Transbronchial Cryobiopsy in Interstitial Lung Diseases

State-of-the-Art Review for the Interventional Pulmonologist

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Summary: **Interstitial lung diseases are a heterogenous group of disorders that are often difficult to diagnose precisely. Clinical, laboratory, radiographic, and histologic information may be needed to arrive at the correct diagnosis. The multidisciplinary discussion has been proven to be useful in this patient group. Transbronchial cryobiopsy has become a popular method for obtaining tissue samples. Over the course of the last decade, there has been a significant amount of research assessing the feasibility, safety, and diagnostic endpoints of transbronchial cryobiopsy in patients with interstitial lung disease. Data continues to mount to support its use, which has been reflected in guidelines and expert panel reports. Patient selection, procedural performance, and appropriate specimen handling are critical factors for success. A coordinated approach by pulmonologists with expertise in interstitial lung diseases, interventional pulmonologists, and thoracic pathologists is essential. In this evidence-based narrative review, we address transbronchial cryobiopsies from these three distinct perspectives. In addition, the current literature was used to address nine common procedural questions.**

Key Words: transbronchial cryobiopsy, interstitial lung diseases, cyroprobe, interventional pulmonology

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Interstitial lung diseases (ILD) encompass a heterogenous group of conditions. They frequently represent a diagnostic challenge for clinicians who rely on a multidisciplinary discussion (MDD) to reach a consensus diagnosis based on clinical, radiologic, and occasionally, histologic data. Histology is not always required when evaluating a patient with ILD; when a biopsy is necessary, a variety of approaches may be considered.[1] Traditionally, the gold standard for biopsy in ILD has been the surgical lung biopsy (SLB). Conventional transbronchial forceps biopsies (TBBs) can be performed for the evaluation of ILD, but their overall diagnostic yield is low. SLB for ILD has, however, been subject to increased scrutiny after several studies suggested prohibitively high morbidity and mortality rates.[2,3]

Since 2009, transbronchial cryobiopsy (TBC) has become an attractive minimally invasive option for the evaluation of ILD. It involves the use of cryotechnology to freeze and extract large frozen biopsy specimens. When compared to TBB, it allows for the procurement of larger pieces of tissue without crush artefact.[4] The multisociety Idiopathic Pulmonary Fibrosis (IPF) Clinical Practice Guideline acknowledged that SLB could be avoided in 80% of cases by performing TBC, but due to the lack of procedural standardization and heterogenous results across institutions, a recommendation for or against TBC could not be made.[5] Yet, even since the publication of these guidelines, data supporting TBC for ILD management continue to mount both qualitatively and quantitatively, and the practice is gaining acceptance across ILD centers.[6] Thus, the American College of Chest Physician's (ACCP) Guideline and Expert Panel Report recently concluded that TBC is a reasonable alternative to SLB for providing histology for ILD MDD.[7] Since the first report in 2009, the number of publications related to TBC has increased exponentially.[8] In general, they continue to support the procedure as a suitable, safer alternative to SLB. In this narrative review, we address the current data that support expert recommendations for TBC from the perspective of ILD pulmonologists, thoracic pathologists, and physicians trained in interventional pulmonology (IP).

METHODS

MEDLINE and Cochrane Library were searched using the term "cryobiopsy" from 2009 through 2020. A total of 352 articles were found.

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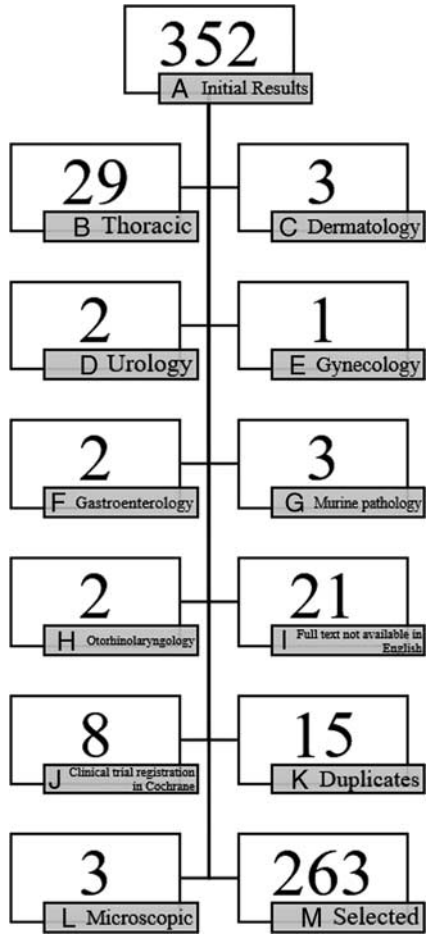

FIGURE 1. A, The initial MEDLINE and Cochrane Library data search ("cryobiopsy," 2009-2020) yielded 352 results. B, Twenty-nine papers were excluded since they did not pertain to cryobiopsy of the lung parenchyma itself. These papers addressed a variety of thoracic medicine topics, including pleural cryobiopsy, endobronchial cryobiopsy, and lung ultrasound. C–H, Thirteen articles were removed since they applied to other specialties or were animal studies. I, Twenty-one were excluded due to the lack of an English language full text. J, Eight were excluded since they were clinical trial registrations in the Cochrane Library. K, Fifteen papers were excluded due to duplicity. L, Three papers were excluded since they pertained to microscopic applications of cryotechnology. M, Two hundred sixty-three articles were included in the final selection.

Fifteen duplicates were removed. Seventy-four articles were excluded for a variety of reasons (Fig. 1). After exclusion, 263 articles were selected for review, many of which were included in meta-analyses and guidelines and not individually referenced in this review.

ILD Pulmonologist Perspective

An accurate diagnosis of ILD has important treatment and prognostic implications.[9] While MDD has supplanted the prior gold standard of SLB, histology is still required in certain cases and remained the most significant contributor to the diagnosis in the seminal study by Flaherty et al.[10] The 2 main routes of tissue acquisition are via bronchoscopy or surgery. The diagnostic yield for a TBB in ILD is highly variable but can be as low as 20% to 30%.[11,12] In comparison, SLB provides larger samples (Fig. 2). SLB related mortality rates vary widely, 0% to 16.7%.[2,3,13–15]

The principal goal of a biopsy is to obtain an adequate amount of lung tissue while minimizing risk to the patient. Although TBB can be useful in specific cases, a significant proportion of patients present with indeterminate radiologic findings and possible IPF. The identification of the underlying histologic pattern generally requires large biopsy specimens.

Data supporting the use of TBC in lieu of SLB continues to accumulate. Studies have evaluated the purported diagnostic and procedural advantages of TBC over SLB contrasting diagnostic yield as assessed by—(a) independent diagnostic yield, (b) contribution to diagnostic yield when incorporated into MDD, and (c) direct comparison with SLB in the same patients—with safety outcomes (d).

Independent Diagnostic Yield of TBC

Due to variability in definitions, the diagnostic yield of TBC is challenging to ascertain. A "diagnostic" sample may range from nonspecific fibrosis (ie, abnormal tissue) to clear features of a known condition such as usual interstitial pneumonia. Since the diagnostic gold standard of ILD diagnosis is MDD, studies that report diagnostic yields alone without MDD should be viewed with caution.[16]

Nonetheless, systematic reviews and meta-analyses suggest that TBC has an acceptable diagnostic yield. Sethi et al[17] analyzed 27 studies that included 1443 patients. Overall, diagnostic yield of 72.9% was found for diffuse parenchymal lung disease. Data from Sharp et al[18] (11 studies, 704 patients) suggested a diagnostic yield of 84.4%. Johannson et al[19] (11 studies, 731 patients) showed that that the diagnostic yield for TBC ranged from 74% to 98% when interpreted in isolation, with a pooled estimate of 79%. A meta-analysis by Ravaglia et al[20] (15 studies, 781 patients) revealed an overall diagnostic yield of 81%. The weighted pool estimate for diagnostic yield in the 2019 ACCP Guideline was 82.5%.[7]

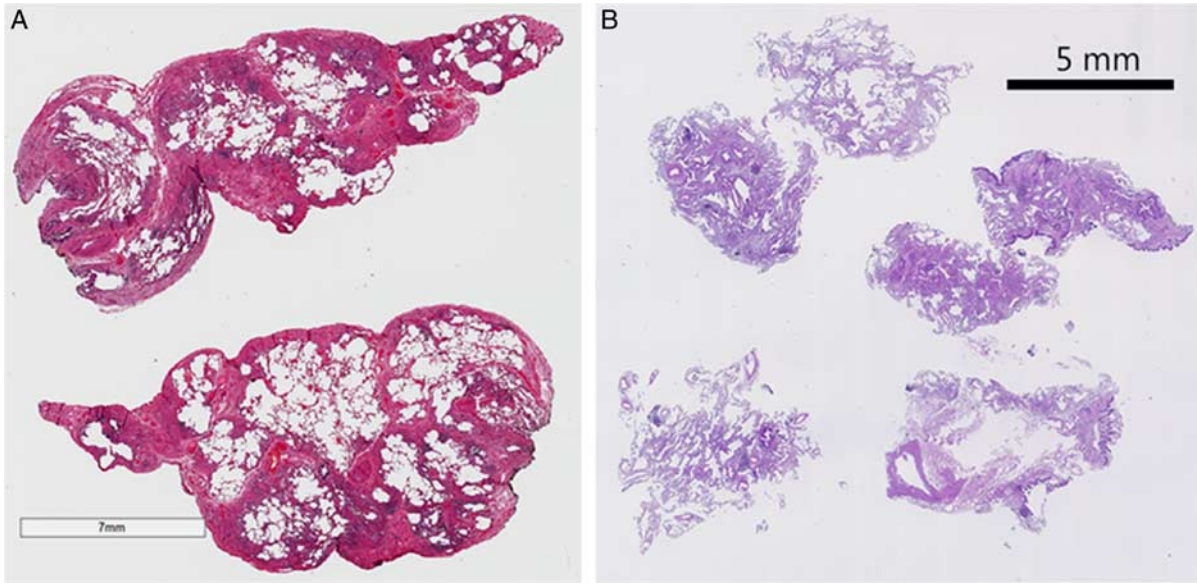

FIGURE 2. Size comparison of a typical surgical lung biopsy (A) and transbronchial cryobiopsy specimens (B). All 6 transbronchial cryobiopsy specimens are ≥5 mm. Both types of samples include features that are diagnostic of usual interstitial pneumonia. *a+*

Contributions of TBC to MDD

MDD is a vital process in ILD management; sequential introduction of clinical, radiologic, and histologic information in a multidisciplinary context has been shown to improve interobserver agreement and diagnostic confidence.[21] When clinical and radiographic data is inconclusive, histologic data is likely to be informative. In a study of 117 patients with fibrotic ILD, the addition of histology from TBC to clinical, radiographic, and bronchoalveolar lavage data increased the prevalence of a highly confident IPF diagnosis from 29% to 63%.[22] The change in diagnostic confidence by +34% was the largest of any individual step in the MDD process. In comparison, information from bronchoalveolar lavage and follow-up data had much smaller impacts on the prevalence of a highly confident IPF diagnosis (+13% and +17%, respectively). Similarly, incorporation of TBC sourced data had the most significant impact in patients with a low confidence IPF diagnosis.[22]

Other studies have corroborated these findings. In a prospective, multicenter study in which patients underwent sequential TBC and SLB, the addition of TBC sourced information was deemed useful in the MDD process in 75% (48/65) of patients.[23] In a systematic review and meta-analysis, the diagnostic yields for TBC ranged between 51% and 98% when reviewed within MDD.[19]

Although studies have shown that TBC can meaningfully contribute to the MDD, diagnostic confidence by MDD may not be the best metric to evaluate its utility. Indeed, experts may have high confidence in the wrong diagnosis.[24] While a comparison between rates of diagnostic misclassification has not been studied, data suggests that changes in diagnostic confidence via MDD are similar between TCB and SLB.[22] While these limitations are recognized, MDD remains a critical step in the diagnostic pathway.

Diagnostic Comparison of TBC to SLB

There is data to support the histologic equivalency of TBC and SLB. Four observational studies that compare the diagnostic yield between TBC and SLB met inclusion criteria for the 2019 ACCP Guideline.[7,20,22,23,25] A summative outline of the studies can be found in Table 1. Two studies evaluated the concordance of sequential TBC and SLB in the same patient.[23,25]

One earlier prospective comparative multicenter (2-center) study suggested poor concordance between sequential TBC and SLB.[25] A single, blinded, independent pathologist concluded that the histologic diagnoses for TBC and SLB were fully concordant in only 8 of the 21 cases (38% agreement). However, the use of a single histopathologist (blinded to clinical data and not a participant in MDD) substantially limited the interpretation of this data.[26–32]

A larger multicenter (9 centers) and more robustly designed prospective study by Troy et al[23]

TABLE 1. Summary of Data From Studies Comparing Diagnostic Yield Between TBC and SLB Which Met Inclusion Criteria in the 2019 American College of Chest Physician's Transbronchial Cryobiopsy Guideline and Expert Panel Report

References	Study Design	Total; Sample Size/Group	Participants	Outcomes
Romagnoli et al[25]	Prospective	21; TBC (n = 21), SLB following TBC (n = 21)	Patients aged 60-69 y with suspected ILD requiring biopsy	Diagnostic yield, safety, agreement, and concordance
Troy et al[23]	Prospective	65; TBC (n = 65), SLB following TBC (n = 65)	Patients aged 32-79 y requiring a lung biopsy to support their ILD diagnosis	Diagnostic confidence in MDD diagnosis, agreement, and concordance
Ravaglia et al[20]	Retrospective	447; TBC (n = 297), SLB (n = 150)	Patients aged 15-78 y with suspected ILD	Diagnostic yield and safety
Tomassetti et al[22]	Retrospective	117; TBC (n = 58), SLB (n = 59)	Patients aged 29-77 y with fibrotic ILD	Diagnostic confidence in the MDD diagnosis

ILD indicates interstitial lung disease; MDD, multidisciplinary discussion; SLB, surgical lung biopsy; TBC, transbronchial cryobiopsy.

was published in 2019. It established good concordance between TBC and SLB for both histologic pattern interpretation and consensus MDD diagnosis.[23] The study assessed 65 patients who underwent TBC, followed by immediate SLB. Samples were obtained from corresponding lobes of the same lung. They were masked and underwent independent assessment for histologic findings by 3 expert pathologists who had to reach an agreement. Clinical and high-resolution computed tomography (CT) findings were used to form provisional diagnoses, histologic data was added to arrive at a final diagnosis. Raw agreement between TBC and SLB for guideline-refined pattern and specific histologic pattern were 70.8% (weighted κ of 0.70; 95% confidence interval: 0.55-0.86) and 69.2% (κ of 0.47; 0.30-0.64) respectively. Raw agreement between TBC and SLB for the MDD final diagnosis was 76.9% (κ of 0.62; 0.47-0.78).

Safety Comparison of TBC to SLB

When assessing endpoints such as death and ILD exacerbation, TBC appears to be the safer option.[20] Hospital length of stay is longer with SLB (6.1 vs. 2.6 d).[20] Mortality due to adverse events was higher in those who underwent SLB, compared to those who underwent TBC (2.7% vs. 0.3%).[20] The most extensive study of SLB in ILD analyzed over 32,000 admissions for patients with ILD who underwent SLB (via open or video-assisted thoracoscopic surgery); it demonstrated an in-hospital mortality rate of 1.7% for elective procedures.[3] The rate was 16% if the procedure was performed nonelectively.[3] A high (16.7%) 30-day mortality rate was also seen in a retrospective single-center study for patients who underwent SLB, who ultimately had a diagnosis of usual interstitial pneumonia.[33] TBC mortality rates are lower, but also subject to high variability. Thirty-day mortality has been reported to range between 0% and 4.0%.[34,35] One report cited a 90-day mortality rate of 2.5%.[36] A meta-analysis showed procedural related mortality of 0.3% for TBC.[17] The 2019 ACCP Guideline estimated a mortality rate of 0.5% for TBC.[7]

Two standard safety endpoints for TBC are pneumothorax and bleeding. It is a challenge to draw comparisons for these complications in SLB for several reasons. Rates of pneumothorax are arduous to define since intraoperative chest tube placement is almost universal for patients undergoing SLB.[37] A more feared and accurately tracked complication is a prolonged air leak.[15] Though more commonly seen in lobe or segment resections, they can occur in wedge resection.[38] Bleeding in SLB is infrequent and often minimal (< 20 mL).[39,40] In comparison, the estimated incidence of pneumothorax and severe bleeding in TBC are <10% and 0.3%, respectively.[7,17]

The similarities in diagnostic yield, contributions to MDD, and diagnostic concordance, in combination with a superior safety profile, serve to suggest TBC is a better alternative to SLB.

Pathologist Perspective

In cases in which histology is determined to be needed, pathologists play a crucial role in the diagnosis of ILD. An exemplar scenario is a patient with suspected IPF, in which high-resolution CT does not provide diagnostic features. The careful assessment of histologic samples is essential to classify ILD accurately. Within MDD, as discussed above, histologic information has the most significant impact on the final MDD diagnosis of ILD.[21] This effect is most pronounced when the initial clinical and radiographic data is

not consistent with IPF. Conditions such as hypersensitivity pneumonitis have a comparatively lower inter MDD agreement.[41]

While TBB can provide useful information in certain ILD (ie, sarcoidosis, hypersensitivity pneumonitis, lymphangitic carcinomatosis, pulmonary alveolar proteinosis, and eosinophilic pneumonia), larger samples of the lung parenchyma that allow pattern recognition are needed for the diagnosis of many other conditions.[42–46] The proper processing, interpretation, and incorporation of TBC specimen interpretation into MDD are all crucial steps taken by pathologists in ILD evaluation.

Considerations for Processing TBC Specimens

TBC specimens are processed similarly to other pathology specimens: fixation in 10% formalin, embedding in paraffin, and sectioned and stained with hematoxylin and eosin (or other stains as indicated) for histologic evaluation. Importantly, TBC specimens are fragile and should be gently thawed (without scraping them off) into saline from the probe, gently transferred from saline to formalin without squeezing, and after processing, embedded in the paraffin block for sectioning at orientation to maximize surface area shown on the slides to optimize the likelihood of pattern recognition (Figs. 3, 4).

Interpretation of TBC Specimens

Pathologists interpreting TBC specimens should have experience in lung pathology as identified on SLB specimens, and a willingness to try to apply this knowledge to the former. They should attempt to define patterns of injury on TBC specimens with the same approach as applied to SLB specimens, recognizing and accepting that TBC specimens are smaller in size.

Incorporation into MDD

The pathologist's diagnostic confidence for pattern and/or diagnosis is often lower on TBC specimens.[22] This makes it more critical for their active involvement in MDD discussion, which allows their diagnostic considerations to be incorporated into context.

Interventional Pulmonologist Perspective

When it is decided that a TBC is the next best step in the evaluation, the IP physician's primary objective is to obtain useful tissue by the safest means. Nine procedural recommendations were developed from the articles that were selected for review. The Grading of Recommendations, Assessment, Development, and Evaluation system was used to quantify the strength of recommendation and certainty of evidence (Table 2).[47] Recommendations are summarized in Table 3.

Who Should Perform TBC, and in What Setting?

There is little data that answers the questions of who and how TBC should be performed, although the advantages and disadvantages of performing complex bronchoscopic procedures in different settings have been discussed elsewhere.[48] Available recommendations are generally based on expert consensus. Hetzel et al[49] recommend that the TBC be performed by IP physicians familiar with the procedure, as well as with the management of severe procedure-related complications (massive

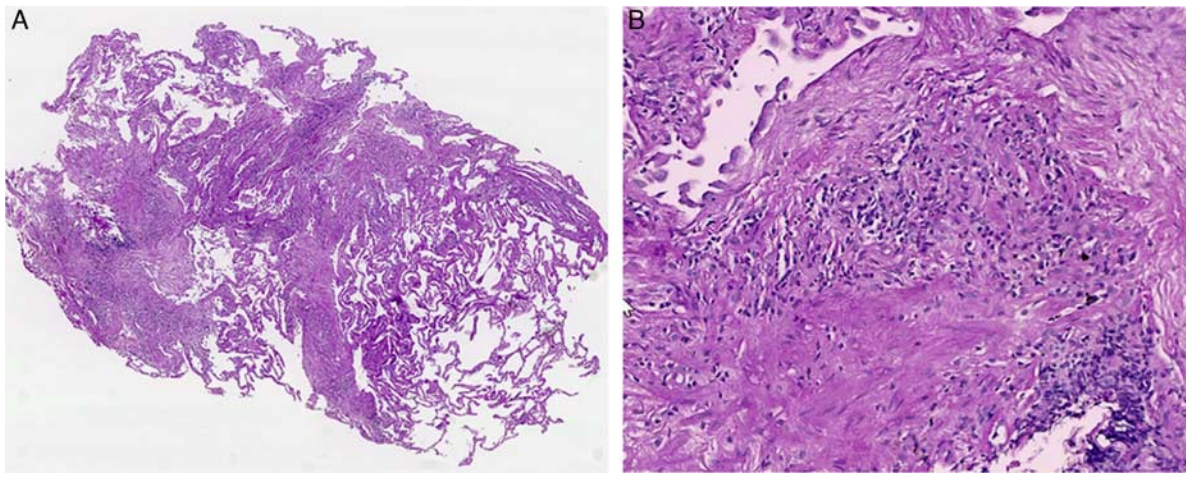

FIGURE 3. Transbronchial cryobiopsy specimens of usual interstitial pneumonia. A, The low-power view highlights patchy destructive fibrosis. B, At higher magnification, a fibroblastic foci and dense scarring can be seen. It is important to note that honeycombing is not required for the diagnosis of usual interstitial pneumonia. It is commonly found in transbronchial cryobiopsies of usual interstitial pneumonia; however, not in this example. a+

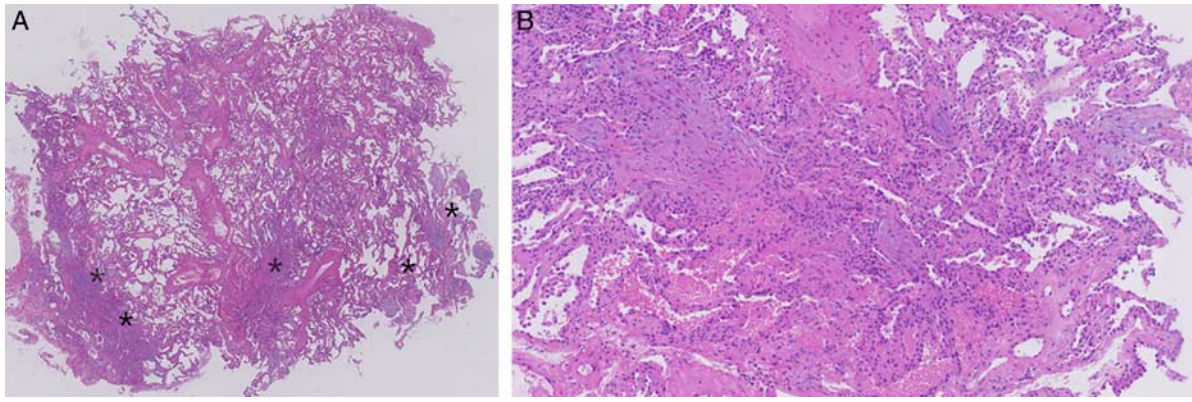

FIGURE 4. Transbronchial cryobiopsy of specimens of cryptogenic organizing pneumonia. Areas of (*) patchy organizing pneumonia can be seen in both low-power (A) and high-power views (B).

hemoptysis and tension pneumothorax). It is suggested that TBC be performed in the operating room with full anesthesia support with emergency equipment immediately available. Ready access to interventional radiology, thoracic surgery, and the intensive care unit should be present.[49]

We recommend (1C, strong recommendation, low quality of evidence) that TBC be performed by interventional pulmonologists trained in cryobiopsy and able to manage complications, in an operating room or endoscopy suite with full anesthesia support with available emergency access to interventional radiology, thoracic surgery, and critical care medicine.

TABLE 2. Grades and Implication of the Grading of Recommendations, Assessment, Development, and Evaluation System

Recommendation Grade	Implication
1A—Strong recommendation, high quality of evidence	Strong recommendation that can apply to most patients without reluctance
1B—Strong recommendation, moderate quality of evidence	Strong recommendation that can likely apply to most patients
1C—Strong recommendation, low quality of evidence	Relatively strong recommendation, which may change when better evidence becomes available
2A—Weak recommendation, high quality of evidence	Weak recommendation in which the best course of action may be modified based on patient or society values
2B—Weak recommendation, moderate quality of evidence	Weak recommendation in which other approaches are likely superior for select patients
2C—Weak recommendation, low quality of evidence	Very weak recommendation in which another course of action may be equally reasonable

What Are the Contraindications for TBC?

Rapid Clinical Decline

Exacerbation of ILD can be due to a variety of causes. Factors that suggest physiologically advanced disease have been associated with exacerbations of certain forms of ILD.[50–52] The development of unexplained patchy ground-glass opacities has been identified as a possible sign of impending exacerbation.[53] The risk of obtaining a biopsy (including SLB) in this patient group may outweigh the benefit. It is essential to recognize that exacerbations of ILD can also occur after TBC; these can carry a high mortality.[20,54,55]

Pulmonary Hypertension

Pulmonary hypertension is an often-cited comorbid condition in patients with ILD.[56] There is inconsistent TBB safety data in patients with pulmonary hypertension; there is no TBC safety data in this patient population.[57–59] Though not universally available, some suggest that transthoracic echocardiographic evidence of a systolic pulmonary artery pressure of >50 mm Hg should be considered a relative contraindication to TBC.[16,60] This is due to the risk of damage to pathologic vasculature that may be seen in this patient group: hypertrophied bronchial arteries and enlarged pulmonary veins and plexuses.[60–62]

Bleeding Diathesis

Although there is no direct data for TBC, bleeding diathesis, concurrent therapeutic anticoagulation, concomitant use of thienopyridines,

TABLE 3. Summary of Procedural Recommendations and Assigned Grade for TBC

Question	Recommendation	Grade
Who should perform TBC, and in what setting?	Interventional pulmonologists who are trained in TBC and able to manage potential complications Endoscopy suite or with full anesthesia support and availability of emergency services (IR, thoracic surgery, and CCM)	1C
What are the contraindications for a TBC?	Rapid clinical decline, uncorrected bleeding diathesis, and impaired pulmonary function test (FVC <50% of predicted, FEV_1 <0.80 L or <50% of predicted, or DLCO <35%)	1C
What type of bronchoscopy is best for performing TBC?	Flexible bronchoscopy through ETT or rigid bronchoscope	1C
What is the best anesthetic approach when performing TBC?	General anesthesia	1C
Should a prophylactic balloon blocker be used?	Yes, in every procedure	1B
What is the optimal position for cryoprobe placement?	One centimeter away from the visceral pleural (the cryoprobe should be passed with fluoroscopic guidance till the resistance of the visceral pleural is felt, then retracted 1 cm before freezing is started)	1C
What is the ideal freezing time for TBC?	3-6 s for each tissue acquisition	2B
What size cryoprobe should be used for the procedure?	1.9 mm	2B
What are the management strategies for the serious complications that can occur with TBC?	For the serious complications of iatrogenic pneumothorax and bleeding, operators performing TBC must be trained in their management, and have immediate access to the necessary equipment*	1C

*Including but not limited to—chest tube insertion kit, drainage apparatus, ultrasound or fluoroscopy placement guidance, additional supplies that may be needed to secure and connect the chest tube, large airway ($\geq$8.5 mm ETT or rigid bronchoscope), and bronchial blocker.

CCM indicates critical care medicine; DLCO, diffusing capacity for carbon monoxide; ETT, endotracheal tube; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IR, interventional radiology; TBC, transbronchial cryobiopsy.

or other new antiplatelet drugs, or thrombocytopenia ($<50\times10^9$/L) are considered absolute contraindications to TBC.[60] Aspirin therapy is regarded as a relative contraindication.

Compromised Pulmonary Function

A European best practice recommendation suggested that forced vital capacity (FVC) < 50% of predicted, forced expiratory volume in 1 second (FEV_1) <0.80 L or <50% of predicted or diffusing capacity for carbon monoxide (DLCO) <35% of predicted should serve as relative contraindications to TBC.[60] The Indian Association for Bronchology position statement had a similar recommendation, with the exception of the DLCO threshold being <30% of predicted.[62] The 2019 ACCP Guideline did not address this question.[7]

No Strict Age Limit Restriction

There is no published data to suggest an upper age limit for performing TBC.[60] Patients as old as 89 years have undergone TBC.[63] However, some data suggest the bleeding complications are more likely to occur in patients that are 65 years of age and older.[64]

We recommend that the presence of a rapid clinical decline, uncorrected bleeding diathesis, and impaired pulmonary function test (FVC <50% of predicted, FEV_1 <0.80 L or <50% of predicted, or DLCO <35% serve as contraindications for TBC; a set chronological age should not (1C, strong recommendation, low quality of evidence).

What Type of Bronchoscopy Is Best for Performing TBC?

TBC can be performed with or without rigid bronchoscopy.[65] A rigid bronchoscope can provide a large working field in the airway, without compromise of ventilation to the contralateral lung. Some centers perform TBC via the use of a flexible bronchoscope through an endotracheal tube (ETT). Less frequently used approaches include flexible bronchoscopy through a supraglottic airway or the use of 2 flexible bronchoscopes with moderate sedation and no advanced airway.[35,66,67] Hetzel et al[49] made no specific recommendations for or against the use of a rigid bronchoscope. The best option between an ETT or a rigid bronchoscope has yet to be directly studied. The 2019 ACCP Guideline recommended TBC be performed via flexible bronchoscopy through an ETT or rigid bronchoscope.[7]

We recommend TBC be performed with a flexible bronchoscope, either via an ETT or through a rigid bronchoscope (1C, strong recommendation, with low-quality evidence).

What Is the Best Anesthetic Approach When Performing TBC?

A variety of anesthetic strategies have been explored for TBC. Hetzel et al[49] recommended that the procedure be performed with general anesthesia or deep sedation. Patient comfort may be enhanced with intubation and the use of general anesthesia.[68]

A special consideration when using general anesthesia and an ETT is the size of the tube. If major bleeding is encountered, a large size ($\geq$8.5 mm) ETT is advantageous when compared to smaller ETT.[69]

The recommendation for the use of general anesthesia is indirectly inferred by the 2019 ACCP Guideline recommendation for the use of an ETT or rigid bronchoscope for TBC.[7]

We suggest that TBC be performed using general anesthesia (1C, strong recommendation, low quality of evidence).

Should a Prophylactic Balloon Blocker Be Used?

Bleeding is a dreaded complication of TBC. A bleeding rate of 72.7% in 359 patients who underwent the procedure was noted in a prospective randomized trial.[64] There was moderate-severe bleeding in 16% of patients (n = 58). Prophylactic balloon blockers were not used in this study; cryoprobe size varied. In a retrospective study (n = 128 patients), moderate-to-severe bleeding occurred less when balloon occlusion was used (1.8% vs. 35.7%).[65] In another study, the protocol was modified to include the use of a balloon blocker after 15 of the first 19 patients suffered either moderate or severe bleeding. After the procedural modification (which also included a reduction of freezing time and reduction of biopsy number), there were no cases of moderate or severe bleeding among 42 patients.[70] Hetzel et al[49] recommend the prophylactic use of an endobronchial blocker when an ETT is used; they felt it was not mandatory in the setting of rigid bronchoscopy. The 2019 ACCP Guideline suggests that a prophylactic balloon blocker be used to block the segment feeding the target area in all TBC procedures.[7]

We recommend that a prophylactic balloon blocker be used for all TBC procedures (1B, strong recommendation, moderate quality of evidence).

What Is the Optimal Position for Cryoprobe Placement?

Selecting a cryoprobe placement location in TBC is a balance of benefits and risks: obtaining enough viable lung tissue in the target area versus bleeding and pneumothorax. Not all ILD affect the lung parenchyma uniformly; the cryoprobe must be placed in the affected area.[71,72] The area 1 cm away from the pleural roughly corresponds to the location of the secondary lobules of the lungs, which is the anatomic area of interest in a variety of ILD.[73,74] Cryoprobe-to-pleural distance is important. Too close to the pleural increases the risk of pneumothorax. A distance of <1 cm from the pleural has been associated with a higher risk of pneumothorax.[75] Due to the proximity of the airways to large vascular structures such as pulmonary veins or bronchial arteries, too much distance from the pleura can lead to bleeding.[49] One centimeter is the approximate length of the metallic tip of the Erbe cryoprobe.[49] Most TBC studies describe the cryoprobe being positioned about 1 cm from the pleura.[76] The use of fluoroscopy may allow for more accurate cryoprobe positioning.

We suggest the cryoprobe be passed with fluoroscopic guidance till the resistance via the visceral pleural is felt, then retracted 1 cm before freezing is started (1C, strong recommendation, low quality of evidence).

What Is the Ideal Freezing Time for TBC?

Suggested freezing times have varied between 3 and 6 seconds.[77–79] The minimum freezing time is dependent on the size of the probe that is used. Animal studies have shown that biopsy weight is directly correlated with both freezing time and the size of the cryoprobe.[80] Freezing time is also directly related to the cross-sectional area of the cryobiopsy specimen.[81] Other difficult to control for factors that may affect freezing time include pressure in the CO_2 or nitrous oxide tank and lung tissue characteristics. Accordingly, a freeze test should always be performed in water to adjust the freezing time, and readjustment may be necessary after the first biopsy.

Based on the current body of literature, we recommend a freezing time of three to six seconds for each tissue acquisition (2B, weak recommendation, moderate-quality evidence).

What Size Cryoprobe Should Be Used for the Procedure?

Cryoprobes exist in a variety of sizes and lengths.[82] Reusable flexible cryoprobes come in sizes of 1.9 mm (900 or 1150 mm length) and 2.4 mm (900 mm length). Single-use flexible cryoprobes come in 3 different probe sizes: 1.1, 1.7, or 2.4 mm. The cryoprobes can be paired with either nitrous oxide or carbon dioxide as a cooling gas. Carbon dioxide is a more commonly used cooling gas.[49,83,84] The 2019 ACCP Guideline recommended using the 1.9 mm probe.[7] Using the 1.9 mm allows for enough tissue to be obtained while having enough maneuverability within the 2.8 mm working channel. There is no difference in diagnostic yield between the 1.9 and 2.4 mm probe; data suggest a higher risk of pneumothorax with the larger probe.[68,76] Although the 1.9 mm probe can be placed through a 2.0 mm working channel, 2 critical limitations exist. The friction between the probe and the walls of the working channel makes the tactile identification of the pleura a challenge. In addition, control of bleeding with the 2.0 mm channel is suboptimal.

We suggest a 1.9 mm cryoprobe be used when performing a TBC (2B, weak recommendation, moderate-quality evidence).

What Are the Management Strategies for the Known Serious Complications of TBC?

Pneumothorax

Rates of occurrence vary (10% to 25%), with a weighted pooled estimate of 9.8%.[7,76,85,86] Specific equipment should be on hand for immediate use: chest tube insertion kit, drainage apparatus, ultrasound or fluoroscopy placement guidance, and additional supplies that may be needed to secure and connect the chest tube.[48]

Bleeding

Bleeding can range from mild to severe and fatal. Severe bleeding is estimated to occur in a minority of patients (0.3%).[7] The definition of severe bleeding is variable but is usually defined as bleeding causing hemodynamic consequences, respiratory compromise, or those needing admission to the intensive care unit, tamponade, surgical interventions, or blood transfusion.[20,35,63,87–89] Having a large, secured airway (appropriately sized ETT) or a rigid bronchoscope is necessary. In the case of hemorrhage, the rigid telescope allows for a large working field and ventilation of the contralateral lung. Balloon blockers have found a use for the prevention and management of bleeding.

For the serious complications of iatrogenic pneumothorax and bleeding, operators performing TBC must be trained in their management, and have immediate access to the necessary equipment that has been detailed above (1C, strong recommendation, with low-quality evidence).

Future Directions

Technological advancement and harmonization with imaging may continue to improve TBC outcomes. Animal pilot studies have evaluated the effectiveness of a 1.1 mm mini-cryoprobe with an oversheath.[90,91] Due to the design of the probe a sheath, the bronchoscope can stay in place while the sample is removed through the working channel. In January 2020, the United States Food and Drug Administration approved the use of this smaller probe.[92] In addition, real-time imaging may mitigate complications an improve yield. A small retrospective case series described the use of radial probe endobronchial ultrasound to visualize and avoid areas with the vasculature.[93] Early studies using cone-beam CT-guided TBC have shown a low pneumothorax rate (1.9%).[94] Additional TBC research is undoubtedly warranted. The need for prospective data advocating for the incorporation of TBC into diagnostic algorithms is an area of ongoing research.[95]

CONCLUSIONS

In summary, TBC is becoming an increasingly popular procedure in ILD management. Over the last decade, it has been well studied, appears safer than SLB, and provides reasonable information for MDD. Appropriate patient selection is of utmost importance, and the potential risks must be appropriately balanced with potential benefits. Complications can usually be managed by expert and trained interventional pulmonologists.

As the use of TBC becomes more widespread, we anticipate the generation of more reliable data to guide future procedures. Nevertheless, the body of current literature prevents us from turning a cold shoulder to this minimally invasive, effective, and safe biopsy technique.

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