Bronchoscopic Cryobiopsy and Forceps Biopsy for the Diagnostic Evaluation of Diffuse Parenchymal Lung Disease in Clinical Practice

Matthew Koslow, MD; Eric S. Edell, MD; David E. Midthun, MD; John J. Mullon, MD; Ryan M. Kern, MD; Darlene R. Nelson, MD; Kenneth K. Sakata, MD; Teng Moua, MD; Anja C. Roden, MD; Eunhee S. Yi, MD; Janani S. Reisenauer, MD; Paul A. Decker, MS; and Jay H. Ryu, MD

Abstract

Objective: To assess the contribution and safety of bronchoscopic cryobiopsy vs traditional forceps biopsy used in clinical practice for diagnosing diffuse parenchymal lung disease (DPLD).

Patients and Methods: We identified 271 patients who underwent bronchoscopic biopsy for DPLD at Mayo Clinic, MN (June 1, 2013, through September 30, 2017). Medical records were reviewed including prebiopsy clinical and radiographic impressions. Diagnostic yield was assessed in terms of a specific histologic pattern resulting in a diagnosis when combined with the clinical-radiologic context. Clinical utility was defined as a biopsy result deemed useful in patient management.

Results: The cohort included 120 cryobiopsy and 151 forceps biopsy cases with mean age 61 ± 14 years and 143 (53%) men. Diagnostic yield (55% vs 41%; odds ratio [OR], 1.73; 95% CI, 1.07 to 2.83; P = .026) and clinical utility (60% vs 40%; OR, 2.21; 95% CI, 1.36 to 3.63; P = .001) were higher for the cryobiopsy group, and the association remained after control for prebiopsy clinical impressions (OR, 2.21; 95% CI, 1.22 to 4.08; P = .010 and OR, 3.23; 95% CI, 1.76 to 6.10; P < .001, respectively). However, pneumothorax (5.4% vs 0.7%; P = .022) and serious bleeding (7.1% vs 0%; P = .001) rates were higher for the cryobiopsy group. Thirty-day mortality was 1.6% in the cryobiopsy group vs 0% for the forceps biopsy group (P = .20).

Conclusion: Bronchoscopic cryobiopsy revealed higher diagnostic yield and clinical utility than did forceps biopsy. However, procedure-related complications were higher in the cryobiopsy group. The choice of bronchoscopic biopsy procedure for patients with DPLD depends on the clinical-radiologic context.

Histologic features provided by lung biopsy may be needed in the multidisciplinary diagnosis of diffuse parenchymal lung disease (DPLD), particularly when findings on chest computed tomography (CT) are nonspecific. However, the optimal means for obtaining histology remains unclear. Surgical lung biopsy (SLB) has the highest diagnostic yield but is associated with significant morbidity and mortality. Transbronchial lung cryobiopsy (TBCB) is potentially safer than SLB yet more effective than TBFB because of larger biopsy samples with less crush artifact. Furthermore, TBCB may provide sufficiently high agreement with SLB for histopathologic patterns to offer a safe yet reliable alternative. Despite multiple studies, however, the role of TBCB in the diagnostic algorithm for DPLD remains...
uncertain. In addition, the clinical utility of bronchoscopic lung biopsy has not been studied with assessment of patient-related outcomes. The Expert Statement from the Cryobiopsy Working Group calls for further studies to clarify patient selection criteria, define clinically important end points, and compare TBCB to “standard of care,” which remains to be defined. The objective of this study was to compare the diagnostic yield and safety of TBCB and TBFB used in the diagnostic evaluation of patients with DLPD in clinical practice.

PATIENTS AND METHODS

Patient Selection
The study was approved by the Mayo Clinic Institutional Review Board (IRB 15-008652). Using a computer-assisted search, we identified 826 patients who underwent bronchoscopic lung biopsy for the evaluation of DPLD at Mayo Clinic, Rochester, Minnesota, from June 1, 2013, through September 30, 2017. Patients were excluded if the procedure was performed for an indication other than DPLD (154 mass lesions and 129 cavitary lesions/infections). We also excluded lung transplant recipients (49 TBFB) and procedures for debulking of airway lesions (215 TBCB). Eight patients did not provide Minnesota research authorization and were excluded. The remaining 271 patients comprised the study cohort.

Data Collection
Medical records were reviewed for patient’s demographic characteristics, body mass index (calculated as the weight in kilograms divided by the height in meters squared), smoking history, clinical presentation, comorbidities, resting oxygen saturation, pulmonary function test, echocardiography, prebiopsy clinical and radiologic impressions, treatment, subsequent procedures, and clinical outcome. Prebiopsy clinical impressions were organized by suspected clinical diagnoses for DPLD, and radiologic impression was categorized according to the revised international consensus criteria for idiopathic pulmonary fibrosis (IPF). UIP pattern, probable UIP pattern, indeterminate for UIP pattern, and alternative diagnosis. Each biopsy procedure report was individually reviewed. Bronchoalveolar lavage (BAL) results were recorded when performed. Specific histologic patterns were categorized as “diagnostic” or “nondiagnostic.”

Procedure
Patients were fiberoptically intubated with an 8.0-mm cuffed endotracheal tube using moderate to deep sedation in the bronchoscopy suite. The Mayo Clinic bronchoscopy protocol has been previously described. For TBCB, we routinely placed a deflated 7F or 9F Arndt bronchial blocker (Cook Medical) external to the tube in the mainstem bronchus on the side chosen for biopsy to occlude the airway in case of bleeding. In patients with advanced pulmonary disease, we blocked the entire lung before biopsy for approximately 1 minute to ensure the patient could tolerate single lung ventilation in the event of a severe bleeding episode or pneumothorax. All anticoagulants were discontinued before the procedure per guidelines. The bronroscope (Olympus XT180) was advanced to the segment chosen for biopsy. The 1.9-mm cryoprobe (Erbe Elektromedizin GmbH) was introduced through the working channel of a flexible bronchoscope and passed into the distal airways until meeting resistance, and then withdrawn typically 1 cm from the pleura, under fluoroscopic guidance. The cryoprobe was cooled for 3 to 7 seconds at the desired location and firmly pulled back, separating the frozen biopsy sample from the lung. The bronchial blocker balloon was inflated as the bronchoscope and cryoprobe were removed as a single unit. The tip of the cryoprobe was submerged in saline at room temperature to thaw the specimen, which was transferred to formalin. We inflated the balloon prophylactically to prevent any potential blood from spilling into the airway while the specimen thawed from the tip of the probe. A biopsy was performed on only 1 lung per patient, and 3 cryobiopsy samples were generally obtained from 1 to 2 lobes. The balloon was deflated once the bronchoscope was back in the airway, and bleeding was assessed. All procedures were performed or directly supervised by one of the coauthors (E.S.E., D.E.M., J.J.M., R.M.K., D.R.N.), who were experienced in advanced interventional procedures including TBCB.
Procedural Complications
Complications were assessed according to similar studies and guidelines.\textsuperscript{2,15,23} Pneumothorax was documented per procedural report, radiologic confirmation, and need for chest tube insertion. Significant bleeding was defined by prolonged or repeated balloon occlusion (per procedural note), use of adjunct measures (eg, cold saline), or blood product transfusion.\textsuperscript{23} Escalation of care was defined by a change in the level of clinical care (eg, hospital/intensive care unit admission or increased oxygen/ventilator support).

Clinical Outcomes
The study had co-primary outcomes: diagnostic yield and clinical utility. Diagnostic yield was assessed in terms of a specific histologic pattern identified and resulting in a diagnosis when combined with the clinical/radiologic context. Clinical utility was defined as a biopsy result assessed to be useful in the treatment or management of the patient per the final diagnosis (eg, obviate the need for SLB or allow the initiation of therapy such as immunomodulators).\textsuperscript{19,24} Final diagnosis was determined independently by 2 investigators (M.K. and J.H.R.) on review of all available data including length of follow-up. Discrepancies were reviewed to provide a composite final diagnosis.

Statistical Analyses
Data were analyzed with R software version 3.4.2 (R Core Team). Continuous variables were expressed as mean \(\pm SD\) and median (interquartile range) and categorical variables as frequency and percentage. Kruskal-Wallis and chi-square tests were performed to compare the 2 groups (TBFB and TBCB) for continuous and categorical variables. The association of biopsy (TBFB vs TBCB) with diagnostic yield and clinical utility was assessed using logistic regression adjusted for prebiopsy clinical impressions that differed between groups. Length of follow-up was calculated as the time from the procedure date to the most recent clinical encounter and/or time of death. In all cases, \(P\) values less than .05 were considered statistically significant.

RESULTS
The baseline characteristics of the 271 patients were as follows: 53% men, mean age 61 \(\pm 14\) years, and 34% with smoking history (Table 1). Comorbidities and lung functions did not differ between groups. The mean resting oxygen saturation was 93\(\pm 11\), and 5% of patients were receiving chronic supplemental oxygen. Most (92%) were outpatient procedures.

Prebiopsy clinical diagnoses (Table 2) were similar between groups, except fibrotic interstitial lung disease (ILD), including UIP and non-UIP fibrotic ILD, and aspiration were more frequently sampled with TBCB whereas eosinophilic pneumonia, organizing pneumonia, and infection were more frequently sampled with TBFB. The radiologic diagnosis (Table 3) of “alternative diagnosis” was more frequently associated with TBFB, while “indeterminate UIP” was more frequently associated with TBCB. Only 4 cases radiologically categorized as “probable UIP” and none categorized as “UIP pattern” were referred for bronchoscopic lung biopsy.

Table 4 lists procedural outcomes and complications. Diagnostic yield (55% vs 41%; \(OR, 1.73; 95\% CI, 1.07 to 2.83; P=.026\)) and clinical utility (60% vs 40%; OR, 2.21; 95% CI, 1.36 to 3.63; \(P=.001\)) were higher for the TBCB group than for the TBFB group. The association of higher diagnostic yield and clinical utility with TBCB remained after control for prebiopsy clinical impressions associated with each procedure (OR, 2.21; 95% CI, 1.22 to 4.08; \(P=.010\) and OR, 3.23; 95% CI, 1.76 to 6.10; \(P<.001\), respectively) (Table 5).

Pneumothorax was more common in the TBCB group (5% vs 0.7%; \(P=.022\)) but few required chest tube insertion, with no significant difference observed between TBCB and TBFB groups (0.9% vs 0.7%; \(P=.59\)). Significant bleeding was more frequent in the TBCB group (7% vs 0%; \(P=.001\)), with no difference for procedure-related escalation of care (6% vs 2%; \(P=.09\)). Two deaths in the TBCB group occurred during the 30-day postprocedural period. The first death occurred in a 45-year-old woman with acute exacerbation of ILD. She received increasing oxygen supplementation postprocedure, requiring mechanical ventilator support and died on day 18; she was diagnosed with dermatomyositis-associated ILD. The second death occurred in a 56-year-old man with acute lung injury (acute fibrinous and organizing pneumonia...
pattern) in the setting of sepsis. He was readmitted for refractory status epilepticus of unknown etiology on postprocedure day 29 and died on day 30. Neither patient underwent autopsy.

The histologic diagnosis and corresponding clinical diagnosis per procedure are described in Supplemental Table (available online at http://www.mcpiqojournal.org). The median length of follow-up for TBFB and TBCB groups was 413.5 days (interquartile range, 65-915 days) and 248 days (interquartile range, 37-590 days), respectively.

Discordant Diagnostic Yield and Clinical Utility

Four biopsies (2 TBFB and 2 TBCB) were diagnostic but deemed not clinically useful. In 3 cases, the histologic pattern organizing pneumonia (1 TBFB and 2 TBCB) was associated with a final diagnosis of indeterminate fibrotic ILD (1 case), granulomatous polyangiitis (1 case), and IPF (1 case). The remaining TBFB case was respiratory bronchiolitis in a nonsmoker with a final diagnosis of UIP (per SLB).

Ten biopsies (1 TBFB and 9 TBCB) were considered clinically useful despite nondiagnostic histology. All histologic samples contained adequate lung tissue but nondiagnostic histologic patterns. In 7 cases, immunosuppressive therapy was initiated on the basis of the exclusion of infection and an alternative diagnosis. These cases included 4 hypersensitivity pneumonitis (HP) and 3 connective tissue disease (CTD) associated nonspecific interstitial pneumonia (rheumatoid arthritis, undifferentiated CTD, and polymyositis). The remaining 3 cases included chronic HP, aspiration pneumonia, and resolving Pneumocystis jirovecii pneumonia supported by clinicoradiologic correlation. Assessment of the subsequent clinical course in these patients did not suggest an alternative diagnosis.

Subsequent SLB and Other Procedures

Among 86 nondiagnostic TBFB cases, 14 (16%) underwent subsequent procedures (12 SLB, 1 CT-guided lung biopsy, and 1 rib biopsy [pulmonary Langerhans cell histiocytosis]) and a definitive diagnosis was revealed in

| TABLE 1. Baseline Demographic and Clinical Features of Study Patientsa,b |
|---------------------|---------------------|---------------------|---------------------|
| Parameter           | Total (N=271)       | TBFB (n=151)        | TBCB (n=120)        | P valuec |
| Age (y)             | 61±14               | 59±14               | 62±14               | .091     |
| Male sex            | 143 (53)            | 76 (50)             | 67 (56)             | .37      |
| Smoking history     | 91 (34)             | 48 (32)             | 43 (36)             | .51      |
| COPD                | 16 (6)              | 11 (7)              | 5 (4)               | .27      |
| Pulmonary hypertensiond | 21 (8)               | 17 (12)             | 4 (3)               | .011     |
| Obstructive sleep apnea | 37 (14)           | 24 (16)             | 13 (11)             | .20      |
| CTD                 | 46 (17)             | 25 (17)             | 21 (18)             | .90      |
| Renal insufficiency | 5 (2)               | 4 (3)               | 1 (1)               | .26      |
| Body mass index (kg/m²) | 30±7                | 30±8                | 30±6                | .99      |
| Resting SpO₂%       | 92.5±11             | 94±4                | 91±15               | .22      |
| Supplemental oxygen | 13 (5)              | 7 (6)               | 6 (5)               | .93      |
| FEV₁% predicted     | 74±20               | 74±20               | 73±21               | .84      |
| FEV₁/FVC            | 77±12               | 77±11               | 76±12               | .81      |
| FVC% predicted      | 77±18               | 78±19               | 75±18               | .27      |
| TLC% predicted      | 82±17               | 84±17               | 79±17               | .065     |
| DLCO% predicted     | 64±19               | 65±19               | 51±27               | .20      |

aCOPD = chronic obstructive pulmonary disease; CTD = connective tissue disease; DLCO = single-breath diffusing capacity for carbon monoxide; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; Hgb = hemoglobin (g/dL); SpO₂ = peripheral capillary oxygen saturation; TBCB = transbronchial cryobiopsy; TBFB = transbronchial forceps biopsy; TLC = total lung capacity.

bData are presented as mean ± SD for continuous variables or as No. (percentage) for categorical variables.

cKruskal-Wallis for continuous variables and χ² test for categorical variables.

dEchocardiographic results not available for 62 patients who underwent TBFB (44.9%) and 55 patients who underwent TBCB (47.4%).

MAYO CLINIC PROCEEDINGS: INNOVATIONS, QUALITY & OUTCOMES

Mayo Clin Proc Inn Qual Out • October 2020;4(5):565-574 • https://doi.org/10.1016/j.mcpiqo.2020.05.005

www.mcpiqojournal.org
Among 45 nondiagnostic TBCB cases, 10 (22.2%) underwent subsequent SLB (2 UIP [IPF], 3 chronic HP, 1 cryptogenic constrictive bronchiolitis, 1 desquamative interstitial pneumonia, and 1 pulmonary veno-occlusive disease) and a definitive diagnosis was revealed in 80%.

**DISCUSSION**

We studied the diagnostic yield, clinical utility, and complications associated with the use of TBCB and TBFB in the diagnostic evaluation of DPLD in a tertiary care center experienced in both procedures. Transbronchial cryobiopsy revealed increased diagnostic yield and clinical utility, and the association remained after adjustment for prebiopsy clinical and radiologic impressions associated with each procedure. Procedure-related complications were uncommon in both groups; however, 2 deaths occurred in the TBCB group at postprocedure day 18 and day 30.

### Diagnostic Yield and Clinical Utility

The diagnostic yield of TBCB was higher than that of TBFB in our cohort but lower compared to previous TBCB studies. Possible explanations include technique and

| TABLE 2. Favored Prebiopsy Clinical Diagnosisa,b |
|-----------------------------------------------|
| Diagnosis              | Total (N=271) | TBFB (n=151) | TBCB (n=120) | P valuec |
|-------------------------|---------------|--------------|--------------|-----------|
| Granulomatous, noninfectousd | 133 (49)      | 76 (50)      | 57 (48)      | .64       |
| Non-IPF fibrotic ILDd   | 66 (24)       | 28 (19)      | 38 (32)      | .012      |
| Infectionsi             | 60 (22)       | 46 (31)      | 14 (12)      | <.0001    |
| Organizing pneumoniad   | 53 (20)       | 36 (24)      | 17 (14)      | .046      |
| Indeterminate ILDd      | 52 (19)       | 31 (21)      | 21 (18)      | .53       |
| IPF/UIPi                | 33 (12)       | 10 (7)       | 23 (19)      | .002      |
| Eosinophilic pneumonia  | 29 (11)       | 23 (15)      | 6 (5)        | .007      |
| Neoplasmi               | 27 (10)       | 14 (9)       | 13 (11)      | .67       |
| Vasculitis              | 21 (8)        | 13 (9)       | 8 (7)        | .55       |
| RB-ILD/DIP              | 19 (7)        | 10 (7)       | 9 (8)        | .78       |
| Aspirationi             | 17 (6)        | 5 (3)        | 12 (11)      | .024      |
| pLCH                    | 4 (2)         | 3 (2)        | 1 (0.8)      | .43       |
| DAH                     | 6 (2)         | 4 (3)        | 2 (2)        | .59       |
| Amyloid                 | 3 (1)         | 1 (0.7)      | 2 (2)        | .43       |
| CHF                     | 3 (1)         | 2 (1)        | 1 (0.8)      | .70       |
| Bronchiolitis           | 3 (1)         | 2 (1)        | 1 (0.8)      | .70       |
| PAP                     | 3 (1)         | 2 (1)        | 1 (0.8)      | .70       |
| Lam                     | 1 (0.4)       | 1 (0.7)      | 0            | .37       |
| Pneumoconiosis          | 1 (0.4)       | 1 (0.7)      | 0            | .37       |

aCHF = congestive heart failure; DAH = diffuse alveolar hemorrhage; DIP = desquamative interstitial pneumonia; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; LAM = lymphangioleiomyomatosis; NSIP = nonspecific interstitial pneumonia; PAP = pulmonary alveolar proteinosis; pLCH = pulmonary Langerhans cell histiocytosis; RB-ILD = respiratory bronchiolitis-interstitial lung disease; TBCB = transbronchial cryobiopsy; TBFB = transbronchial forceps biopsy; UIP = usual interstitial pneumonia.
bData are presented as No. (percentage).
cChi-square test.
dNoninfectious granulomatous process, eg, sarcoidosis (well-formed noncaseating granulomas), hypersensitivity pneumonitis (poorly formed granulomas, lymphocytic interstitial infiltrates, and cellular bronchiolitis).

#CHF : congestive heart failure; DAH : diffuse alveolar hemorrhage; DIP : desquamative interstitial pneumonia; ILD : interstitial lung disease; IPF : idiopathic pulmonary fibrosis; LAM : lymphangioleiomyomatosis; NSIP : nonspecific interstitial pneumonia; PAP : pulmonary alveolar proteinosis; pLCH : pulmonary Langerhans cell histiocytosis; RB-ILD : respiratory bronchiolitis-interstitial lung disease; TBCB : transbronchial cryobiopsy; TBFB : transbronchial forceps biopsy; UIP : usual interstitial pneumonia.

#Data are presented as No. (percentage).

#CHF : congestive heart failure; DAH : diffuse alveolar hemorrhage; DIP : desquamative interstitial pneumonia; ILD : interstitial lung disease; IPF : idiopathic pulmonary fibrosis; LAM : lymphangioleiomyomatosis; NSIP : nonspecific interstitial pneumonia; PAP : pulmonary alveolar proteinosis; pLCH : pulmonary Langerhans cell histiocytosis; RB-ILD : respiratory bronchiolitis-interstitial lung disease; TBCB : transbronchial cryobiopsy; TBFB : transbronchial forceps biopsy; UIP : usual interstitial pneumonia.

#Data are presented as No. (percentage).

#CHF : congestive heart failure; DAH : diffuse alveolar hemorrhage; DIP : desquamative interstitial pneumonia; ILD : interstitial lung disease; IPF : idiopathic pulmonary fibrosis; LAM : lymphangioleiomyomatosis; NSIP : nonspecific interstitial pneumonia; PAP : pulmonary alveolar proteinosis; pLCH : pulmonary Langerhans cell histiocytosis; RB-ILD : respiratory bronchiolitis-interstitial lung disease; TBCB : transbronchial cryobiopsy; TBFB : transbronchial forceps biopsy; UIP : usual interstitial pneumonia.

#Data are presented as No. (percentage).
patient selection. For example, a more peripheral placement of the cryoprobe might increase the diagnostic yield, particularly for predominantly subpleural disease process such as UIP, but is associated with an increased risk of pneumothorax. Our group has not intentionally tried to include pleura in the biopsy. Diagnostic yield may be affected by patient selection. This was assessed in our study by prebiopsy clinical and radiographic impressions. Of 271 patients in our cohort, only 1.7% of patients with a “probable UIP pattern” and none with a “UIP pattern imaging pattern were referred for bronchoscopic biopsy, which may reflect a preference in our practice to avoid biopsy in such patients. This may also explain the observation that UIP (3.3% TBFB and 7.5% TBCB) was far less common in our study compared with other TBCB studies.15

“Diagnostic” histopathologic patterns attained by bronchoscopic biopsies, in the absence of clinicalradiologic correlation, may be misleading as suggested by the recent study by Romagnoli et al25 comparing TBCB and SLB. In contrast, Troy and coworkers13,14 reported a good concordance between TBCB and SLB for both histopathologic pattern and consensus diagnosis in the context of multidisciplinary discussion, particularly for high-confidence patterns. Some cases without high-confidence diagnoses deserve a “provisional diagnosis” to emphasize the need to reassess over time.26

Clinical utility, in our study, was defined as a biopsy result useful in the treatment or management of the patient and consistent with the final diagnosis. In addition to subsequent SLB results (when available), the final diagnosis was supported by the clinicoradiologic course

| TABLE 3. Prebiopsy Radiologic Diagnosisa,b |
|------------------------------------------|
| Diagnosis | Total (N=271) | TBFB (n=151) | TBCB (n=120) | P valuec |
|----------|-------------|-------------|-------------|----------|
| UIP      | 0           |             |             | .002     |
| Probable UIP | 4 (1.7)  | 2 (2)       | 2 (2)       |          |
| Indeterminate UIP | 60 (25) | 20 (16)     | 40 (36)     |          |
| Alternative diagnosis | 174 (73) | 104 (83)    | 70 (63)     |          |

*TBCB = transbronchial cryobiopsy; TBFB = transbronchial forceps biopsy; UIP = usual interstitial pneumonia.

aData are presented as No. (percentage).

Chi-square test.

| TABLE 4. Procedural Outcomes and Complications per Bronchoscopic Procedurea,b |
|------------------------------------------|
| Parameter | Total (N=271) | TBFB (n=151) | TBCB (n=120) | P valuec |
|-----------|-------------|-------------|-------------|----------|
| BAL performed | 223 (89) | 137 (95) | 86 (81) | <.001 |
| Diagnostic yield | 128 (47) | 62 (41) | 66 (55) | .025 |
| Clinical utility | 133 (49) | 61 (40) | 72 (60) | .001 |
| Pneumothorax | 7 (3) | 1 (0.7) | 6 (5) | .022 |
| Chest tube insertion | 2 (1) | 1 (0.7) | 1 (0.9) | .59 |
| Significant bleeding | 8 (3.1) | 0 | 8 (7) | .001 |
| Escalation of care | 10 (4) | 3 (2) | 7 (6) | .09 |
| 30-d mortality | 2 (0.7) | 0 | 2 (1.6) | .20 |

*BAL = bronchoalveolar lavage; TBCB = transbronchial cryobiopsy; TBFB = transbronchial forceps biopsy.

aData are presented as No. (percentage).

Chi-square test.

**Significant bleeding was defined as the need for blood products (n=0) or change in procedure protocol to control excessive bleeding (eg, prolonged tamponade).

*Escalation of care was defined as the change in disposition (hospitalization/intensive care unit admission) or increase in ventilator/oxygen requirements upon discharge from the postprocedural recovery unit.
and strengthened the diagnostic reliability in certain cases. Ten cases (9 TBCB and 1 TBFB) were clinically useful despite nondiagnostic biopsies. In all cases, adequate lung tissue was obtained and deemed sufficient to exclude infection/alternative diagnoses and enable immunomodulatory therapy in 7 cases and confirm clinical suspicion in 3 cases.

Surgical Lung Biopsy for Nondiagnostic Bronchoscopy

Diagnostic bronchoscopy may prevent the need for SLB according to clinical pathways proposed in recent guidelines. In our study, only 22.2% and 16.2% of nondiagnostic TBCB and TBFB cases, respectively, underwent SLB (or other procedures) for a definitive diagnosis. Of 14 TBFB and 10 TBCB nondiagnostic cases that underwent additional procedures (22 SLB, 1 CT-guided lung, and 1 CT-guided rib biopsy), 91.6% had a definitive diagnosis.

Mortality

The Expert Statement from the Cryobiopsy Working Group recommends TBCB as a safer alternative to SLB. However, reports of life-threatening complications and mortality, including the 2 cases described in our study, raise some concern over the safety profile and patient selection criteria. If TBCB is to offer a safer alternative to SLB, then observations from the SLB literature may have relevance. For example, preoperative risk factors for mortality in patients undergoing SLB have included supplemental oxygen, ventilator dependence, increased age, and pulmonary hypertension as well as specific underlying diagnoses, particularly IPF. In the study by Kreider et al, the 3 patients who died shortly after SLB exhibited new infiltrates on chest CT unexplained by infection, congestive heart failure, or pulmonary embolism; postmortem examination revealed diffuse alveolar damage superimposed on UIP, suggesting acute exacerbation of IPF. In a similar report, Parambil et al observed high mortality (86%) in patients after SLB in whom histopathology revealed diffuse alveolar damage superimposed on UIP; all patients presented with bilateral infiltrates, BAL neutrophilia without infection, and normal echocardiography at the time of presentation. Utz et al observed increased mortality (16% vs 0%) in patients with idiopathic UIP (IPF) compared to CTD-associated UIP. Finally, Hutchinson et al studied 32,022 cases of SLB for the diagnosis of ILD in which inpatient mortality ranged from 1.7% to 16% for elective and nonelective procedures, respectively. All these studies suggest increased preoperative risk in patients presenting with acute exacerbation, particularly those with underlying IPF.

Mortality in patients undergoing TBCB may be underestimated. Although procedure-related complications such as pneumothorax and bleeding are well documented in multiple TBCB studies, reports of 30-day deaths appear limited to those deemed related to the procedure. This limitation may explain the very low 0.3% mortality in the meta-analysis by Sethi et al. The true mortality risk may be higher as indicated in our study and the 2% 30-day mortality rate in the recent prospective study by Hagmeyer et al. More recently, Pannu et al also reported a 30-day mortality rate of 2.0% in 187 patients undergoing TBCB.

The complication rate was otherwise low in our study. The low bleeding rate may be attributed to the routine use of an endobronchial blocker, and the procedure-related escalation of care was low and did not differ between groups. Selective balloon occlusion of the predetermined side for biopsy, to predict ventilatory reserve in the event of bleeding.

### TABLE 5. Comparative Outcomes Adjusted by Prebiopsy Clinical and Radiographic Impressions

| Outcome                          | Odds ratio | 95% CI  | P value |
|---------------------------------|------------|---------|---------|
| Association with diagnostic yield | TBCB       | 1.73    | 1.07-2.83 | .026    |
| Association with clinical impression | TBCB       | 2.21    | 1.22-4.08 | .010    |

*ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; TBCB = transbronchial cryobiopsy; TBFB = transbronchial forceps biopsy; UIP = usual interstitial pneumonia.

$P$-values: $<.001$. For dependent $t$-test.

**TABLE 5.** Comparative Outcomes Adjusted by Prebiopsy Clinical and Radiographic Impressions

1. IPF = idiopathic pulmonary fibrosis; CTD-associated UIP = connective tissue diseases-associated usual interstitial pneumonia.
2. UBB = unobtainable biopsy; UIP = usual interstitial pneumonia, indeterminate UIP = indeterminate UIP.
3. TBCB: transbronchial cryobiopsy; TBFB: transbronchial forceps biopsy; UIP: usual interstitial pneumonia.
4. *ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; TBCB = transbronchial cryobiopsy; TBFB = transbronchial forceps biopsy; UIP = usual interstitial pneumonia.*
5. Prebiopsy clinical impressions: UIP/IPF, non-IPF fibrotic ILD, and aspiration pneumonitis were associated with TBCB ($P=0.002$, $P=0.012$, and $P=0.024$, respectively). Eosinophilic pneumonia, organizing pneumonia, and infection were associated with TBFB ($P=0.007$, $P=0.046$, and $P=0.001$, respectively).
6. Radiographic impression “indeterminate UIP” was associated with TBCB, whereas “alternative diagnosis” was associated with TBFB ($P=0.002$).
or pneumothorax, may explain the low rate of procedure-related respiratory compromise. The pneumothorax rate was higher for TBCB than for TBFB, but the need for chest tube insertion did not differ significantly between groups. Notably, the TBCB pneumothorax rate was lower in our study than in previous TBCB studies, which report higher histopathologic yield. 

The decision to pursue bronchoscopy and which sampling methods to use (ie, BAL and biopsy modality) should be made on the basis of the nature of the diagnostic dilemma at hand. The desire for increased diagnostic certainty may be achieved with biopsy, and thus TBCB appears to have increased utility compared with TBFB. In certain cases, however, increased confidence for a treatment decision may be achieved with BAL alone. For example, 7 of 10 cases in this study were deemed “clinically useful despite nondiagnostic histology” because the procedure enabled immunosuppressive therapy on the basis of the exclusion of infection and alternative diagnoses; all histologic samples contained adequate lung tissue but nondiagnostic histologic patterns.

**Limitations**

Limitations in our study include those inherent in the retrospective design. In particular, the preferential selection of suspected UIP cases and non-UIP fibrotic ILD for TBCB may have reduced the comparative efficacy of TBCB over TBFB. Because of the lack of randomization, the study does not address whether TBFB and TBCB reveal comparable yield in diseases with bronchocentric and perilymphatic distribution, such as sarcoidosis and lymphangitic carcinomatosis, although this premise is suggested by previous studies and experience. The applicability of our findings to the spectrum of DPLD is supported by the wide range of prebiopsy clinical impressions and final diagnoses distributed between both groups.

**CONCLUSION**

Transbronchial cryobiopsy revealed increased diagnostic yield and clinical utility in the diagnostic evaluation of DPLD in clinical practice despite selection for more challenging cases. Both procedures were associated with low complication rates, but 2 deaths occurred in the TBCB group during the 30-day postprocedural period; both patients underwent bronchoscopy during the acute worsening of lung disease. For patients with nondiagnostic bronchoscopic biopsy results, the clinical utility of an additional biopsy procedure for diagnostic clarification needs to be decided on a case-by-case basis. Future studies of TBCB should include systematic reporting of 30-day mortality to identify patients at an increased risk of delayed complications and mortality.

**ACKNOWLEDGMENTS**

Drs Koslow and Ryu act as scientific guarantors taking responsibility for the content, data, and analysis.

**SUPPLEMENTAL ONLINE MATERIAL**

Supplemental material can be found online at: http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

**Abbreviations and Acronyms:** BAL = bronchoalveolar lavage; CT = computed tomography; CTD = connective tissue disease; DAH = diffuse alveolar hemorrhage; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; OR = odds ratio; SLB = surgical lung biopsy; TBCB = transbronchial cryobiopsy; TBFB = transbronchial forceps biopsy; UIP = usual interstitial pneumonia

**Affiliations (Continued from the first page of this article):** (A.C.R., E.S.Y.), Department of Health Sciences Research (P.A.D.), and Department of Thoracic Surgery (J.S.R.), Mayo Clinic, Rochester, MN; and Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Interstitial Lung Disease Program, National Jewish Health, Interstitial Lung Disease and Autoimmune Lung Center, Denver, CO (M.K.).

**Potential Competing Interests:** The authors report no competing interests.

**Correspondence:** Address to Matthew Koslow, MD, Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, National Jewish Health, Denver, CO 80206 (mkoslow73@gmail.com).

**REFERENCES**

1. Lynch DA, Sverzellati N, Travis WD, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. Lancet Respir Med. 2018;6(2):138-153.
2. Ravaglia C, Bonfazi M, Wells AU, et al. Safety and diagnostic yield of transbronchial lung cryobiopsy in diffuse parenchymal lung diseases: a comparative study versus video-assisted thoracoscopic lung biopsy and a systematic review of the literature. *Respiration*. 2021;101(9):215-227.

3. Sriraman T, Aragaki A, Baughman R, et al. A single US center experience of transbronchial lung cryobiopsy for diagnosing interstitial lung disease with a 2-scope technique. *J Bronchology Interv Pulmonol*. 2017;24(2):131-135.

4. Ravaglia C, Wells AU, Tomassetti S, et al. Diagnostic yield and risk/benefit analysis of transbronchial lung cryobiopsy in diffuse parenchymal lung diseases: a large cohort of 699 patients. *BMJ Pulm Med*. 2020;19(1):16.

5. Cooley J, Balesta R, Aragaki-Nakahodo AA, et al. Safety of performing transbronchial lung cryobiopsy on hospitalized patients with interstitial lung disease. *Respirology*. 2018;140(7):76.

6. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JSRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*. 2018;198(5):e44-e68.

7. Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States: 2000 to 2011. *Am J Respir Crit Care Med*. 2016;193(10):1161-1167.

8. Sheth JS, Belperio JA, Fishbein MC, et al. Utility of transbronchial vs surgical lung biopsy in the diagnosis of suspected fibrotic interstitial lung disease. *Chest*. 2017;151(2):389-399.

9. Wall CP, Gaensler EA, Carrington CB, Hayes JA. Comparison of transbronchial and open biopsies in chronic infiltrative lung diseases. *Am Rev Respir Dis*. 1981;123(3):280-285.

10. Steth SJ, Al-Saady M, Mohanaray N, Nanchal R, Maldonado F, Mulsani A. Are transbronchial cryobiopsies ready for prime time? A systematic review and meta-analysis. *J Bronchology Interv Pulmonol*. 2019;26(2):22-32.

11. Colby TV, Tomassetti S, Cazzava A, Dubini A, Poletti V. Transbronchial cryobiopsy in diffuse lung disease: update for the pathologist. *Arch Pathol Lab Med*. 2017;141(7):891-900.

12. Roder AC, Kern RM, Aubry MC, et al. Transbronchial cryobiopsies in the evaluation of lung alfragia: do the benefits outweigh the risks? *Arch Pathol Lab Med*. 2016;140(4):303-311.

13. Troy LK, Grange C, Corti TJ, et al. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. *Lancet Respir Med*. 2020;8(2):171-181.

14. Vuckovic D, Grange C, Corti TJ, et al.; COLDICE Investigator Team. Cryobiopsy versus open lung biopsy in the diagnosis of interstitial lung disease (COLDICE): protocol of a multicentre study. *BMJ Open Respir Res*. 2019;6(1):e000443.

15. Lentz RJ, Argento AC, Colby TV, Rickman OB, Maldonado F. Transbronchial cryobiopsy for diffuse parenchymal lung disease: a state-of-the-art review of procedural techniques, current evidence, and future challenges. *J Thorac Dis*. 2017;9(7):2185-2203.

16. Casani GL, Tomassetti S, Cazzava A, et al. Transbronchial lung cryobiopsy in the diagnosis of fibrotic interstitial lung diseases. *PLoS One*. 2014;9(2):e86716.

17. Ussavangsuy K, Kern RM, Roder AC, Ryu JH, Eidel ES. Transbronchial cryobiopsy in diffuse parenchymal lung disease: retrospective analysis of 74 cases. *Chest*. 2017;151(2):400-408.

18. Ramaswamy A, Honer R, Killam J, et al. Comparison of transbronchial and cryobiosies in evaluation of diffuse parenchymal lung disease. *J Bronchology Interv Pulmonol*. 2016;23(1):1-42.

19. Ersnimer SA, Prakash UB. Is bronchoscopic lung biopsy helpful in the management of patients with diffuse lung disease? *Eur Respir J*. 2006;28(6):1081-1084.

20. Pimpalwar V, Sagade C, Jadhav C, et al. Transbronchial cryobiopsies for the diagnosis of diffuse parenchymal lung diseases: expert statement from the Cryobiopsy Working Group on Safety and Utility and a call for standardization of the procedure. *Respiration*. 2018;95(3):188-200.

21. Hofheberger LA, DePew ZS, Utz JP, Edell ES, Maldonado F. Utilizing an endobronchial blocker and a flexible bronchoscope for transbronchial cryobiopsies in diffuse parenchymal lung disease. *Respiration*. 2018;88(6):521-522.

22. Baron TH, Kamath PS, McAnas RD. Management of antimicrobial therapy in patients undergoing invasive procedures. *N Engl J Med*. 2017;376(22):213-212.

23. Du Rand IA, Blakley J, Boothon R, et al; British Thoracic Society Bronchoscopy Guideline Group. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. *Thorax*. 2013;68(suppl 1):i1-i44.

24. Philipponn C, Cassagnes L, Pereira B, et al. Diagnostic yield and therapeutic impact of open lung biopsy in the critically ill patient. *PLoS One*. 2011;6(5):e196795.

25. Ramagno M, Colby TV, Berthet JP, et al. Poor concordance between sequential transbronchial lung cryobiopsy and surgical lung biopsy in the diagnosis of diffuse interstitial lung diseases. *Am J Respir Crit Care Med*. 2019;199(10):1249-1256.

26. Ryerson CJ, Corti TJ, Lee JS, et al. A standardized diagnostic ontology for fibrotic interstitial lung disease: an international working group perspective. *Am J Respir Crit Care Med*. 2017;196(10):1249-1254.

27. Thomerson CC, Duggal A, Rice T, Ledener DJ, Wilson KC, Raghu G. 2018 Clinical Practice Guideline Summary for Practicing Clinicians: Diagnosis of Idiopathic Pulmonary Fibrosis. *Am Thorac Soc*. 2019;16(3):285-290.

28. DiBardino DM, Haas AR, Lanfranco AR, Litsky LA, Sterman D, Bessich JL. High complication rate after introduction of transbronchial cryobiopsy into clinical practice at an academic medical center. *Ann Am Thorac Soc*. 2017;14(4):575-587.

29. Lentz RJ, Argento AC, Rickman OB, et al. Transbronchial cryobiopsy: a cautionary tale and opportunities for improvement. *Ann Thorac Soc*. 2017;14(7):1230-1231.

30. Echevarria-Uraga JF, Perez-Izquierdo J, Garcia-Garai N, et al. Usefulness of an angioplasty balloon as selective bronchial blockade device after transbronchial cryobiopsy. *Respirology*. 2016(12):1094-1099.

31. Hagmeyer L, Theegarten D, Tremi M, Prieznitz C, Randerath W. Validation of transbronchial cryobiopsy in interstitial lung disease— interim analysis of a prospective trial and critical review of the literature. *Sarcoidosis Vascul Disord Lung Dis*. 2016;13(2):2-9.

32. Tomassetti S, Wells AU, Costabel U, et al. Bronchoscopic lung cryobiopsy increases diagnostic confidence in the multidisciplinary diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2016;88(7):745-752.

33. Kayatta MO, Ahmed S, Hammel JA, et al. Surgical biopsy of suspected interstitial lung disease is superior to radiographic diagnosis. *Ann Thorac Surg*. 2013;89(2):399-401.

34. Kreider ME, Hansen-Flaschen J, Ahmad NN, et al. Complications of video-assisted thoracoscopic lung biopsy in patients with interstitial lung disease. *Ann Thorac Surg*. 2007;83(3):1140-1144.

35. Cambillo G, Estrada A, Pedroza J, et al. Preoperative risk factors associated with mortality in lung biopsy patients with interstitial lung disease. *J Invest Surg*. 2005;18(1):39-45.

36. Parambil JG, Myers JL, Aubry MC, Ryu JH. Causes and prognosis of diffuse alveolar damage diagnosed on surgical lung biopsy. *Chest*. 2007;132(1):50-57.

37. Utz JP, Ryu JH, Douglas WW, et al. High-short mortality following lung biopsy for usual interstitial pneumonia. *Eur Respir J*. 2001;17(2):175-179.

38. Hutchinson JP, McKeever TM, Fogarty AW, Navarathnam V, Hubbard RB. Surgical lung biopsy for the diagnosis of interstitial lung disease. *Respirology*. 2016;21(6):303-311.

39. Hagmeyer L, Theegarten D, Wohlschläger J, et al. The role of transbronchial cryobiopsy and surgical lung biopsy in the diagnosis of diffuse alveolar damage diagnosed on surgical lung biopsy. *Respiration*. 2016;85(6):573-580.
diagnostic algorithm of interstitial lung disease. Clin Respir J. 2016;10(5):589-595.

40. Hagmeyer L, Theegarten D, Wohlschlager J, et al. Transbronchial cryobiopsy in fibrosing interstitial lung disease: modifications of the procedure lead to risk reduction. Thorax. 2019;74(7):711-714.

41. Pannu J, Roller LJ, Maldonado F, Lentz RJ, Chen H, Rickman OB. Transbronchial cryobiopsy for diffuse parenchymal lung disease: 30- and 90-day mortality. Eur Respir J. 2019;54(4):1900337.

42. Descombes E, Gardiol D, Leuenberger P. Transbronchial lung biopsy: an analysis of 530 cases with reference to the number of samples. Monaldi Arch Chest Dis. 1997;52(4):324-329.

43. Gilman MJ. Transbronchial biopsy in sarcoidosis. Chest. 1983;83(1):159.

44. Gilman MJ, Wang KP. Transbronchial lung biopsy in sarcoidosis: an approach to determine the optimal number of biopsies. Am Rev Respir Dis. 1980;122(5):721-724.