Surgical Lung Biopsy in Adult Respiratory Distress Syndrome: A Meta-Analysis

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Background. Adult respiratory distress syndrome (ARDS) has a high mortality rate and consumes considerable health care resources. It is not clear whether specimens obtained from open lung biopsy (OLB) in ARDS provide a specific diagnosis, alter therapy, or affect outcome. This meta-analysis attempts to determine whether OLB is safe, provides a specific diagnosis, changes therapy, or affects survival.

Methods. A computerized search was performed of Medline and PubMed from January 1988 to December 2012 of English language studies of acute respiratory failure and diffuse pulmonary infiltrates that evaluated OLB in primarily adult mechanically ventilated patients. Of 194 abstracts retrieved, 64 articles were reviewed; 130 articles were excluded because they did not evaluate OLB. After applying the selection criteria, 24 articles were included.

Results. OLB in ARDS provided a specific diagnosis in 84% of patients and altered management in 73%. Hospital mortality was 43%. The complication rate for OLB in ARDS was 22%, but death from OLB was rare.

Conclusions. OLB in ARDS is a potentially productive procedure that provides a specific diagnosis and leads to a change in management in high proportions of patients. ARDS has a high mortality rate, which OLB does not appear to increase. Owing to a lack of randomized controlled trials, a survival advantage of OLB in ARDS could not be demonstrated.

Material and Methods

English language studies of acute respiratory failure and diffuse pulmonary infiltrates were eligible for the meta-analysis if they fulfilled the following criteria: original publication evaluating the use of OLB as a diagnostic tool and the inclusion of predominantly ventilated adult patients. Exclusion criteria were studies conducted solely on pediatric patients and studies that contained no ventilated patients. Five outcomes of interest were hospital mortality rate, surgical complication rate, change in management, frequency of making a specific diagnosis, and mortality rate associated with OLB. Surgical death from OLB was defined as death within 24 hours of the procedure.

Literature Search

A search of Medline and PubMed from January 1988 to December 2012 was conducted. Search terms included “acute respiratory distress syndrome,” “adult respiratory distress syndrome,” “diffuse alveolar damage,” “diffuse pulmonary infiltrates,” “undiagnosed pulmonary infiltrates,” “surgical lung biopsy,” “open lung biopsy,” and...
“video-assisted thoracoscopic surgery (VATS).” Full articles of appropriate abstracts and bibliographies were reviewed to identify studies that met the inclusion criteria.

Of the 194 abstracts returned from the Medline and PubMed searches, 64 articles were reviewed (Fig 1). Of these, 130 articles were not included because they did not investigate patients who underwent OLB or investigated the use of fine-needle aspiration or transbronchial biopsies, and 40 articles were excluded based on study population. Twenty-four articles were identified for meta-analysis (Appendix Table 1).

Study Quality Assessment
Most of the studies were retrospective reviews. There were some prospective trials, but no prospective randomized controlled trials were identified.

Statistical Considerations
We conducted a meta-analysis of four of the five outcomes of interest. The procedural mortality rate was excluded because it was 0% in most studies and could not be combined statistically. One to 3 studies were not included in some of the pooled results because outcome data were missing. Pooled outcome proportions were calculated using a random-effects (DerSimonian-Laird) model, and forest plots were generated to display the individual study and pooled outcome proportions. Random-effects models were used to combine the studies because of the variability in the outcomes of interest between the studies. To assess the combinability of the outcome proportions, we reported the p value from the Cochrane Q statistical heterogeneity test. Because the heterogeneity test p values were all less than 0.05 (all <0.0001), the random-effects analysis was used for all outcome proportions rather than a fixed-effects analysis. The random-effects analysis allows for more variability in the individual study proportion estimates when generating the pooled outcome proportion. Calculations were performed with StatsDirect 2.7.9 software (7/9/2012 StatsDirect Ltd, Cheshire, UK).

Results
The frequency of making a specific diagnosis by OLB specimen was examined. The Cochrane Q statistical heterogeneity test had a p value of less than 0.0001. The random-effects (DerSimonian-Laird) pooled proportion for the specific diagnosis rate was 0.84 (95% confidence interval, 0.75 to 0.92; Appendix Table 2 and Fig 2A). One study was excluded due to lack of available data on specific diagnosis.

The frequency of each pathologic diagnosis is shown in Figure 3 (also see Appendix Table 3). The most common diagnoses were infections and interstitial lung diseases. Of a total of 1,205 pooled patients, 284 (23.6%) had histology and tissue culture positive for infection: 7.3% cytomegalovirus, 2% tuberculosis, 3% Pneumocystis, 1% viral, and 2% fungal. Interstitial lung diseases accounted for 25% of all the pathologic diagnoses: usual interstitial pneumonitis, 13%; diffuse alveolar damage, 8.5%. Pulmonary embolism (1.1%), drug reaction (1.6%), diffuse alveolar hemorrhage (0.6%), and other diagnoses accounted for small percentages. Autoimmune processes such as cryptogenic organizing pneumonia, sarcoidosis, and Wegener granulomatosis accounted for 7%. Neoplastic diseases (primary lung cancer, metastatic disease, and lymphoma) accounted for 12%.

The rate of change in management was examined. The Cochrane Q statistical heterogeneity test had a p value of less than 0.0001. The random-effects (DerSimonian-Laird) pooled proportion for the change in management rate for the 23 included studies was 0.73 (95% CI, 0.65 to 0.80; Appendix Table 2 and Fig 2B). Two studies were excluded due to lack of data on change in management.

Changes in management achieved by OLB are reported in Table 1. Of 169 patients included in the Tables outlining the specific complications and pathologic diagnoses made by OLB, 2 studies, Hill and colleagues [1] (42 patients) and Neuhaus and colleagues [2] (127 patients), did not supply data on specific change in management. Of the remaining 1,210 patients, OLB led to a change in management in 73%. The addition or increase in the dose of steroids accounted for 17%. A change in antibacterial antibiotics occurred in 3%, in antivirals in 2%, and in antifungals in 0.5%. Chemotherapy was initiated in 3%, and anticoagulation was started in 0.6%. Treatment was limited or withdrawn in 4% of patients after OLB.

Of 1,336 patients who underwent OLB, 9.5% had VATS. The surgical complication rate between types of procedures was not reported separately, and only 3 studies reported numbers of bedside procedures vs OLB done in the operating room. The exact number of lobes samples was not consistently reported. Specific information about preoperative diagnostic testing was provided in 20 of 24 studies. Of 1,013 patients where these data were available, 688 (68%) had a bronchoscopy with BAL before OLB. Only 4 studies supplied data concerning the rate of
consistency of preoperative BAL to the pathologic diagnoses made by OLB [3–6]; 13 of 119 patients (10.9%) had a positive BAL results before OLB that was subsequently consistent with the pathologic diagnosis (Table 2).

For the overall hospital mortality rate, the Cochran Q statistical heterogeneity test had a p value of less than 0.0001. The random effects (DerSimonian-Laird) pooled proportion for the hospital mortality rate for the 24 included studies was 0.44 (95% CI, 0.36 to 0.52; Appendix Table 2 and Fig 2C). One study was not included because the hospital mortality rate was not reported.

For the complication rate of OLB, the Cochrane Q statistical heterogeneity test p value was less than 0.0001. The random-effects (DerSimonian-Laird) pooled proportion
for the surgical complication rate for the 22 included studies was 0.23 (95% CI, 0.16 to 0.31; Appendix Table 2 and Fig 2D). Two studies were excluded because they did not include data on the surgical complication rate.

The surgical complication rate from OLB was 22%, but mortality from OLB was infrequent. The most common OLB complication was pneumothorax, which was effectively treated (Fig 4). Earlier studies generally used thoracotomy to perform OLB, whereas later studies included VATS as an optional technique. Overall, almost all patients underwent thoracotomies for OLB because single-lung ventilation was not an option in the patients supported with mechanical ventilation with high fraction of inspired oxygen (FiO2) and positive end-expiratory pressure (PEEP) requirements preoperatively.

**Comment**

Although diagnostic techniques such as BAL are commonly performed in patients with ARDS, they uncommonly lead to a specific diagnosis: 70% of patients had at least 1 bronchoscopy with BAL before OLB, but in only 10% was BAL consistent with the pathologic diagnosis from OLB. The high mortality rate of ARDS without a specific diagnosis raises the question of whether OLB should be performed. Several studies (Appendix Table 1) have examined OLB in patients who are critically ill, mechanically ventilated, and have diffuse pulmonary infiltrates. It is difficult to draw conclusions from individual studies, which are frequently from single institutions, retrospective, and contain biases such as indications for biopsy referral and quality of surgical and postsurgical care. This meta-analysis sought to combine the experience from multiple studies to determine how often OLB results in a specific diagnosis that changes management in ARDS.

In 1994 at the North American-European Consensus Conference, criteria were established for ARDS and ALI. The onset had to be acute and persistent. Patients had to have diffuse bilateral pulmonary infiltrates consistent with pulmonary edema and demonstrate impaired oxygenation regardless of the PEEP, with a partial pressure of arterial oxygen (PaO2)/FiO2 ratio of 300 mm Hg or less (40 kPa) for ALI and 200 mm Hg or less (27 kPa) for ARDS. Exclusion criteria included clinical evidence of left atrial hypertension (pulmonary artery catheter occlusion pressure, pulmonary capillary wedge pressure ≥18 mm Hg). In 2012 the Berlin Definition of ARDS defined ARDS as an acute illness, within 1 week of clinical insult, with progression of respiratory symptoms, bilateral opacities on chest imaging. The Berlin Definition2 removed the pulmonary capillary wedge pressure criterion except when no risk factors for ARDS were identified. The ALI category was removed, and three distinct subgroups of ARDS were described: mild ARDS as a PaO2/FiO2 ratio of 201 to 300 mm Hg (≤39.9 kPa); moderate ARDS as a PaO2/FiO2 ratio of 101 to 200 mm Hg (≤26.6 kPa); and severe ARDS as a PaO2/FiO2 ratio of 100 mm Hg or less (≤13.3 kPa). A minimum PEEP of 5 cm H2O is required delivery could be noninvasively with continuous positive air pressure. The patients included in this meta-
analysis conformed to the Berlin and European definitions for ARDS. This meta-analysis confirms that the diagnostic accuracy of an OLB specimen is superior to BAL in ARDS, provides a specific diagnosis in 84%, and leads to a change in management 73% of patients. Because the literature primarily contains retrospective observational studies, a survival benefit of OLB could not be ascertained. In 1998 Reynolds and colleagues [27] reported 5 million patients with ARDS and found that overall mortality ranged from 36% to 52%, comparable to the present pooled outcome 43% (95% CI, 36% to 53%). Zambon and Vincent [28] analyzed patients with ARDS from 1994 to 2006 and found a wide range (15% to 72%) and a pooled mortality rate of 43% (95% CI, 40% to 46%). One trial of OLB in ARDS with negative result from BAL found that a contributive OLB result improved the outcome (67% survival in patients with a contributive OLB vs 14% survival in patients where results did not modify treatment; \( p < 0.001 \)) [23]. Others observed improved survival for patients who underwent OLB early rather than at a later stage (4 days [64% survival] vs 11 days [11% survival]) and reported that the primary determinants of death were \( \text{PaO}_2/\text{FiO}_2 \) ratio, the Charlson age–comorbidity score, and the number of organ dysfunctions [24]. Some reports suggest that for patients with hematologic malignancy or hematopoietic stem cell transplantation presenting with unexplained pulmonary infiltrates, making a specific diagnosis from OLB was associated with a lower mortality rate when compared with a nonspecific finding [5, 6, 10]. There seemed to be a trend toward improved survival for patients with interstitial infiltrates on imaging, negative BAL, and negative cultures [6, 29–32]. Some studies showed a trend toward improved survival in immunocompromised patients who underwent early OLB, had a pathologic diagnosis of interstitial pneumonia, and were treated with steroids. Others showed that the addition of new therapies once a definitive diagnosis was made by OLB was more beneficial in the early OLB group than in patients who underwent OLB later [12]. However, others did not find that the timing of OLB led to changes in diagnoses, achieving specific diagnoses, treatment alterations, procedure-related complications, or in-hospital mortality [20]. Some studies found no benefit

<table>
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<th>Study (First Author)</th>
<th>Total Patients (No.)</th>
<th>Thoracotomy Patients (%)</th>
<th>VATS Patients (%)</th>
<th>Preoperative Bronchoscopy/BAL (%)</th>
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BAL = bronchoalveolar lavage; OLB = open lung biopsy; VATS = video assisted thoracoscopic surgery.
to urgent OLB before less invasive diagnostic modalities such as imaging, cultures, and BAL [17].

It is difficult for a single diagnostic or therapeutic intervention to reduce death in ARDS. Few interventions achieve this goal because patients with ARDS have complex medical illnesses with multiorgan system involvement. Changes in management, such as initiating anticoagulation, steroids, chemotherapy, or radiotherapy, may improve outcomes. The addition of new antibiotics to address specific microorganisms diagnosed by OLB should provide benefit. Eliminating unnecessary medications in critically ill patients may reduce drug toxicity, decrease the emergence of drug-resistant organisms, limit the suffering of patients and families, and reduce financial costs.

When treating patients with refractory ARDS, despite empiric treatment and appropriate diagnostic evaluation such as BAL, one must decide whether a specific diagnosis could change therapy and whether that patient could tolerate further insult to lung compliance and oxygenation from OLB. Patients already on 100% FiO2 and PEEP (>10 mm Hg) may be at excessive risk for pneumothorax and subsequent persistent air leak after OLB. When unilateral or bilateral pneumothorax or hemodynamic instability have already developed, the patient should likely be excluded. Although a statistically significant trend could not be determined for the timing of when to seek an OLB, performing an OLB within 7 to 10 days of the onset of ARDS would seem to provide more benefit because patients would be less likely to already have entered the irreversible fibrotic phase of ARDS.

In conclusion, OLB is a safe procedure in ARDS, provides a specific diagnosis in 84% of patients, and leads to a change in management in 73% of patients. The overall mortality rate of patients who undergo OLB is similar to patients with ARDS who do not undergo OLB, probably because survival in ARDS is primarily predicted by the number of organ failures, preexisting comorbidities, and the PaO2/FiO2 ratio. We believe a more aggressive diagnostic approach, including OLB, is warranted for a selected group of patients with ARDS where conventional diagnostic modalities, including BAL, have been unrevealing. Demonstrating a survival benefit of OLB for patients with ARDS would require a multiinstitutional, prospective, properly powered, randomized controlled trial.

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References