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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