Open Lung Biopsy Among Critically Ill, Mechanically Ventilated Patients

A Metaanalysis

Alexandra K. Wong¹ and Allan J. Walkey²

¹Department of Internal Medicine, Boston University School of Medicine, Boston Medical Center, Boston, Massachusetts; and ²Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, The Pulmonary Center, Boston University School of Medicine, Boston, Massachusetts

Abstract

Rationale: Open lung biopsy may be performed to guide therapy in mechanically ventilated patients with diagnostic uncertainty regarding etiology of pulmonary infiltrates. Current evidence for open lung biopsy in mechanically ventilated patients comes from single-center case series.

Objectives: We performed a metaanalysis of case series to determine diagnoses, complications, and changes in therapy after lung biopsy in critically ill patients requiring mechanical ventilation.

Methods: We searched Medline for case series of lung biopsies in critically ill patients requiring mechanical ventilation. We pooled results of individual case series using random effects metaanalysis models to obtain summary proportions.

Measurements and Main Results: We identified 14 case series including a total of 512 mechanically ventilated patients with 530 histopathological diagnoses. The most common diagnoses were

“fibrosis/pneumonitis” (n = 155, 25%; 95% confidence interval [CI], 14–37%) and infection (n = 113, 20%; 95% CI, 15–27%). Viruses were the most commonly identified infectious etiology identified on open lung biopsy, representing 50% of potential pathogens. Diffuse alveolar damage was present in a minority of specimens (n = 100, 16%; 95% CI, 8–25%). Therapeutic changes after lung biopsy occurred in 399 patients (78%; 95% CI, 64–81%). Procedure-related complications occurred in 29% of patients (95% CI, 25–33%), most commonly persistent air leak. Mortality among mechanically ventilated patients after diagnostic open lung biopsy was 54%.

Conclusions: Among mechanically ventilated patients with respiratory failure of unclear etiology, lung biopsy yielded a wide range of diagnoses and was associated with a change in therapy in most patients.

Keywords: acute respiratory distress syndrome; respiratory failure; diffuse pulmonary infiltrate; biopsy; humans

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Correspondence and requests for reprints should be addressed to Alexandra K. Wong, M.D., Boston University Medical Center, 72 East Concord Street, Evans 124, Boston, MA 02118. E-mail: alexandra.wong@bmc.org

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Approximately 5 to 15% of critically ill patients requiring mechanical ventilation may not have an etiology identified after initial diagnostic evaluation (1). Open lung biopsy may be considered in the diagnostic evaluation of mechanically ventilated patients with unclear etiology of pulmonary infiltrates or acute respiratory distress syndrome (ARDS) who fail to improve after

initial evaluation and/or empiric therapy. Reports of the diagnostic usefulness and safety of open lung biopsy in mechanically ventilated patients come primarily from small, single-center retrospective case series. More generalizable outcomes associated with open lung biopsy for mechanically ventilated patients are unclear. Given the lack of clinical trials

and difficulty performing matched observational studies comparing outcomes of patients who received open lung biopsy to those who did not, a description of common diagnoses and complications from open lung biopsy may provide data to aid clinicians considering this procedure in critically ill, mechanically ventilated patients. Our analysis seeks to determine

the most likely diagnoses, frequency of changes to therapy, and rate of complications among published reports of open lung biopsy for critically ill patients receiving mechanical ventilation with unclear etiology of pulmonary infiltrates. Preliminary results of our investigation have previously been reported in the form of an abstract (2).

Methods

We performed a Medline search through December 31, 2014 to identify relevant studies investigating diagnostic outcomes associated with use of open lung biopsy in critically ill patients requiring mechanical ventilation. Our search strategy combined the following Medical Subject Headings and keywords: diffuse alveolar damage, ARDS, acute respiratory distress syndrome, adult respiratory distress syndrome, acute lung injury, shock lung, hypoxic respiratory failure, hypoxemic respiratory failure, respiratory failure, diffuse pulmonary infiltrate, diffuse lung disease, acute respiratory insufficiency, pathology, biopsy, humans. Search results were screened by both authors for relevance. Studies identified by title for possible inclusion then underwent evaluation of abstract and then full manuscript. The bibliographies of all selected articles were also reviewed for additional relevant titles. We included studies that reported the diagnostic results of lung biopsies obtained from patients receiving mechanical ventilatory support. We excluded studies with predominantly immunocompromised patients, children younger than 18 years, or patients who were not mechanically ventilated, and studies in which biopsies were obtained by alternative methods (such as transbronchial biopsy) or histopathological findings were not reported. Because nonresolving ARDS of unclear etiology is a frequent indication for open lung biopsy among critically ill patients undergoing mechanical ventilation, we performed a sensitivity analysis among only case series including patients meeting American–European Consensus Criteria for acute lung injury and ARDS.

In addition to the pathological diagnoses obtained from open lung biopsy among patients requiring mechanical ventilation, where available we recorded operator type, procedure location, patient demographics, the number of days on

mechanical ventilation before biopsy, biopsy-related complications, therapeutic changes after biopsy, and hospital mortality rates. Because patients included in case series do not likely emerge from the same underlying population, we report pooled, weighted summary proportions across studies, with 95% confidence intervals (CIs) derived from metaanalysis using a DerSimonian and Laird random effects models. (MedCalc Software v14, Ostend, Belgium).

Results

Among 6,452 articles identified by MEDLINE search, we identified 14 studies of open lung biopsy among 512 mechanically ventilated patients (Figure 1).

Table 1 demonstrates patient characteristics from included studies. Average patient age was 56 ± 5 years, 56% of patients were men, and biopsies were performed an average of 7.8 ± 4.3 days (range, 0–65 d) after initiation of mechanical ventilation.

Procedural characteristics and diagnostic evaluation before open lung biopsy were variably reported. Among four studies reporting operator, all open lung biopsy procedures were performed by a thoracic surgeon. Among 10 studies reporting hospital location, open lung biopsy was performed exclusively in an operating room in 7 studies, and either in an operating room or in the intensive care unit in 3 studies. Of eight studies reporting diagnostic testing performed before open lung biopsy, bronchoscopy was routinely performed in all patients and computed

tomography of the thorax was performed in the majority of patients.

A total of 530 pathological results were obtained from 512 patients (Figure 2). The most common diagnosis obtained from open lung biopsy among mechanically ventilated, critically ill patients was “fibrosis/pneumonitis” ($n = 155$, 25%; 95% CI, 14–37%). Specific reports of fibrosis included “interstitial fibrosis with concomitant infection,” “interstitial pulmonary fibrosis,” “interstitial pneumonitis,” “alveolitis,” and “desquamative interstitial pneumonia.”

Infection represented the second most common diagnostic category ($n = 113$, 20% of diagnoses; 95% CI, 15–27%). Among studies that reported specific pathogens ($N = 84$ patients), viral infection was found to be most common (42/84, 50%). The most common viral diagnosis was cytomegalovirus (25 of 42 viral diagnoses), followed by influenza ($N = 3$), herpes simplex virus ($N = 2$), adenovirus ($N = 2$), and 10 not otherwise specified. Remaining etiologies of infection included bacterial (20 cases, 23%), fungal (19, 23%), and parasitic (3, 4%). One case (1%) was reported as “necrotizing pneumonia” without pathogen identification (3).

Diffuse alveolar damage was the third most common diagnostic category ($n = 100$, 16%; 95% CI, 8–25%). Additional histopathological diagnoses included cryptogenic organizing pneumonia (33 cases, 7%; 95% CI, 3–11%), malignancy (28 cases, 6%; 95% CI, 4–8%), and vasculitis/connective tissue disease (15 cases, 3%; 95% CI, 2–5%), which included granulomatosis with polyangiitis,

Figure 1. Flow diagram of study inclusion.

Table 1. Patient characteristics

Study	N	Sex, % Men	Age (yr) Mean $\pm$ SD or (Range)	Days of Mechanical Ventilation, Prebiopsy Mean $\pm$ SD or (Range)	PaO ₂ /FiO ₂ Prebiopsy Mean $\pm$ SD or (Range)	PEEP Prebiopsy (cm H ₂ O) Mean $\pm$ SD or (Range)
Canver and Mentzer, 1994 (6)	27	48	51 $\pm$ 5	9 $\pm$ 4	NR	9 $\pm$ 0.8
Hughes and McGuire, 1997 (7)	27	52	57 (22–80)	14 (2–65)	NR	NR
Papazian <i>et al.</i> , 1998 (8)	36	NR	59 $\pm$ 15	10 (5–55)	118 (60–190)*	10.3 $\pm$ 2.6
Flabouris and Myburgh, 1999 (9)	24	33	49 $\pm$ 16	NR	161	NR
Patel <i>et al.</i> , 2004 (12)	57	63	53 $\pm$ 18	3 (0–25)	145 $\pm$ 61	10.3 $\pm$ 4.1
Soh <i>et al.</i> , 2005 (21)	32	75	51 $\pm$ 22	7 (0–31)	163 $\pm$ 90.4	NR
Barbas <i>et al.</i> , 2006 (4)	12	58	65 $\pm$ 14	4.5 $\pm$ 4	157 [†]	NR
Kao <i>et al.</i> , 2006 (13)	41	68	55 $\pm$ 17	3 $\pm$ 2	116 $\pm$ 43	11.1 $\pm$ 3.1
Arabi <i>et al.</i> , 2007 (10)	14	50	51 $\pm$ 19	9 (1–30)	153 $\pm$ 60	8 $\pm$ 4
Lim <i>et al.</i> , 2007 (3)	36	69	59 (20–77)	4 (1–23)	119.5 (53–267)	10 (5–18)
Papazian <i>et al.</i> , 2007 (14)	100	67	57 $\pm$ 17	11 (6–23)	129 $\pm$ 41	10 $\pm$ 3.1
Baumann <i>et al.</i> , 2008 (11)	27	44	49 $\pm$ 14	13 $\pm$ 16	188 $\pm$ 109	NR
Melo <i>et al.</i> , 2009 (5)	19	53	58 $\pm$ 16	13 $\pm$ 7	171 [†]	9 [†]
Depuydt <i>et al.</i> , 2013 (16)	60	60	62 $\pm$ 14	2 (1–28)*	189 (140–216)	8 (5–10)

Definition of abbreviations: NR = not reported; PEEP = positive end expiratory pressure.

*Reported as median.

[†]SD or range not provided.

systemic lupus erythematosus, Goodpasture, dermatomyositis, and rheumatoid lung. Authors reported 27 biopsies as “nonspecific” (4%; 95% CI, 1–9%), and nine diagnoses occurred in single cases: bronchopulmonary dysplasia, foreign body reaction, transplant rejection, interstitial emphysema, allergic bronchopulmonary aspergillosis, alveolar proteinosis, metastatic calcification, sarcoidosis, and aspiration pneumonia.

A change in therapy or management occurred in 78% (399 of 512; 95% CI, 74–81%) of patients after open lung biopsy. The type of therapeutic change was available for 356 patients; the majority ($n = 317$, 79%; 95% CI, 75–83%) of therapeutic changes were either initiation of new therapy or the tailoring of therapy (i.e., change to new antimicrobial therapy) based on biopsy data. Therapy was discontinued in 10% ($n = 39$, 95% CI, 7–13%) of patients. Two studies (20 patients, 5%) did not report therapeutic changes (4, 5).

Complications were reported in 147 (29%; 95% CI, 25–33%) patients (Figure 3). The most common complication associated with open lung biopsy was persistent air leak, occurring in 104 patients (71% of complications, 95% CI, 63–78%). One patient had perioperative mortality attributed to the open lung biopsy procedure. Patient mortality (defined variably as hospital, intensive care unit, or

28–30 days after open lung biopsy) was 54%. Mortality rates stratified by histopathological diagnosis did not differ significantly by diagnosis ($P = 0.15$; Table 2, reported in eight studies) (4–11).

Results were similar in a sensitivity analysis among five studies (8, 11–14), including 261 patients and 267 histopathological diagnoses specifically identifying patients using American–European Consensus definition of acute lung injury. The most common diagnoses remained fibrosis/pneumonitis (26%; 95% CI, 11–46%), followed by infection (25%; 95% CI, 18–32%) and diffuse alveolar damage (20%; 95% CI, 10–32%). Treatment was altered among 84% of patients (219 of 261; 95% CI, 79–88%), and mortality was 49% among patients with Consensus-definition ARDS who underwent open lung biopsy.

Discussion

We performed metaanalysis to pool prior single-center experience with open lung biopsy among mechanically ventilated, critically ill patients with unclear etiology of pulmonary infiltrates. We found that that open lung biopsy in mechanically ventilated patients with pulmonary infiltrates revealed a wide range of diagnoses. Interestingly, diffuse alveolar damage—the pathological hallmark of ARDS—was not commonly

identified, even among analyses including patients meeting Consensus ARDS criteria. Instead, common diagnoses included fibrosis/pneumonitis and viral infection. In general, open lung biopsy among mechanically ventilated patients appeared to show high histopathological yield, which resulted in therapeutic change in the majority of patients. Obtaining a diagnosis came at the cost of complications among nearly 30% of patients, most commonly persistent air leak and bronchopleural fistulae. Hospital mortality after the procedure was 54% and did not appear to vary significantly based on histopathological diagnosis. In the absence of controlled studies, our results provide clinicians with data that may be used when weighing potential risks and benefits of open lung biopsy among mechanically ventilated patients with pulmonary infiltrates of unclear etiology after initial diagnostic evaluation.

Few studies have explored outcomes of open lung biopsy among mechanically ventilated patients with unclear etiology of pulmonary infiltrates. Libby and colleagues performed a metaanalysis of surgical lung biopsy among patients with suspected ARDS; however, many patients included were not mechanically ventilated (15). Of the 24 studies included in the metaanalysis by Libby and colleagues, 12 were included in our report, and we included an additional 2 studies (5, 16). Our results

Figure 2. Histopathological diagnoses of open lung biopsies. *Includes viral, bacterial, fungal, parasitic, and otherwise not specified infections. **Includes bronchopulmonary dysplasia, foreign body reaction, transplant rejection, interstitial emphysema, allergic bronchopulmonary aspergillosis, alveolar proteinosis, metastatic calcification, sarcoidosis, and aspiration pneumonia. DAD = diffuse alveolar damage; GVHD = graft versus host disease; PNA = pneumonia.

more specifically inform clinical decisions among mechanically ventilated patients, who may have different etiologies of respiratory failure and different complications and outcomes than patients who are not mechanically ventilated. For example, neoplastic disease was a more common finding (12%) from Libby and colleagues than in our analysis (6%), whereas diffuse alveolar damage was more common in our study (16 vs. 9%).

Interestingly, diffuse alveolar damage was identified among few patients with a clinical diagnosis of ARDS. The low prevalence of histologically identified diffuse alveolar damage among patients with suspected ARDS is consistent with autopsy studies among patients who were clinically suspected to have ARDS. For example, Thille and colleagues evaluated autopsy findings of patients meeting Berlin criteria

for ARDS and identified that 45% of patients had histological findings consistent with diffuse alveolar damage (17). Earlier autopsy studies using the American-European Consensus Criteria for clinical ARDS used by studies in our analysis also demonstrated even lower rates of diffuse alveolar damage (30 and 29%, respectively) (18, 19). However, autopsy studies showed higher prevalence of diffuse alveolar damage than our study of open lung biopsy, possibly resulting from selection bias for more stable patients deemed candidates for lung biopsy than patients dying with severe ARDS. Patients selected for open lung biopsy would also be more likely to present atypically, without a clearly identified ARDS triggers, further decreasing the likelihood for detecting diffuse alveolar damage. Finally, the relatively small amount of tissue obtained during open lung

biopsy than in autopsy may decrease sensitivity to diagnose a multifocal disease such as ARDS.

The most common pathological diagnoses among mechanically ventilated patients receiving open lung biopsy were fibrosis and (mostly viral) infections, a finding that may reflect the difficulty of obtaining these diagnoses less invasively. Among ARDS mimics, conditions such as acute eosinophilic pneumonia, hypersensitivity pneumonitis, bronchoalveolar carcinoma, or diffuse alveolar hemorrhage (20) may potentially be diagnosed through bronchoscopy (a procedure performed before open lung biopsy in all studies), decreasing the frequency of these diagnoses among patients undergoing open lung biopsy. In addition, the average time to biopsy of 7 days in our study may select for identification of the fibroproliferative phase of ARDS and account for some proportion of “fibrosis” diagnoses we observed, rather than an earlier exudative phase ARDS with diffuse alveolar damage. Although our findings may be representative of mechanically ventilated patients proceeding to open lung biopsy, they do not likely reflect the distribution of diagnoses among mechanically ventilated patients with pulmonary infiltrates of unclear etiology who have not had further evaluation with less-invasive measures such as bronchoscopy, computed tomography scanning, or serological testing for connective tissue disease.

Limitations of our study reflect the limitations of the individual case series. These include heterogeneous preoperative diagnostic evaluation, surgical expertise, timing of open lung biopsy, comorbidities, advanced directives, severity of illness, classification of disease between studies, and variable pathologist interpretation. However, despite this heterogeneity, only 27 patients (4.2%) had a nondiagnostic or “nonspecific” biopsy. Furthermore, included studies used the American-European Consensus Criteria to clinically define ARDS, rather than the Berlin definition. However, given that all patients were receiving positive end-expiratory pressure on mechanical ventilation, we suspect most included patients meeting American-European Consensus Criteria would also meet Berlin criteria. In addition, one study (14) duplicated nine patients from a prior

Figure 3. Complications of open lung biopsy. Complications were reported in 147 of 512 patients.

Table 2. Mortality rate by histopathological diagnosis

Diagnosis	Mortality N (%)
Fibrosis/pneumonitis, N = 62	37 (60)
Infection, N = 40	21 (53)
Diffuse alveolar damage, N = 35	19 (54)
Organizing pneumonia, N = 17	6 (35)
Malignancy, N = 7	6 (86)
Embolic disease, N = 7	2 (29)
Connective tissue disease, N = 6	1 (17)
Nonspecific, N = 5	3 (60)
Alveolar hemorrhage, N = 3	1 (33)
Drug reaction, N = 3	3 (100)
Normal, N = 3	2 (67)
Graft versus host disease, N = 3	2 (67)
Eosinophilic pneumonia, N = 2	1 (50)
Bronchiolitis, N = 1	0 (0)
Other,* N = 6	3 (50)

Among 8 studies reporting outcomes by pathological diagnosis, N = 200 diagnoses among 186 patients. Chi-square $P = 0.15$.

*Other diagnoses include: bronchopulmonary dysplasia, transplant rejection, foreign body reaction, interstitial emphysema, aspiration pneumonia, sarcoidosis.

report (8); however, it is unlikely that results would substantively differ if these patients could be identified. Finally, whether open lung biopsy might be

associated with improved outcomes among patients with unclear etiology of respiratory failure cannot be determined from our data. Although the mortality

rate among mechanically ventilated patients undergoing open lung biopsy for suspected ARDS is somewhat higher than contemporaneous mortality rates among patients with ARDS, such differences in outcome are not unexpected given the clinical complexity and diagnostic uncertainty leading clinicians to pursue open lung biopsy.

In conclusion, our findings suggest that open lung biopsy may have high histopathological yield and associated therapeutic changes in selected patients. Further controlled studies may better determine whether certain mechanically ventilated patients might benefit from open lung biopsy. Until then, our findings regarding diagnostic yield and complication rates may be useful to inform clinical decision making when considering open lung biopsy among mechanically ventilated patients with unclear etiology of nonresolving respiratory failure despite initial evaluation. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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