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Which Patients With ARDS Benefit From Lung Biopsy?

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A central tenet of caring for patients with ARDS is to treat the underlying cause, be it sepsis, pneumonia, or removal of an offending toxin. Identifying the risk factor for ARDS has even been proposed as essential to diagnosing ARDS. Not infrequently, however, the precipitant for acute hypoxemic respiratory failure is unclear, and this raises the question of whether a histologic lung diagnosis would benefit the patient. In this review, we consider the historic role of pathology in establishing a diagnosis of ARDS and the published experience of surgical and transbronchial lung biopsy in patients with ARDS. We reflect on which pathologic diagnoses influence treatment and suggest a patient-centric approach to weigh the risks and benefits of a lung biopsy for critically ill patients who may have ARDS.

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ABBREVIATIONS: AECC = American-European Consensus Committee; CMV = cytomegalovirus; DAD = diffuse alveolar damage; IPF = idiopathic pulmonary fibrosis; OLB = open lung biopsy; VATS = video-assisted thoracoscopic surgery

Since its earliest description,[1] ARDS has been recognized as an entity that can complicate various severe environmental insults.[2,3] One of the principal tenets of ARDS management includes understanding the inciting precipitant, because treating the underlying infection or inflammatory condition is considered an important therapeutic goal.[4,5] Identification of a risk factor is now considered essential to diagnosing ARDS.[6] Less certain, however, is the requirement for a precise pathologic or microbiologic identification of an ARDS precipitant. On the one hand, several conditions may mimic ARDS clinically and radiographically yet have distinct treatments, as in the case of pulmonary alveolar proteinosis, acute eosinophilic pneumonia, or hypersensitivity or organizing pneumonias. Some infections may elude our empirical antimicrobial coverage, or patients may have so little immunologic reserve because of either multiorgan failure or an underlying immunocompromised state that a specific microbiologic diagnosis is urgently needed. These considerations may prompt a discussion of an aggressive strategy to obtain a precise diagnosis, including biopsy of the lung. Yet countering this "desire to know" are the inherent risks of performing invasive procedures in a critically ill patient, including the risk that the procedure will yield little or no actionable information.

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In this review, we consider both the published experience regarding lung biopsies in critically ill patients with hypoxemia and the empirical and experiential concerns that we have encountered in caring for such patients. Our goal is to provide the physician with realistic expectations about the risks and benefits of open lung biopsy (OLB) for patients with ARDS of uncertain cause, to aid in a personalized decision as to whether a patient may benefit from this procedure.

Historic Role of Pathology to Define ARDS

ARDS was first described in 1967 by Ashbaugh and colleagues[1] in a collection of 12 cases of respiratory failure characterized by severe hypoxemia, decreased lung compliance, and diffuse infiltration on chest radiograph. For each patient, the syndrome complicated another process of critical illness, including trauma, viral pneumonia, or pancreatitis, which we now recognize as clinical risk factors associated with the syndrome.[2,3] Autopsy specimens were available in seven cases, and all but one revealed "a striking finding," the presence of hyaline membranes.[1] Prior to this landmark publication, hyaline membranes were considered specific for respiratory distress syndrome in the newborn, and this prompted the authors initially to label the syndrome adult respiratory distress syndrome. The authors suggested the possibility that a common mechanism of lung injury may exist despite various clinical insults.

Katzenstein and colleagues[7] coined the term "diffuse alveolar damage" (DAD) to describe the histopathologic changes in the lung that occur following a variety of insults including hemorrhagic shock, severe trauma, sepsis, and others. These changes include the early findings of capillary congestion, atelectasis, intraalveolar hemorrhage, and pulmonary edema.[7] In patients who survived beyond 72 h, the early changes were followed by hyaline membrane deposition, epithelial cell hyperplasia, and interstitial edema. The link between the clinical syndrome of ARDS and DAD was established. However, even in the landmark initial description of ARDS, DAD was not universally present.[7] Katzenstein and colleagues[7] concluded that "DAD is not a diagnosis: it is a concept which is useful in understanding the pathogenesis of a group of similar pulmonary lesions which result from numerous and dissimilar agents."

Biopsy to Detect DAD: Is It Helpful?

To improve the clinical recognition of ARDS and to assist in the design of clinical ARDS studies, the American-European Consensus Committee (AECC) published its definition of ARDS in 1994 (Table 1). This definition was widely adopted as the academic and clinical standard, persisting until the publication of the Berlin definition in 2012 (Table 1).[6,8] Notably, neither definition incorporates pathologic findings as diagnostic criteria for ARDS. To evaluate the construct validity of the AECC definition, Esteban and colleagues[9] compared this clinical ARDS definition with the reference standard of autopsy specimens. In their cohort, the AECC clinical definition of ARDS had 74% sensitivity and 84% specificity for the pathologic findings of DAD (hyaline membranes plus at least one of the following: alveolar cell type 1 or endothelial cell necrosis, edema, organizing interstitial fibrosis, or prominent alveolar cell type 2 proliferation) on autopsy. Thus, in the cohort of Esteban and colleagues,[9] the AECC definition had only moderate accuracy in predicting the classic pathologic findings of ARDS.

The Berlin definition included a conceptual model stating that the morphologic hallmark of the acute phase of this disease is DAD (ie, edema, inflammation, hyaline membrane, or hemorrhage), citing the description of this syndrome from Katzenstein and colleagues[7] (Table 1).[6] However, using DAD on autopsy specimens as the reference standard, Thille and colleagues[10] determined the sensitivity and specificity of the Berlin definition to be 89% and 63%, respectively. Among all patients who met the clinical criteria for ARDS, DAD was found in only 45%, although DAD was more common in those with severe ARDS and in those who had had ARDS for at least 72 h. Other histopathologic findings at autopsy included pneumonia (49%), severe emphysema (7%), pulmonary hemorrhage (6%), and cancer infiltration (5.5%). No pulmonary lesions were found in 27 patients (14%).[10]

It is clear from the autopsy studies that the clinical syndrome ARDS is not synonymous with the pathologic diagnosis of DAD. Multiple pathologic processes result in the clinical syndrome of ARDS. In addition, DAD can have other causes, such as connective tissue diseases, that are not considered classic risk factors for ARDS.[11-13] Although establishing DAD may be useful in creating a group of patients with more homogenous lung injury for research purposes, at present there is no therapy for ARDS that has been shown to reverse this pattern of injury on lung histology. As discussed by Thompson and Matthay[14] in a 2013 editorial, in the ARDS Network lung protective ventilation trial, low tidal volume ventilation reduced mortality in all clinical disorders associated with lung injury, including in patients who did not likely have DAD.[15] We, thus, do not recommend pursuing OLB for the sole purpose of

TABLE 1] Comparison of the AECC[8] and Berlin[6] Consensus Criteria for ARDS

Criteria	AECC Definition	Berlin Definition
Timing	"Acute onset," undefined	Acute defined as onset within 1 wk
Oxygenation, Pao_2 reported in mm Hg	$Pao_2/FIO_2 \leq 300$	$Pao_2/FIO_2 \leq 100$: severe
		$100 < Pao_2/FIO_2 \leq 200$: moderate
		$200 < Pao_2/FIO_2 \leq 300$: mild
	No PEEP specified	Above with a minimum of 5 cm H_2O PEEP
Chest radiograph	Bilateral infiltrates observed on frontal chest radiograph	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema (exclusion of hydrostatic edema)	PAWP ≤ 18 mm Hg when measured, or no clinical evidence of left atrial hypertension	Not explained by cardiac failure or fluid overload
Risk factor	Not specified in definition	Must be present or else hydrostatic edema excluded by an objective assessment such as echocardiography

AECC = American-European Consensus Committee; PAWP = pulmonary arterial wedge pressure; PEEP = positive end-expiratory pressure.

establishing the pathologic diagnosis of DAD or to establish the need for lung protective ventilation.

Published Experience of OLB in Undiagnosed Respiratory Failure

Although we advise that it is unnecessary to histologically prove ARDS, OLB may be considered when the inciting event that resulted in ARDS is unclear or when an alternative diagnosis is under consideration. Several observational studies published prior to the Berlin definition have attempted to clarify the usefulness of OLB in patients who are mechanically ventilated with undiagnosed acute respiratory failure.[16-21] These studies clearly demonstrate that biopsy often leads to a pathologic diagnosis. In a recent meta-analysis, Libby and colleagues[22] reviewed a total of 24 observational studies published from 1988 through 2009. Although the result is an extensive review of surgical lung biopsy for diffuse pulmonary infiltrates, several of the studies, including the two largest, were not performed in critically ill subjects or those who were mechanically ventilated and, as such, may temper the applicability to patients with ARDS.[23-25] The meta-analysis reports a specific diagnosis rate of 84%. Only 9% of 1,205 biopsies demonstrated DAD. Other findings included 284 (24%) with histology and tissue culture positive for infection: 7% cytomegalovirus, 2% TB, 3% *Pneumocystis*, 1% viral, and 2% fungal. Interstitial lung disease accounted for 25% of pathologic diagnoses, with usual interstitial pneumonia accounting for the majority. Autoimmune processes were diagnosed in 7% and neoplastic diseases in 12%.[22] No specific diagnosis was made in 9% of biopsies, and a small fraction included other disorders such as pulmonary edema, drug reaction, pulmonary or fat embolism, and bronchiectasis.[22]

In one of the included case series that focused exclusively on patients meeting the AECC definition for ARDS,[26] biopsies revealed a diagnosis other than DAD in 60% of patients.[27] The most common diagnoses made after DAD included specific infections (14%), diffuse alveolar hemorrhage (8%), bronchiolitis obliterans organizing pneumonia now commonly called cryptogenic organizing pneumonia (8%), and bronchiolitis (5%). Based on biopsy results, therapy was changed in the majority of patients; 60% had a new therapy begun, most commonly steroids, whereas 37% had a therapy discontinued.[27] The authors commented that biopsy was performed in only 4% of all patients with ARDS at the institution during the study period, highlighting that these observational studies cannot be generalized to all patients with ARDS. Those referred for lung biopsy are a distinct group. They are the patients with atypical presenting features or those who have failed to respond to empirical therapy. In addition, they were deemed by the performing surgeon to have an acceptable surgical risk, thus excluding those who may have been too ill, deteriorated too rapidly, or had an underlying coagulopathy.

Lung Biopsy in Persistent ARDS

In 1998, Papazian and colleagues[28] published an observational case series to evaluate the safety and usefulness of OLB in patients with ARDS. Given the publications suggesting a reduction in mortality following the treatment of fibroproliferative ARDS with corticosteroids,[29-31] these investigators sought to identify a group of patients in whom steroid therapy may be indicated. Because Papazian and colleagues[28] routinely performed biopsy if no clear cause for ARDS was identified by day 5, this study was uniquely poised to examine the role of OLB

on a predetermined group of patients with ARDS. OLB was performed on 36 patients with persistent ARDS defined by failure to show an improved Lung Injury Score[32] after 5 days and negative bacterial cultures. All patients met the criteria for ARDS defined by the AECC. Biopsy was performed a median of 10 days after the onset of ARDS (range, 5-55 days), and the Pao_2/Fio_2 ratio was < 150 mm Hg in most cases. Given that biopsies were performed with the intent of excluding infection prior to initiation of corticosteroid therapy for fibroproliferative ARDS, the authors commented that 15 patients had findings of fibrosis at the time of biopsy. Perhaps most notable in this series was the finding of cytomegalovirus (CMV) pneumonia (defined by characteristic viral inclusions) in 50% of patients. Other findings included systemic lupus erythematosus, granulomatosis with polyangiitis, TB, and intravascular bronchoalveolar tumor in one patient each. Biopsy resulted in a change in management in the majority of patients, most commonly the addition of ganciclovir, but also the addition of corticosteroid therapy in the six patients with fibrosis and no evidence of active infection. The authors reported a similar survival rate in the group that had a therapeutic change and in the group that did not.

Papazian and colleagues[33] published a subsequent prospective study in 2007 that included 100 patients who underwent OLB between 1996 and 2003 for persistent ARDS. All patients had BAL performed 3 days prior to open lung biopsy, and the biopsy was performed 7 days after the onset of ARDS. On average, patients required mechanical ventilation support for 11 days prior to the biopsy. Pathology revealed fibrosis in > 50% and detected infection, either alone or infection accompanying fibrosis, in almost 60% of patients. Again, CMV was the most common infection diagnosed by histology, found in 30% of patients. The significance of histologic CMV infection is uncertain. Limaye and colleagues[34] reported that reactivation of CMV in the blood occurs in approximately one-third of critically ill, nonimmunocompromised patients and is associated with prolonged hospital stay. It is unknown whether CMV reactivation is causally related to adverse outcomes or whether it is a marker of impaired host defenses or of critical illness severity.

Even less is known about the significance of CMV detection in the lungs. In a prospective study of 242 patients in the ICU, CMV positivity in BAL fluid or serum antigenemia combined with pulmonary disease was found in 16% of patients.[35] We do not yet know whether targeting CMV reactivation during critical illness influences outcome, although the Study of Ganciclovir/Valganciclovir for Prevention of Cytomegalovirus Reactivation in Acute Injury of the Lung and Respiratory Failure (GRAIL)[36] should shed light on whether preemptively treating CMV reduces inflammatory cytokines. Although the Papazian and colleagues series[33] remains the largest observational study of OLB in ARDS, it remains difficult to apply these results to the majority of patients. Steroids are not indicated routinely for fibroproliferative ARDS,[37,38] and the significance of CMV detection in lung tissue remains unclear, especially because we now have less invasive means to detect CMV.[39]

"Contributive Result": Do the Ends Justify the Means?

In their 2007 series of OLB for persistent ARDS, Papazian and colleagues[33] defined a "contributive result" from biopsy as "one that led to the addition of a new drug." Based on this definition, 78 of the 100 biopsies provided contributive results, and survival was higher in patients with a contributive result than in those in whom OLB did not result in the addition of a new medication (67% vs 15%, $P < .001$).[33] This impressive mortality difference led the authors to conclude that a contributive OLB improves survival in persistent ARDS.[33] An alternative perspective is that reversible lung conditions are associated with a lower mortality than are irreversible ones, and whether the biopsy influenced our knowledge or certainty of potential reversibility remains debatable. Furthermore, it is important to note that the majority of medication changes in the study by Papazian and colleagues[33] were the addition of ganciclovir for CMV or glucocorticoids for fibroproliferative ARDS, with caveats to both of these therapies, as discussed previously. The authors also comment that three patients decided on a do-not-resuscitate order following biopsy results "without a treatable cause."[33] We must be cautious when interpreting mortality as an outcome given that the biopsy result was almost certainly used to inform decisions surrounding end-of-life care. When there is clinical suspicion that the biopsy may reveal an untreatable condition and, thus, may prompt a reevaluation of the patient's goals of care, we advocate a thorough discussion of this potential finding before biopsy. Some patients and families choose to forego an invasive procedure when the expected histologic result lacks therapeutic options.

The concept of a contributive result as coined by Papazian and colleagues[33] provides a useful framework for evaluating biopsy results. As discussed previously, OLB has led to a variety of histopathologic diagnoses. Although

the finding of DAD may support the diagnosis of ARDS, it is neither necessary nor sufficient to establish the diagnosis. Given the lack of therapy targeted to DAD, we do not consider the presence or absence of DAD to be a contributive result. Papazian and colleagues[33] argue that the diagnosis of CMV infection resulted in a change in management for patients in their case series because ganciclovir was added to therapy. We await the results of the GRAIL study to demonstrate whether treating CMV based on serum positivity by polymerase chain reaction will influence ARDS outcomes. Leaving aside subjects whose OLB detected CMV, fibrosis, or DAD, it was a minority of subjects in the Papazian and colleagues[33] series whose biopsy results provided additional information.

The diagnosis of interstitial lung disease in a patient previously determined to have ARDS would likely result in a change in management. We argue that lung-protective ventilation is appropriate for both groups, but the approach to positive end-expiratory pressure titration may differ,[40] and there may be treatment options specific to interstitial lung disease. Acute eosinophilic pneumonia would warrant glucocorticoid therapy, although BAL eosinophilia in the absence of a known precipitant may obviate the need for lung biopsy.[41] Idiopathic pulmonary fibrosis (IPF) may be suggested by imaging. Lung biopsy, even in ambulatory patients, predisposes patients with IPF to an increased risk of acute exacerbation[42] and may contribute to mortality.[41] Although there are new pharmacologic therapies for outpatients with IPF,[43,44] these have not been studied in patients with IPF who are mechanically ventilated. If clinical suspicion for IPF is high, we do not recommend pursuing biopsy for definitive histologic diagnosis, because it is unclear whether this result is truly contributive. As new therapies emerge and are applied in broader settings, however, we anticipate that this may warrant reconsideration.

Atypical infections not detected by BAL were reported consistently in a small fraction of the observational studies of lung biopsy as discussed previously. Bronchoscopy is very useful in identifying an infectious cause of lung infiltrates, even in the immunocompromised host, where it detects about 80% of bacterial, fungal, and viral agents.[45] Several infectious agents (including nocardia, actinomyces, fungal organisms, and mycobacteria) may be missed on BAL and will not be treated by empirical antimicrobial therapy targeting routine bacterial pathogens. Isolation of one of these infectious agents can be expected in very few open lung biopsies of ARDS; we estimate 1% to 5%. However, such a finding would prompt a change in management.

In the reviewed case series of OLB in ARDS, a small number of biopsies resulted in a diagnosis of malignancy. Should this be considered a contributive result? The decision to initiate chemotherapy for a patient with respiratory failure is undoubtedly complex and involves consideration of the patient's current and premorbid functional status. Respiratory failure necessitating mechanical ventilation is associated with poor outcomes in patients with malignancy,[46,47] and Eastern Cooperative Oncology Group performance status[48] >4 has generally been considered a contraindication for the initiation of chemotherapy.[49] In the era of precision medicine, however, we can anticipate these basic tenets to be challenged. Biopsy results may provide information about molecular targets for new therapeutic agents, such as crizotinib for ALK mutations in the case of metastatic lung cancer. In fact, a small case series describes three patients liberated from mechanical ventilation with the initiation of crizotinib therapy for metastatic lung adenocarcinoma.[50] Although there may be reasons to pursue OLB in a patient with suspected malignancy, we caution that an invasive procedure should be undertaken only in a patient who is deemed a treatment candidate. Both the patient's wishes for therapy and the oncologist's assessment of possible therapeutic options should weigh heavily in this decision.

Finally, should we consider the decision to limit an existing therapy a "contributive result?" In the meta-analysis by Libby and colleagues,[22] OLB very rarely contributed to the discontinuation of antimicrobials ($<4\%$ of all biopsies) or steroids ($<1\%$). A small number of patients had treatment withdrawal (30 of 1,210 patients) or discontinuation of life support (six patients) considered a result of the biopsy procedure. In contrast, the study of Patel and colleagues,[27] which included only patients mechanically ventilated in the ICU, discontinued therapy in 37% after OLB. We do consider the limitation of drug therapy to be a contributive result. The fact that therapy is stopped as a result of an OLB for only a minority of patients probably reflects both the acuity of the patients undergoing biopsy and the diagnostic uncertainty that persists even with pathology results. Future work may test whether algorithms incorporating biomarkers such as procalcitonin[51] can identify critically ill patients in whom the risk of discontinuing antibiotics is low; such data are not currently available.

Timing of Lung Biopsy

The optimal time for performing OLB in the clinical course of a patient with ARDS is unknown. The desire to maximize diagnostic yield and minimize exposure to

unnecessary medications must be weighed against the desire to avoid an invasive procedure in a patient who otherwise may respond to empirical therapy. To address this question, Chuang and colleagues[52] compared urgent OLB, performed upon admission to the hospital, with elective OLB in a subset of patients presenting with diffuse pulmonary infiltrates. Only nine of the 34 patients in their study required mechanical ventilation, limiting its applicability to the ARDS population, but urgent biopsies were associated with higher complication rates without any change in management. We agree with the conclusion of Chuang and colleagues[52] in recommending against early biopsy prior to pursuing noninvasive diagnostic modalities.

Countering this recommendation to maximize noninvasive testing before biopsy, however, is the possibility that the diagnostic yield of OLB may decline with the duration of mechanical ventilation. For instance, the 2007 study of Papazian and colleagues[33] study demonstrated fibrosis in the majority of patients who underwent biopsy for persistent ARDS. Patients had received mechanical ventilation for a median of 11 days, with all patients receiving mechanical ventilation for at least 6 days prior to the OLB.[33] The high proportion of fibrosis may reflect the somewhat rapid evolution of ARDS; alternatively, because some patients in the study by Papazian and colleagues[33] were enrolled prior to seminal trials highlighting the benefit of low tidal volume ventilation in ARDS,[53,54] fibrosis may have represented ventilator-induced lung injury. With increasing duration of mechanical ventilation before biopsy, our ability to discern the contribution of ventilator-induced lung injury from the patient's underlying disease or from a secondary insult such as nosocomial pneumonia may be limited.

Our overall approach is to perform less invasive diagnostic procedures early in a patient's clinical course (Fig 1). The option of OLB should be considered if the initial diagnostic evaluation, including imaging, cultures, and BAL with cell count, is unrevealing and if there is a high clinical suspicion for an alternative diagnosis to ARDS. When considering a biopsy, we generally recommend that it be performed prior to day 7 of mechanical ventilation if possible.

Safety of Lung Biopsy in Patients Who Are Mechanically Ventilated

OLB is not without risk in a critically ill patient who is mechanically ventilated. The meta-analysis by Libby and colleagues[22] reported an overall surgical complication rate of 22%. In more recent case series including only patients who are mechanically ventilated, the complication rate ranged from 20% to 59%.[18-21,27] Video-assisted thoracoscopic surgery (VATS) was included as an alternative to open thoracotomy in some studies enrolling both inpatients and outpatients but was used in < 10% of cases.[22] The main limitation of VATS for a critically ill patient with hypoxemia is the necessity of tolerating single lung ventilation during the procedure.[55] Because this is not feasible for many patients and given a more robust published experience with OLB through a mini-thoracotomy, sometimes at the patient's bedside, OLB is more conventional.[28,33] The surgical complication rates in OLB and VATS have not been compared directly in a population with ARDS; we compare the risks and benefits of OLB with those of transbronchial biopsy in Table 2. The most common postoperative complication of OLB is a persistent air leak, with incidence varying depending on the case series examined and the definition applied.[18,19,21,22,33,56] The strongest association with persistent air leak in one review was higher preoperative peak airway pressure (43 cm H_2O in those with a persistent air leak compared with 32 cm H_2O in those without; $P = .0005$).[57] Minimizing airway pressures is recommended immediately prior to and during the lung biopsy to reduce this risk. Other reported complications include procedure-related bleeding,[19,20,33,56] hypotension,[21,56] acute myocardial infarction,[58] and worsening of hypoxia.[56] Although pain is not mentioned explicitly in any case series of OLB in patients who are ventilated, it is difficult to imagine that chest tubes would be pain free; thus, it is our practice to counsel patients and their proxies that if a chest tube is required, pain will be present and likely will require treatment.

The overall mortality rate in patients who underwent OLB was estimated to be 44% in the meta-analysis of Libby and colleagues,[22] which included many subjects who were not mechanically ventilated before the biopsy. This is a similar mortality rate to that reported for patients with severe ARDS.[6] Few studies attributed patient mortality to the procedure itself, although one case series examining OLB only in patients who were mechanically ventilated reported an estimated operative mortality of 8.4%, all of which occurred among patients with two or more organ dysfunctions in addition to respiratory failure.[56] Among ambulatory patients with radiographically suspected interstitial lung disease, mortality is consistently 2% to 5%.[41,59] Patients with persistent ARDS and multiorgan failure, and those with suspected IPF, may represent groups in whom the risk of OLB outweighs a potential benefit.

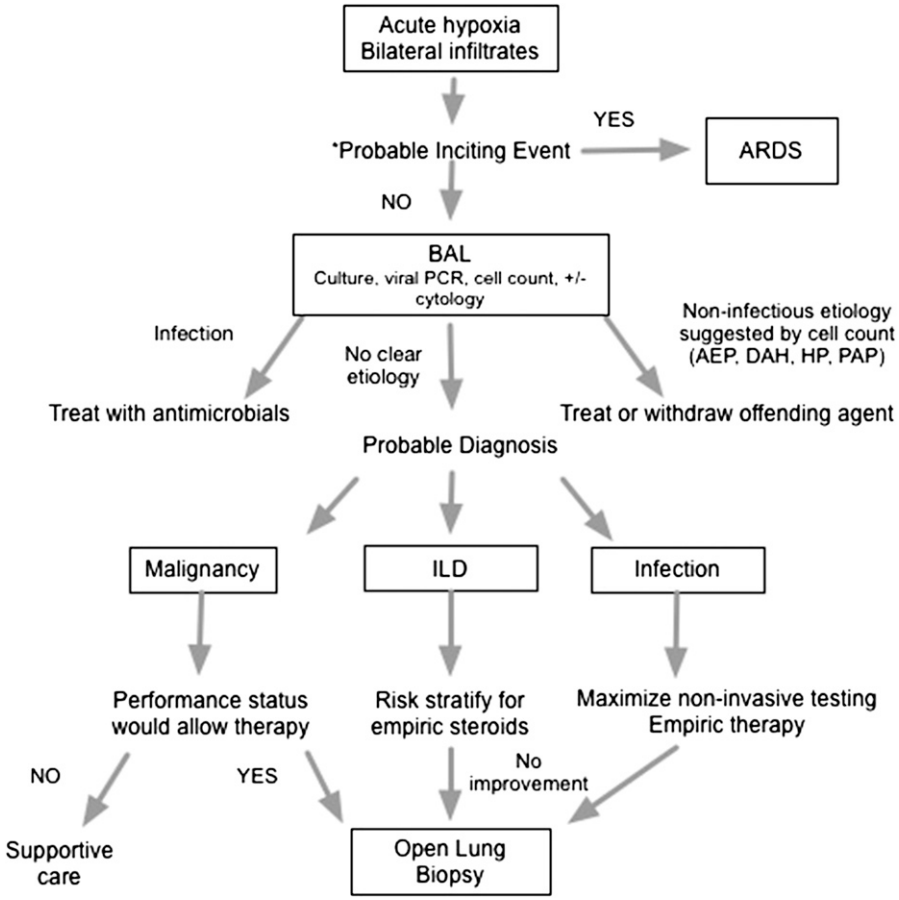

Figure 1 – *Decision-making algorithm for open lung biopsy.* *Pneumonia, sepsis, trauma, aspiration, pancreatitis. *AEP = acute eosinophilic pneumonia; DAH = diffuse alveolar hemorrhage; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; PAP = pulmonary alveolar proteinosis; PCR = polymerase chain reaction.*

Should We Consider Transbronchial Lung Biopsy?

Transbronchial biopsy may be considered as an alternative approach for histologic lung sampling. There is limited published literature on the usefulness and safety of this procedure in patients who are mechanically ventilated. In the early bronchoscopy literature, mechanical ventilation was considered a contraindication to transbronchial biopsy,[60] yet several case series have now reported the relative safety of this procedure, although perhaps with limited yield (Table 2).[61-64] The incidence of pneumothorax ranged broadly, from 1% to 23%, and clinically important bleeding ranged from 2% to 20%.[61-64] In one case series, patients with late ARDS had the highest complication rate, with four of 11 developing a pneumothorax, leading the authors to conclude that the

TABLE 2] Relative Advantages and Disadvantages of Surgical vs Transbronchial Lung Biopsy

Benefits and Risks	Transbronchial Biopsy	Open Lung Biopsy
Benefit	No open incision required	Many published case series in critically ill
	Minimal postprocedure pain	More tissue for histopathology
	Performed at bedside	Pathologic diagnosis usually obtained (>80%)
	Combined routinely with BAL	Experienced centers perform at bedside
Risk	Limited published data in critically ill	Complication rate ≥ 20%
	Pathologic yield limited: 35%?	• Persistent air leak
	• False-negative results	• Bleeding
	• Inadequate tissue	May require operating room
	Pneumothorax risk may approach 20%	Pain with postoperative chest tube

safety profile was unfavorable in these patients.[61] The contributive result of transbronchial biopsy is difficult to discern given the limited data. In the largest case series, a specific diagnosis other than DAD, including cancer, hemorrhage, cryptogenic organizing pneumonia, and previously undiagnosed infection, was reported in 35% of patients with undiagnosed pulmonary infiltrates.[62] It is important to consider that many patients in these series were lung allograft recipients and immunocompromised hosts; it is more difficult to apply these studies to the critically ill patient with ARDS.

Conclusions

The question as to whether to pursue OLB in a patient with the clinical syndrome of ARDS does not have a clear answer. The benefit of obtaining a potentially treatable diagnosis must be weighed carefully against both the inherent risk of an invasive procedure in a mechanically ventilated patient and the risk of a result that does not influence therapy. Although this decision is always personalized to an individual patient, we recommend a few key principles to help the physician with this decision (Fig 1).

Do Not Perform a Biopsy to Demonstrate the Presence or Absence of DAD

Finding DAD on pathology is neither specific nor sensitive for the diagnosis of ARDS and does not alter the treatment course. In a patient with a probable inciting event and clear clinical and radiographic features of ARDS, there is no clear benefit to biopsy.

Consider Biopsy if There Is High Clinical Suspicion for a Contributive Result and the Risk of Empirical Therapy Is Too High, or When Empirical Therapy Has Been Unsuccessful: This requires a personalized approach. If there is no clear inciting event for the development of ARDS and interstitial lung disease is considered as an alternative diagnosis, biopsy should be considered. It is our practice to perform BAL first to evaluate for occult infection, lymphocytosis, and eosinophilia. If BAL is nondiagnostic, the physician is often left with the decision as to whether to give empirical steroids or to pursue histopathologic diagnosis. We argue that the safety profile favors a trial of empirical steroids in most cases, although we appreciate that this may decrease the yield of a diagnostic result in certain instances. If a diagnosis of IPF is suspected based on presentation and imaging, we exercise particular caution in pursuing open lung biopsy, given the risk in this patient population[42] and the lack of new treatment options if a diagnosis is confirmed.

If malignancy is suspected, we recommend pursuing surgical lung biopsy only if obtaining pathology will be helpful in determining treatment, as may be the case in lung cancer. This should be pursued only if the patient is deemed a treatment candidate both in terms of performance status and personal choice.

OLB Does Carry Additional Risks but They Are Not Disproportionate to the Risk of the Underlying Illness

Adverse outcomes are difficult to attribute to surgical biopsy itself given the high morbidity and mortality in this patient population. Reported mortality rates in case series of OLB are similar to rates in patients with severe ARDS who did not undergo biopsy, recognizing that published series were observational and biopsy was unlikely to have been offered to patients with a poor prognosis. The safety profile of OLB is tolerable once patients are counseled about the risks of pneumothorax, bleeding, pain, and a noncontributive result.

Do Not Perform a Biopsy to Satisfy the Physician's Desire for Certainty

Finally, as providers, we must carefully evaluate our own desire for diagnostic certainty. In the arena of critical care, certainty is rare, although we take great comfort from this knowledge. In the case of OLB, the results may provide us with confirmation that our suspected diagnosis is, in fact, correct. It may improve our ability to prognosticate in our discussion with patients and surrogate decision-makers. However, as intensivists, we are trained to communicate our level of certainty to patients and their loved ones and to acknowledge the tension between diagnostic uncertainty and therapeutic risk. If we can effectively communicate this tension, then frequently the patient or family will tell us how much they value certainty, even in the face of additional pain, or a new chest tube, or a noncontributive biopsy result. A patient's desire for certainty seems to us a reasonable consideration for pursuing biopsy, but our own desire to know does not meet the same threshold.

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