity pneumonitis, infection, and malignancy.[81] The yield of TBLB for focal peripheral lung lesions varies considerably with the location and size of the lesion, as well as the other modalities used to guide the biopsy. The use of radial probe-EBUS imaging, electromagnetic navigation, virtual bronchoscopy, and ultrathin bronchoscopy has significantly improved the diagnostic yield and are discussed in detail in other articles within this issue.

There are multiple variations and sizes of forceps available for TBLB. Alligator and cup forceps are the most common used for TBLB. In general, larger forceps and alligator forceps, which tear tissue, provide larger tissue specimens.[82,83] The size, however, does not necessarily improve the yield. Larger forceps can be more challenging to

use in the periphery because they can be difficult to open in the small airways, resulting in samples with less alveolar tissue. The alligator forceps can result in more crush artifact then cup forceps and limit the quality of the tissue specimen.

Transbronchial Needle Aspiration

TBNA allows for cytologic specimens from endobronchial lesions, lymph nodes, and masses abutting the airway in the mediastinum and hilum, as well as peripheral pulmonary lesions.[19,20,84] The indications for TBNA are summarized in **Box 1**. With the advent of linear EBUS imaging, blind central TBNA is infrequently performed; however, many investigators believe that the technique should be retained in the education of future generations of bronchoscopists. EBUS imaging is not uniformly available, especially in developing countries, and can become temporarily unavailable as a result of damage. The sensitivity of TBNA within the mediastinum depends on multiple factors. In a 2013 metaanalysis of 53 studies and more than 8000 procedures, predictors of success included lymph node size 2 cm or greater in short axis diameter, abnormal endobronchial findings on white light examination, lymph node location in the station 7 or 4R positions, operator experience, and use of larger 18-G or 19-G needles.[85] Although investigators many argue that the integration of EBUS imaging into training programs has a negative effect on the quality of conventional TBNA, a recent retrospective review suggests otherwise. In this study, after the integration of EBUS TBNA, diagnostic yields increased for conventional TBNA performed in the station 7 and 4R lymph nodes.[86] Overall, TBNA has largely been replaced by EBUS TBNA for the diagnosis of sarcoidosis, with a randomized trial showing its inferiority to EBUS TBNA for diagnosing stage I and II sarcoidosis.[87] However, within the station 7 and 4R lymph nodes, conventional TBNA is still excellent with diagnostic yields comparable to that of EBUS TBNA.[88] Conventional TBNA remains an important tool in the sampling of endobronchial tumors, especially when the tumor is covered by mucosa or necrosis debris, which would limit the diagnostic usefulness of endobronchial forceps or brushes.[89] For the diagnosis of peripheral pulmonary lesions, TBNA has rapidly expanded in recent years largely owing to the availability of newer tools to improve localization of lesions, such as radial probe EBUS imaging and electromagnetic navigational bronchoscopy.[90,91] Major factors that influence diagnostic yield with peripheral TBNA include lesion size, location, and relationship to the bronchus.[92] TBNA has been shown to improve the diagnostic yield when added to standard conventional bronchoscopic techniques such as TBLB and brushing for peripheral lesions.[84,93] An advantage of TBNA over other conventional biopsy techniques is the ability to easily obtain rapid onsite cytologic evaluation, which can confirm sampling of target lesions and, if negative, prompt the bronchoscopist to modify their approach. Touch imprint cytology obtained from TBLB can also be evaluated with rapid onsite cytologic evaluation; however, cytologists are often less comfortable with this technique and data are lacking regarding the diagnostic accuracy from bronchoscopically obtained specimens.[45]

Compared with other instruments inserted through the working channel of the flexible bronchoscope, TBNA needles pose the greatest risk of damaging the bronchoscope and care must be taken to always keep the needle retracted into the outer protective sheath while in the working channel. TBNA needles come in a variety of lengths, needle gauges, and degrees of flexibility. Most needles are between 4 and 15 mm in length with a diameter between 18 and 22 G; however, recently a 23-G needle became available as well as a 25-G EBUS TBNA needle that can be inserted through a standard flexible bronchoscope using the manufacturer's proprietary adapters.[94–96] Typically, peripheral sampling is performed with

Box 1
Indications for transbronchial needle aspiration

Mediastinal or hilar
- Lymphadenopathy
- Tumors or masses

Mediastinal cysts
- Diagnosis
- Drainage

Mediastinal abscess
- Diagnosis
- Drainage

Peripheral nodules or masses

Insertion of fiducial markers for stereotactic body radiation therapy

Endobronchial tumors

Submucosal injection
- Cyanoacrylate glue
- Cidofovir
- Triamcinolone

shorter and more flexible needles, which are more easily inserted through a slightly bent working channel or guide sheath resulting in lower risk of scope damage. With central TBNA, longer stiffer needles are typically used to provide the directed force required to penetrate the airway wall.[97] When the needle is inserted into the working channel of the bronchoscope care must be taken to keep the distal tip of the bronchoscope in a neutral position to avoid scope damage. In endobronchial or parabronchial lesions, once the tip of the catheter is visible outside the bronchoscope, the needle is extended outside of the catheter and locked before puncturing the airway wall as the target site. There are 4 common methods used to penetrate the needle tip through the airway wall and into the target lesion. The "hub against the wall" technique where the catheter is in contact with the airway wall before needle extension, and the "jabbing technique" in which the extended needle is quickly thrust forward through the airway wall by grasping the catheter at the insertion point of the working channel while the bronchoscope remains in a fixed position within the airway are the most commonly used methods. The "piggyback method," in which the bronchoscope is advanced toward the airway wall with the needle extended and locked in the out position, and the "cough technique," where the patient is instructed to cough to move the airway wall toward the locked and extended needle within the airway, are less frequently used. After the needle penetrates the airway wall, suction is applied through an attached syringe before agitating the needle back and forth within the lesion, and suction is released before withdrawing the needle into the airway to reduce aspirated bronchial tissue contamination of the specimen. Aspirated blood within the suction tubing suggests vascular puncture and the needle should be immediately retracted and introduced into a new puncture site.[94] In peripheral TBNA, the needle is advanced either directly thorough the working channel of the bronchoscope or through an extended sheath with fluoroscopic observation in a manner like TBLB. Once the outer protective sheath is within 1 to 2 cm of the lesion the needle is extended into the lesion and agitated with suction using the same technique as in central TBNA.[84]

Except for damage to the bronchoscope, complications of TBNA such as pneumothorax and bleeding are extremely rare.[94,98,99] With respect to bronchoscope damage, care must be taken to ensure that the needle is always retracted into the outer sheath when in the working channel, keeping in mind that the bronchoscope should remain in a neutral fixed position during insertion.

INDICATIONS, COMPLICATIONS, AND CONTRAINDICATIONS IN FLEXIBLE BRONCHOSCOPY

Preprocedural evaluation for flexible bronchoscopy requires, at a minimum, review of the clinical circumstances necessitating bronchoscopy, relevant radiographic and laboratory studies, and consideration of the potential benefits and harms related to the procedure. As with all invasive procedures, preprocedural planning is critically important in both maximizing benefits and minimizing risks. One must always consider how the procedure might change the management of the patient. An occasionally encountered scenario is when consultative services demand biopsy of a localized radiologic abnormality in a high-risk immunosuppressed, coagulopathic patient on broad antimicrobial coverage despite having no intentions to modify coverage based on the results. In these situations, it is the responsibility of the bronchoscopists to advocate for the patient, remembering that "just because we can does not mean we should."

A thorough airway examination should be standard practice; current imaging modalities are not sensitive enough to rule out endobronchial disease and cannot effectively evaluate mucosal changes that might be encountered.[100] A detailed knowledge of airway anatomy and mucosa is essential. More than 80% of flexible bronchoscopies performed today are for diagnostic purposes.[67] However, the bronchoscopist must be aware that, owing to unexpected findings or complications, biopsy procedures initially planned as diagnostic can occasionally become therapeutic and one must be prepared for these situations. The specific list of indications is continually expanding but in general the diagnostic indications include evaluation of pulmonary signs and symptoms, to evaluate radiographic abnormalities and for monitoring disease activity in known disease.[101] A detailed discussion of the therapeutic indications for flexible bronchoscopy is beyond the focus of this review. A more complete list of the diagnostic and therapeutic indications for flexible bronchoscopy are summarized in **Table 1**.

Complications in Flexible Bronchoscopy

In general, flexible bronchoscopy is very safe with a low rate of complications. However, the risks depend on patient factors, such as clinical stability and patient comorbidity, as well as procedure-related factors, most specifically the associated procedures performed through the flexible bronchoscope. Even in healthy adults undergoing simple inspection or research bronchoscopies,

Table 1
Indications for flexible bronchoscopy

Diagnostic Indications	Therapeutic Indications
Signs and symptoms of pulmonary disease • Hemoptysis • Stridor • Unilateral wheezing • Hoarseness • Unexplained chronic cough Evaluation of suspected pulmonary infections • Pneumonia in an immunocompromised host • Nonresolving pneumonia • Cavitary lesion • Ventilator-associated infections • Suspected resistant organisms Diffuse lung disease • Atypical chronic interstitial lung disease • Acute and subacute diffuse consolidative conditions • Diffuse alveolar damage and hemorrhage • Drug-induced lung disease • Parenchymal nodule or mass Known or suspected malignancy • Endobronchial tumor • Mediastinal or hilar adenopathy or mass • Airway compression of invasion • Early detection of central lung cancers • Staging and restaging of lung cancer Miscellaneous • Airway stent evaluation • Evaluation of benign airway diseases and strictures • Diagnosis of tracheoesophageal fistula • Lung transplant surveillance • Thermal and chemical airway injury • Confirmation of endotracheal tube position • Bronchopleural fistula	Malignant central airway obstruction • Endobronchial obstruction ◦ Laser ◦ Argon plasma coagulation ◦ Cryotherapy ◦ Brachytherapy ◦ Photodynamic therapy ◦ Electrocautery snare • Extrinsic tumors ◦ Self-expandable airway stents Benign central airway obstruction • Radial cuts • Balloon dilation • Airway stenting • Intrabronchial injections Tracheoesophageal fistula • Stenting • Laser-induced closure Hemoptysis • Hemostasis of centrally located bleeding lesions ◦ Laser ◦ Argon plasma coagulation Bronchopleural fistulas closure • Airway spigots • Endobronchial valves • Sealants Miscellaneous • Aspiration of cyst • Abscess drainage • Bronchial thermoplasty • Endoscopic lung volume reduction • Bronchoscopic intubation • Mucous plugging • Foreign body removal

complications can occasionally develop and one must always consider the risks and benefits of the procedure. This is no better illustrated than in the tragic case of Hoiyan Wan, a healthy nursing student, who in 1996 died of lidocaine toxicity after a simple research flexible bronchoscopy.[102] Minor complications of flexible bronchoscopy and associated bronchoscopic instrumentation include laryngospasm, bronchospasm, epistaxis, transient hoarseness, fever, nausea, cough, and mild airway bleeding, and major complications include severe airway hemorrhage, pneumothorax, severe hypercapnia or hypoxia, arrhythmias, seizures, and cardiac arrest. There are no controlled studies of factors that would make a specific patient unfit for bronchoscopy, so the decision to undertake the procedure needs to be based on a combination of factors to include the potential benefit, likelihood of complications, patient preference, and available alternative methods of diagnosis and treatment. Most studies report an incidence of major complications from flexible bronchoscopy of between 1% and 5%, with most major complications related to TBLB.[67–69,103,104] Mortality is rare, at less than 0.04%.[104–106]

Absolute and Relative Contraindications in Flexible Bronchoscopy

There are few absolute contraindications to flexible bronchoscopy. They include refractory hypoxemia, hemodynamic instability, life-threatening arrhythmias, lack of informed consent, inadequate equipment or facility, and an inexperienced operator.[101,107] Relative contraindications (discussed elsewhere in this article) that increase the risk of

flexible bronchoscopy are much more frequently encountered, and the risk and benefit of the procedure must be weighed carefully. In the setting of relative complications, if the decision is made to proceed with the bronchoscopy, measures to both mitigate the risk and manage complications should always be considered.

Severe hypoxemia is a relative contraindication to flexible bronchoscopy. However, there is no specific minimum P_{O_2} or oxygen saturation that must be maintained during the bronchoscopy. Additionally, bronchoscopy is often performed for the purpose of improving oxygenation, such as in a patient with pulmonary hemorrhage or atelectasis related to mucous plugging or foreign body aspiration. In a study by Albertini and colleagues,[108] evaluating changes in P_{O_2} during bronchoscopy by performing serial arterial blood gas analysis showed reductions of average reductions in P_{O_2} ranging from 4 to 38 mm Hg with an average decline of 20 mm Hg. Considering if a specific patient would be expected to tolerate this reduction can be useful in considering whether hypoxia should preclude bronchoscopy. In patients with significant hypoxemia undergoing biopsy, the risks are greater; complications of the biopsy, namely, hemorrhage and pneumothorax, can exacerbate hypoxemia in already tenuous patients. If the procedure cannot be postponed using general anesthesia, with a protected airway such as an endotracheal tube or rigid bronchoscope, should always be considered. In the intubated patient, prebronchoscopy hypoxia is less of an issue, and studies evaluating the risk of bronchoscopy in patients with acute respiratory distress syndrome have shown it to be relatively safe.[109–111] There has been increasing attention drawn to the usefulness of high-flow nasal cannula during bronchoscopy. Although most published data specifically are related to patients in the intensive care unit, there are potential advantages in the outpatient setting as well in patients with borderline preprocedure oxygenation. Additionally, the small amount of positive end-expiratory pressure induced by high-flow oxygen likely provides some degree of pneumatic stenting, which can improve visualization of the airways and maneuverability of the bronchoscope.[112]

Bronchoscopy within 4 to 6 weeks of myocardial infarction is generally felt to be contraindicated owing to expected worsening of ischemia induced by the adrenergic response of bronchoscopy and procedural related hypoxia,[106,113,114] although supporting literature is scant.[115] In one of the few studies evaluating the safety of bronchoscopy in the cardiac patient retrospective data were compiled from 40 patients who had undergone bronchoscopy in the cardiac care unit. Eighty-eight percent of the patients were previously intubated and 53% had a recent myocardial infarction. Complications were rare with only 2 patents developing arrhythmias related to the bronchoscopy. Only 5 patients in this review were not already intubated and 1 (20%) in this subgroup required intubation after the procedure.[116] This paper does not necessarily imply that the procedure is safe, but rather that it is safer in the previously intubated and deeply sedated patient because much of the theoretic risks are associated with the underlying adrenergic response and hypoxemia attributable to bronchoscopy in the moderately sedated patient. Additionally, one should consider that the degree of adrenergic response and potential hypoxemia associated with the bronchoscopy is variable depending on the complexity of the procedure. A simple lavage in a patient who is already intubated and deeply sedated will likely result in significantly less risk than in a moderate sedation bronchoscopy with transbronchial biopsies. Again, just as in patients with significant hypoxia, the risks of inducing myocardial ischemia are likely greater when lung biopsy is performed because these patients are less likely to tolerate complications such as pneumothorax or bleeding. Although the data regarding the recommendation to avoid bronchoscopy within 4 to 6 weeks of myocardial infarction are limited, it is a reasonable precaution. In a setting where bronchoscopy cannot be delayed, we recommend maximizing oxygenation, minimizing suction to avoid tachycardia and hypoxemia, and providing adequate sedation and analgesia to reduce adrenergic response with a low threshold for terminating the procedure if evidence of acute ischemia develops. Although bronchoscopy using moderate sedation is generally considered safe for patients with stable coronary artery disease, hemodynamic changes associated with the procedure may induce ischemia in rare cases.[117]

Coagulopathy in flexible bronchoscopy for airway inspection, and BAL without biopsy is generally safe even in severe coagulopathies. This finding has been demonstrated in multiple studies of patients with severe pancytopenia related to chemotherapeutics or bone marrow transplantation.[118,119] In a profoundly coagulopathic patient, significant epistaxis related to nasal introduction of the bronchoscope can develop and the oral route is preferable. Coagulopathy is much more problematic when tissue sampling is required, especially in TBLB, which has a higher risk of procedure-related bleeding than brush or needle biopsy.[67,106,120] Although there is reasonable evidence regarding the safety of platelet

inhibitors before TBLB, there is a paucity of high-quality data regarding the safety of TBLB in coagulopathic or thrombocytopenic patients. The use of daily aspirin alone has been shown to have no significant increase bleeding risk in bronchoscopy, even with TBLB, and clinical guidelines recommend continuing medically necessary aspirin in the periprocedural period.[106] Although the use of aspirin alone has minimal if any increased bleeding risk, the same cannot be said for thienopyridines such as clopidogrel, especially when used in combination with aspirin. The initial animal study evaluating the effect of clopidogrel with and without aspirin before TBLB in swine showed no significant increased bleeding risk.[121] However, when clopidogrel with or without aspirin was evaluated prospectively in humans, a substantial risk was identified, with bleeding occurring in 89% of patients on clopidogrel alone and 100% of patients on combination aspirin and clopidogrel therapy.[122] Current recommendations are to hold clopidogrel for 5 to 7 days before bronchoscopic biopsies.[106] When bronchoscopy cannot be delayed, in patients with continued need for thienopyridines, such as in drug-eluding stents placed within the previous 12 months, using a GP IIb/IIIa inhibitor as a bridge could be considered in consultation with interventional cardiology.[123] Data regarding TBLB in the setting of thrombocytopenia are less robust; however, the available data support caution in severe thrombocytopenia. In a small study of 24 patients with platelet counts of less than 60,000/mm^3 as a result of chemotherapeutics or bone marrow invasion from malignancy who received platelet transfusions within the hour before intervention, significant bleeding occurred in 21% of patients, with 1 patient developing fatal pulmonary hemorrhage.[124]

Although little evidence exists regarding management safety of bronchoscopy in the setting of anticoagulants or intrinsic coagulopathy, this also must be considered a relative contraindication for bronchoscopy biopsy. In a swine model evaluating rates of bleeding after TBLB with or without warfarin-induced coagulopathy, no difference in bleeding was identified between controls and animals on anticoagulation with an International Normalized Ratio of up to 10.[125] These findings should be considered with caution, however, because similar results were seen in swine after the administration of clopidogrel, which did not correlate with findings on subsequent human studies.[121] Given the paucity of data, guidelines for bronchoscopy have been extrapolated from surgical studies with the general recommendation being to delay bronchoscopy with biopsy until the International Normalized Ratio is less than 1.5.[106] Similarly, recommendations from extrapolated data are to withhold heparin for at least 6 hours and low-molecular-weight heparins for at least 12 hours. With the multitude of new oral anticoagulants, we recommend using surgical protocols and manufacturer recommendations to define the necessary gap in medications before bronchoscopy with biopsy.[106,126]

The need for checking platelets and coagulation studies before bronchoscopy in patients not suspected to have abnormalities is controversial. Most patients who have significant bleeding during bronchoscopy do not have clinical risk factors or abnormal coagulation profile.[127] The British Thoracic Society recommends preprocedural testing only when clinical factors exist that indicate coagulation factors might be abnormal, such as use of anticoagulants, evidence of liver disease, personal or family history of excessive bleeding, or the presence of active bleeding.[106] In the United States, preprocedural laboratory analysis is often mandated by institutional protocol and our general practice is to obtain preprocedural laboratory tests if biopsy is considered and to avoid biopsy for platelet counts of less than 50,000/mm^3, elevated partial thromboplastin time, or an International Normalized Ratio of more than 1.5 unless corrected.

The safety of bronchoscopy in patients with elevated intracranial pressure (ICP) is controversial. ICP increases during bronchoscopy are felt be related to airway stimulation and increased intrathoracic pressure causing functional obstruction to cerebral venous outflow.[128] In trauma patients with ICP monitors in place, bronchoscopy has been shown to induce clinically significant increases in the ICP.[129,130] In a prospective observational review of 23 severe brain injury patients requiring bronchoscopy in the intensive care unit, ICP increased in 81% of patients with an average increase of 25.4 mm Hg.[130] However, the adrenergic response related to the bronchoscopy initially induced a proportional increase in mean arterial pressure, resulting in only minimal changes to the cerebral perfusion pressure. After a few minutes, the mean arterial pressure does begin to return toward baseline and the ICP remains elevated, resulting in a reduction in the cerebral perfusion pressure in longer procedures.[130] Recently, Grosu and colleagues[131] published a retrospective evaluation of patients undergoing flexible or rigid bronchoscopy in the setting of malignant space-occupying brain lesions, of which 40% had evidence of increased ICP on preprocedural imaging. There were no episodes of neurologic deterioration in the periprocedural period or requirement for postprocedural escalation of

care. It is difficult to say with certainty that bronchoscopy in patients with significantly elevated ICP is safe, even with preserved cerebral perfusion pressure, because the risk of brain herniation remains. If bronchoscopy is required in a patient with severe intracranial hypertension caution is warranted and one should attempt to minimize the procedural duration while maximizing sedation to mitigate some of the hemodynamic effects.

Pulmonary hypertension (PH) is another situation in which evidence and practice habits do not always parallel each other. In a 2005 survey of North American bronchoscopists, 59% of respondents believed that PH was a relative contraindication to TBLB, whereas 29% of respondents believed to be an absolute contraindication.[65] The theoretic concerns are that PH would increase bleeding complications because of hypertrophy of bronchial veins and potentially induce cardiovascular decompensation. In nonsevere PH, this has not been borne out in literature.[132,133] A recent observational review evaluating the safety of bronchoscopy with TBLB, endobronchial biopsy or TBNA in 107 patients with echocardiographic evidence of PH (pulmonary artery systolic pressure of $\geq$36 mm Hg) compared with 83 patients without PH (pulmonary artery systolic pressure of <36 mm Hg). In this study, no difference in safety outcomes such as major bleeding, pneumothorax, sedation complications, or procedure-related deaths, were found.[134] Although it seems that TBLB is likely safe in patients with mild or moderate PH, there is very little evidence regarding the safety of bronchoscopy and TBLB in patients with severe PH. In our practice, we avoid TBLB in patients with systolic pulmonary pressures of greater than 50 mm Hg, although we do not consider it an absolute contraindication.

The final special situation that we address is bronchoscopy in the pregnant patient. Pregnancy induces physiologic changes in the upper airway as well reduction in venous return related to compression of the inferior vena cava by the uterus.[135] Additionally, hypoxemia, sedative medications, and fluoroscopy potentially can result in fetal injury.[136] For nonemergent bronchoscopy, recommendations are to until at least 28 weeks of gestation and preferably until after delivery to minimize the risk of fetal morbidity.[137] When bronchoscopy is required, fetal monitoring and consultation with an obstetrician is strongly recommended. Patients should be positioned in the left lateral decubitus position in the later stages of pregnancy. Fluoroscopy should also be avoided, especially during the 8th to 15th weeks of pregnancy when the fetus is most sensitive to radiation effects.[138]

SUMMARY

Flexible bronchoscopy is an essential tool for those practicing pulmonary medicine and a thorough understanding of the indications, contraindications, risks, and benefits of the procedure is mandatory. Despite rapid advancements in technology and applications in bronchoscopy, such as navigational bronchoscopy and EBUS imaging, the foundational core bronchoscopic procedures retain their relevance and proficiency is a prerequisite to competently performing new and emerging bronchoscopic procedures. It has been half a century since Dr Ikeda, along with the Machida Company, first introduced the fiberoptic bronchoscope, forever changing the field of pulmonary medicine. We look forward with excitement as the role of this extraordinary tool continues to expand in the next half century.

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