

A contributive result of open-lung biopsy improves survival in acute respiratory distress syndrome patients

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Objective: The impact of a contributive result of open-lung biopsy on the outcome of patients with acute respiratory distress syndrome (ARDS) has not been extensively investigated. The aim of this study was therefore to determine the rate of contributive open-lung biopsy and whether it improved the prognosis of ARDS patients.

Design: Prospective study conducted during an 8-yr period.

Setting: A 14-bed medico-surgical intensive care unit and a 12-bed medical intensive care unit from the same hospital.

Patients: One hundred open-lung biopsies were performed in 100 patients presenting ARDS.

Interventions: Open-lung biopsy was performed after ≥ 5 days of evolution of ARDS when there was no improvement in the respiratory status despite negative microbiological samples cultures and potential indication for corticosteroid treatment.

Measurements and Main Results: Ten patients presented a mechanical complication following open-lung biopsy (two pneumothoraces and eight moderate air leaks). The unique independent factor associated with this complication was the minute ventilation when open-lung biopsy was performed (odds ratio,

1.20; 95% confidence interval, 1.03–1.41; $p = .02$). Fibrosis was noted in 53 patients but was associated with an infection in 29 of these 53 patients (55%). A contributive result of open-lung biopsy (defined as the addition of a new drug) was noted in 78 patients. Simplified Acute Physiology Score II was the only independent predictive factor of a contributive open-lung biopsy (odds ratio, 0.96; 95% confidence interval, 0.92–0.99; $p = .04$). Survival was higher in patients with a contributive open-lung biopsy (67%) than in patients in whom open-lung biopsy results did not modify the treatment (14%) ($p < .001$). The factors predicting survival were a contributive result of open-lung biopsy, female gender, and the Organ System Failures score the day of open-lung biopsy.

Conclusions: The present study shows that open-lung biopsy provided a contributive result in 78% of ARDS patients with a negative bronchoalveolar lavage. Survival of ARDS patients improved when open-lung biopsy was contributive. (Crit Care Med 2007; 35:755–762)

KEY WORDS: acute respiratory distress syndrome; lung biopsy; fibrosis; outcome; cytomegalovirus; pneumonia; diagnosis; bronchoalveolar lavage

Acute respiratory distress syndrome (ARDS) is associated with high morbidity and mortality. There is a need for the development of new strategies that might improve clinical outcomes in acute lung injury and ARDS. The majority of recent studies report mortality in the 35–60% range when all patients who meet the American-European Consensus Conference definitions are included (1). For example, in the recently published ALIVE

study, a cohort study of 6,522 patients admitted to 78 intensive care units in ten European countries, the hospital mortality rate was 57.9% in patients with ARDS (2). Death may occur when fibrosis predominates over the healing response, as it results in worsening lung compliance and oxygenation. Certain studies have suggested that this fibrosis is potentially reversible (3, 4). Meduri et al. (5, 6) proposed the use of corticosteroids at the fibroproliferative phase of ARDS and found in a small randomized study a decrease in mortality rate in patients treated with corticosteroids (7). This result was not confirmed by the recently published LaSRS study done by the ARDSnet (8). However, one important issue is to be sure that the indication of corticosteroids is correct by answering the following questions. Is the patient free from infectious pneumonia? Is the cause of ARDS correctly identified? Is fibrosis present? The safety of open-lung biopsy (OLB) in ARDS patients has been

suggested (9, 10). However, the impact of a contributive result of OLB on the outcome of ARDS patients has not been extensively investigated. The aim of this prospective study was therefore to determine the rate of contributive OLB in ARDS patients with negative bronchoalveolar lavage (BAL) and to determine whether their outcome was improved by a contributive result of OLB.

MATERIALS AND METHODS

Study Design. This prospective study was conducted during an 8-yr period (January 1, 1996, to December 1, 2003) in a 14-bed medico-surgical intensive care unit (ICU) and a 12-bed medical ICU from the same hospital. Only nine patients included in a previous published study (8) were also included in the present work. In accordance with French law, no informed consent was mandatory, given that this epidemiologic study did not modify current diagnostic or therapeutic strategies. The decision to perform an OLB required the agreement of at least three intensivists and a thoracic surgeon. OLB was indicated, after ≥ 5

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days of evolution of ARDS, for a lack of improvement of respiratory status (defined as the absence of decrease of the Lung Injury Score) (11) despite negative microbiological samples cultures and potential indication for corticosteroid treatment.

Patients. All adult patients met the criteria of ARDS defined by the American-European Consensus Conference (12). The following data were recorded: age, gender, diagnosis on admission, Simplified Acute Physiology Score (SAPS) II on admission, the number of organ failures on admission evaluated by the Organ System Failures (OSF) score, and the cause and the date of onset of ARDS. The following data were recorded the day of OLB: temperature, white blood cell and platelet counts, radiologic classification using Weinberg's score (13), Lung Injury Score, ongoing antibiotic treatment, and ongoing vasopressive agents. An arterial blood gas determination was performed just before the biopsy procedure.

Microbiological Exams Performed Before Open-Lung Biopsy. BAL was carried out 3 days before OLB. BAL was considered to be positive when at least one bacterium grew at a concentration exceeding 10^4 colony-forming units/mL (14). For the diagnosis of cytomegalovirus (CMV) on BAL, blood, and urine, we used a shell-vial culture technique with antibodies directed against immediate-early antigen. Serologies and conventional cultures (all herpesviruses, respiratory syncytial virus, rhinovirus, adenovirus, and influenza and parainfluenza viruses) were also performed in all patients. Transthoracic aspirates were never used in these mechanically ventilated patients with a profound hypoxemia and a high risk of pneumothorax. Antigenemia pp65 for CMV was performed in all patients. BAL cultures for herpesvirus, *Legionella* (in addition to antigenuria), *Mycoplasma pneumoniae*, *Mycobacteria* (direct examination and culture), *Pneumocystis carinii*, and aspergillosis were also done. The presence of *Aspergillus* sp. was also assessed by tracheal aspirates performed ≥ 5 days prior to OLB. Cytology of BAL was also performed by an experienced cytologist. When these exams were negative (except for mycobacterial culture, which requires several weeks) we decided to perform OLB. This procedure was carried out within the following 24 hrs.

Open-Lung Biopsy Procedure. The procedure was carried out in the ICU (at bedside) or in the operating room by experienced thoracic surgeons (PT or CD). When the $\text{PaO}_2/\text{FiO}_2$ ratio was < 120 mm Hg, OLB was performed in the ICU. No blood gas value contraindicated the procedure. Anticoagulant therapy was stopped for ≥ 12 hrs before the procedure. In patients with a risk of bleeding and/or pleural symphyses (evaluated by the patient's history and/or computed tomography scan), the procedure was performed in the operating room. The surgical procedure has been previously described (9). Only one lung biopsy was performed per patient. The piece of lung was

divided into five parts: one for bacteriology, one for viral cultures, one for mycology and parasitology, one for pathologic examination, and one to be frozen. Average operative time (including installation of the patient) was 30 mins. The biopsy procedure was facilitated by disconnecting the patient from the ventilator when the stapler was applied. When the biopsy was carried out, the ventilator was reconnected immediately. Two chest tubes were inserted before closing the chest. Chest radiography was obtained in each patient after the procedure.

Ventilator Management During Open-Lung Biopsy Procedure. All patients were mechanically ventilated in volume-assist/control mode, sedated with sufentanil and midazolam, and paralyzed with cisatracurium. Tidal volume was 6–8 mL/kg predicted body weight. The FiO_2 was increased to 1.0 during the biopsy procedure. Oxygen saturation was monitored continuously by pulse oximetry in all patients.

Open-Lung Biopsy Processing. Biopsies were fixed in 10% buffered formalin for 24 hrs at room temperature. Then samples were dehydrated in a modified alcohol series: 95% for 15 mins, 100% for 15 mins, and xylene for 15 mins. After dehydration, samples were embedded in a single paraffin block and serially cut at 4- μm thickness with standard microtomes with disposable blades. Slides were stained with hematoxylin-eosin-saffran. Cytomegalovirus pneumonia was diagnosed on pulmonary samples by the identification of large cells with large nuclei containing a basophilic or eosinophilic inclusion surrounded by a light halo (15, 16). These typical findings were always associated with a diffuse interstitial pneumonia characterized by the presence of inflammatory cells (predominantly lymphocytes), thickened alveolar septi, and interstitial inflammation. When a profound nuclear cytopathic effect suggestive of viral pneumonia was found (17), we used an immunohistochemistry technique using the primary antibodies to CMV early antigen (monoclonal, DAKO, Glostrup, Denmark). Diffuse fibrosis was diagnosed when there was a myxoid interstitial fibrosis, an interstitial and intra-alveolar fibrosis, or a distortion of usual pulmonary architecture by dense fibrous tissue. Bacterial pneumonia was defined by the presence of scattered neutrophilic infiltrates localized to terminal bronchioles and surrounding alveoli with evident confluence of infiltrates between adjacent lobules (18). Bacteriologic investigation performed on OLB included Gram and Ziehl-Neelsen staining and culture for bacteria, mycobacteria, and fungi. Lung tissue culture for CMV was performed in all patients.

Follow-Up. Possible pleural space infection, air leak, and pneumothorax were recorded during the ICU stay. If corticosteroids were indicated (presence of a diffuse fibrosis and absence of infection), they were given according to the recommendations of Meduri

et al (7). The duration of mechanical ventilation was recorded. Weaning from volume-assist/control mode was allowed when oxygenation was $> 92\%$ using a positive end-expiratory pressure of 10 cm H_2O and an $\text{FiO}_2 < 0.6$. No other particular weaning recommendation was required.

Definition. An OLB was considered as contributive when its results led to the addition of a new drug (anti-infective, corticosteroids).

Statistics. All statistics were performed using SPSS 13.0 software (SPSS, Chicago, IL). Median values and interquartile ranges are reported for nonnormally distributed data. For normally distributed data, values are reported as mean \pm sd. We selected a sample size of ≥ 90 subjects because it allowed us to detect a difference of 25% in the survival rate when there was a contributive result of OLB, assuming a two-tailed test and $\alpha = .05$ and $\beta = .10$ (power of 90%). The chi-square test was used to compare categorical variables. Continuous variables were compared using Student's *t*-test for normally distributed variables and Mann-Whitney rank-sum test for nonnormally distributed variables. We conducted three multivariate analyses: one using survival at day 28 as the outcome, one determining the predictive factors of a contributive OLB, and one determining the predictive factors of mechanical complications after OLB. These analyses were performed using a binary logistic regression analysis with a forward-selection procedure with 0.10 as the limit for accepting and removing newly entered terms. All variables with $p < .25$ by univariate analysis and those classified as pertinent by the main investigator (LP) were considered. Baseline factors included in the analysis for the survival model prediction were gender, SAPS II score on admission, surgical patients, duration of ARDS prior to OLB, the use of vasopressive agents the day of OLB, the OSF score the day of OLB, the Lung Injury Score the day of OLB, the use of corticosteroids related to histologic results, the histologic diagnosis of fibrosis, the development of mechanical complications following OLB, and a contributive result of OLB. For the model aiming to predict a contributive result of OLB, six variables with $p < .25$ by univariate analysis or classified as pertinent by the main investigator (LP) were considered: gender, SAPS II score on admission, duration of ARDS before OLB, antibiotic use the day of OLB, the $\text{PaO}_2/\text{FiO}_2$ ratio before OLB, and the Weinberg's radiologic score the day of OLB. For the model predicting mechanical complications following OLB, ten variables were considered: the SAPS II score on admission, the OSF score the day of OLB, the use of vasopressive agents the day of OLB, the duration of ARDS prior to OLB, the use of corticosteroids related to histologic results, the histologic diagnosis of fibrosis, the level of positive end-expiratory pressure when the OLB was performed, the plateau pressure when OLB was performed, the minute ventilation (or the tidal volume) when OLB was performed, the Wein-

berg's radiologic score the day of OLB, and the place where the OLB was performed (ICU or operating room). At each step of these analyses there was a goodness-of-fit test of the null hypothesis (Hosmer and Lemeshow test), which verifies that the model adequately fits the data. For all statistical tests used, $p < .05$ was considered as statistically significant.

RESULTS

Characteristics of the Patients. During the study period, 790 patients presented with ARDS (age, 57 ± 17 yrs; SAPS II on admission, 48 ± 22 ; ICU mortality rate, 54%). In all, 100 OLBs were performed in 100 of these patients presenting with ARDS (female gender, 33; age, 58 ± 16 yrs; SAPS II on admission, 56 ± 21). None of the families refused OLB. Among the 100 patients enrolled in the study, 26 were surgical (three were admitted to the ICU after multiple trauma and 23 were admitted with post-operative complications following major surgery), and 74 were admitted for an acute medical illness. Only four patients were immunocompromised on admission. The cause of ARDS was a direct lung injury in 84 patients (community-acquired pneumonia, $n = 40$; ventilator-associated pneumonia, $n = 27$; aspiration pneumonitis, $n = 9$; nosocomial pneumonia, $n = 6$; lung contusion, $n = 1$; intra-alveolar hemorrhage, $n = 1$) and an indirect lung injury process in the remaining 16 patients (sepsis, $n = 10$; septic shock, $n = 4$; multiple trauma, $n = 2$).

Characteristics of the Patients at the Time of Biopsy. Twenty-eight of the 100 patients had computed axial tomographic examination of the chest during the 72-hr period preceding OLB.

The median time for mechanical ventilatory support before OLB was 11 days (6–23 days). OLB was performed 7 days (6–13.5 days) after the onset of ARDS. The day of OLB, all patients had a Lung Injury Score >2.5 (mean, 3.1 ± 0.4). Thirty patients presented at least two visceral dysfunctions (as defined by the OSF scoring system) at the time of biopsy.

At the time of biopsy, mean temperature was $38.0 \pm 1.1^\circ\text{C}$ (range, 36.0 – 40.5°C). Mean white blood cell count was $14.3 \pm 7.2 \text{ g}\cdot\text{L}^{-1}$ with a predominance of neutrophils ($84 \pm 9\%$). Weinberg's radiologic score was 10.0 ± 2.1 . Sixty-three patients were receiving antibiotic treatment. The platelet count was $>100 \text{ g}\cdot\text{L}^{-1}$ in all but 11 patients. All patients were hemodynamically stable, but 57 patients

were receiving cardiovasoactive drugs. Steroids (200 mg of hydrocortisone every day) had been systematically used for septic shock since 2000.

Concerning ventilatory variables at the time of biopsy, the tidal volume was $7.8 \pm 2.1 \text{ mL}\cdot\text{kg}^{-1}$ of predicted body weight, the minute ventilation was $11.7 \pm 3.9 \text{ L}\cdot\text{min}^{-1}$, the plateau pressure was $32.3 \pm 4.6 \text{ cm H}_2\text{O}$, and the positive end-expiratory pressure was set at $10.0 \pm 3.1 \text{ cm H}_2\text{O}$. In addition, 34 patients were under nitric oxide, and 19 of these 34 patients were receiving a concomitant continuous infusion of almitrine. Twenty-one patients had been treated by prone positioning before OLB, and five other patients had received high-frequency oscillatory ventilation. No patient received corticosteroids at the time of biopsy. Arterial blood gas samples showed that $\text{PaO}_2/\text{FiO}_2$ ratio was $129 \pm 41 \text{ mm Hg}$ and PaCO_2 was $49 \pm 14 \text{ mm Hg}$ just before OLB.

OLB was performed at bedside in 64 patients and in the operating room in the remaining 36 patients. OLB was performed on the right side in 53 patients and on the left side in the remaining 47 patients. There was no intraoperative morbidity or mortality.

Follow-Up. Only one patient required blood transfusion during the 48-hr period following OLB, for a hemothorax of 250 mL. No arrhythmia or hemodynamic instability was precipitated by OLB. No significant change in arterial blood gases or ventilator variables was noted as linked to the biopsy procedure (data not shown). No pleural space infection was diagnosed until discharge from the hospital or until death of the patients. Ten patients presented a mechanical complication beginning during the 48-hr period following OLB (two pneumothoraces and eight moderate air leaks from operative chest tubes for ≥ 24 hrs that did not require surgery). The unique independent factor associated with the diagnosis of mechanical complication following OLB procedure was the minute ventilation when OLB was performed (odds ratio, 1.20; 95% confidence interval, 1.03–1.41; $p = .02$), which was higher in patients developing a mechanical complication than in patients not developing such a complication ($12.35 \text{ L}\cdot\text{min}^{-1}$ [11 – $18.2 \text{ L}\cdot\text{min}^{-1}$] vs. $10.6 \text{ L}\cdot\text{min}^{-1}$ [9 – $13.55 \text{ L}\cdot\text{min}^{-1}$], respectively; $p < .05$). Other factors, especially the presence of fibrosis, the use of corticosteroids, or when OLB was per-

Table 1. Histologic results of open-lung biopsy (OLB)

Result of OLB	No.
Fibrosis	16
Fibrosis and infection	29
Infection	28
Diffuse alveolar damage	13
Miscellaneous	
Systemic lupus erythematosus	2
Bronchioloalveolar carcinoma	1
Amiodarone toxicity	2
Intra-alveolar hemorrhage	1
Allograft rejection	1
Drug toxicity	2
Rheumatoid lung and mycobacterial infection	1
Acute eosinophilic pneumonia	1
Carcinomatous lymphangitis	2
Microangiitis	1

formed at the bedside, were not retained by the model.

Diagnostic Results and Changes in Therapy. The diagnostic results of OLB are shown in Table 1. All biopsy specimens exhibited abnormalities. Fibrosis was noted in 53 patients. However, fibrosis was associated with an infection in 29 of these 53 patients (55%). Corticosteroid therapy was initiated in only 28 patients. No patient was treated empirically with corticosteroids for late ARDS during the study period. A definite cause of infection was established in 42 of the 57 histologic diagnosis of infection. Cytomegalovirus pneumonia was diagnosed by histology in 30 patients and herpes simplex virus in three patients. Lung tissue culture for CMV, which was performed in all patients, was positive for this virus in ten patients. A mycobacterial infection was diagnosed in four patients and an invasive aspergillosis in two patients. Finally, a contributive result of OLB, which implied the addition of a new drug, was noted in 78 patients (Table 2). No predictive factor of a contributive OLB was retained by the univariate analysis (Table 3). SAPS II was the only independent predictive factor of a contributive OLB (odds ratio, 0.96; 95% confidence interval, 0.92–0.99; $p = .04$).

Outcome. Ventilator-free days and numbers alive at day 28 tended to be higher in patients who had a contributive OLB (0 day (0–5 days) vs. 0 day (0–0 day); $p = .065$; Figure 1). The mortality rate at day 28 was 45%. The mortality rate was 48% for the first 50 patients and 42% for the last 50 patients. Survival was higher in patients with a contributive OLB (67%) than in patients in whom

Table 2. New drugs according to the histologic results of open-lung biopsy (OLB)

Result of OLB	New Drugs	No.
Fibrosis	Methylprednisolone 2–3 mg/kg/day	16
Fibrosis and CMV infection (H+C:2 – H:2)	Ganciclovir + methylprednisolone 2–3 mg·kg·day	4
Fibrosis + miscellaneous diagnosis + mycobacterial infection (1) (H+C) or bacterial infection (2) (H)	Antibiotics + methylprednisolone 2–3 mg·kg·day	3
Fibrosis + miscellaneous diagnosis	Methylprednisolone 5–10 mg·kg·day ^a	5
CMV pneumonia (H+C:8, H:18)	Ganciclovir	26
Herpes simplex virus pneumonia (H+C)	Acyclovir	3
Aspergillosis (H+C)	Voriconazole	2
Mycobacterial infection (H+C)	Antibiotics	3
Bacterial pneumonia (H+C)		
<i>Enterobacter aerogenes</i>	Imipenem—gentamycine	1
<i>Pseudomonas aeruginosa</i>	Ceftazidime—amikacin	1
<i>Klebsiella pneumoniae</i>	Imipenem—gentamycine	1
Nuclear cytopathic effect (H)	Ganciclovir (2)-acyclovir (1)	3
Histological bacterial pneumonia (H)	Antibiotics	10

CMV, cytomegalovirus; H, histologic result; C, lung tissue culture.

^aThis dose regimen of methylprednisolone was related to the disease associated with fibrosis (systemic lupus erythematosus, two; intraalveolar hemorrhage, one; acute eosinophilic pneumonia, one; and microangiitis, one).

Table 3. Factors associated with a contributive result of open-lung biopsy (OLB): Univariate analysis

	Contributive OLB (n = 78)	Noncontributive OLB (n = 22)	p
Female gender, n (%)	29 (37)	4 (18)	.16
Surgical, n (%)	20 (26)	6 (27)	.90
SAPS II at admission (range)	54 (50–54)	58.5 (52–69)	.13
Direct lung injury, n (%)	66 (85)	18 (82)	.75
Duration of ARDS prior to OLB, days (range)	8 (6–13)	7 (6–14)	.73
On antibiotics the day of OLB, n (%)	48 (62)	15 (68)	.75
Tidal volume, mL·kg ⁻¹ PBW (range)	7.7 (6.7–8.8)	7.5 (6.3–8.6)	.54
Plateau pressure, cm H ₂ O	33 ± 5	32 ± 6	.87
Minute ventilation, L·min ⁻¹ (range)	10.8 (9.2–13.8)	10.8 (9.4–12.7)	.74
PaCO ₂ , mm Hg (range)	45 (39.5–53)	42.5 (38–60)	.50
PaO ₂ /FIO ₂ , mm Hg	133 ± 39	115 ± 45	.065
Vasopressors at the time of OLB, n (%)	43 (55)	14 (64)	.64
Weinberg lung radiologic score the day of OLB (range)	10 (9–12)	10 (8–12)	.26
OSF the day of OLB (range)	1 (1–2)	1 (1–2)	.84

SAPS, Simplified Acute Physiology Score; ARDS, acute respiratory distress syndrome; PBW, predicted body weight; OSF, Organ System Failures score.

OLB results did not modify the treatment (14%) ($p < .001$). This is illustrated by the Kaplan-Meier analysis (Fig. 2). The median delay between OLB and death of all the 19 patients without a treatable cause was 6 days (2.25–15.75 days). Only eight patients without a treatable cause died during the first 5 days following OLB. In three patients, do-not-resuscitate orders were given following the OLB result. Concerning the remaining five patients, four of them presented with multiple organ failure and one patient presented with intractable cardiogenic shock 5 days after OLB. Only three of these eight patients presented with a mechanical complication.

Survival at day 28 was slightly higher in the 28 patients receiving corticosteroids (64%) than in patients not receiving corticosteroids (51%), but the difference did not reach statistical significance. As shown in Table 4, the univariate analysis identified eight factors associated with survival. Development of a mechanical complication was not associated with mortality. Finally, as showed in Table 5, only three factors were retained by the model predicting survival. These factors were a contributive result of OLB, female gender, and the OSF score the day of OLB. The year of admission did not alter these results. The model correctly predicted outcome in 78.6% of the patients.

DISCUSSION

The present study shows that OLB provided a contributive result in 78% of ARDS patients with a negative BAL. Survival of ARDS patients improved when OLB was contributive.

The mechanisms that regulate fibrosis following ARDS are not entirely understood. As described by some authors (5, 6, 19), corticosteroids could improve the oxygenation status and the outcome of ARDS at the fibroproliferative phase. Although one study (20) showed that determination of type III procollagen peptide in BAL fluid is highly correlated with an increased risk of fatal outcome, to our knowledge no study has demonstrated a correlation between the presence of fibrosis assessed by lung histology and the level of type III procollagen peptide in BAL fluid in ARDS patients. Biopsies not only establish the diagnosis of fibrosis but also provide valuable information to rule out pulmonary infection as the continuing cause of respiratory distress. It is well recognized that nosocomial pneumonia is a major complication of ARDS, and the use of corticosteroids, if sepsis was the cause of continuing ARDS, would be contraindicated. On the other hand, the false-negative rate of all sampling procedures in the diagnosis of nosocomial pneumonia in ventilated patients could require the use of the histologic assessment of lung parenchyma (18, 21). It has been shown that, in ventilated patients, nosocomial pneumonia can be related to virus, especially CMV (22). A low sensitivity of BAL using shell-vial culture technique has also been reported (22). More than one third of infectious pneumonia diagnosed by OLB in the study of Patel and coworkers (10) was related to CMV. OLB has been demonstrated as a useful procedure for the diagnosis of infection (23, 24). It has been reported that a BAL performed before OLB failed to isolate the infectious agent found in lung tissue culture in 80% of OLBs performed in children with respiratory failure (25). A diagnosis of CMV pneumonia may be made in the absence of a positive culture when definitive CMV viral inclusions are seen on histopathologic evaluation of lung biopsy samples (26, 27). One of the limitations of the study was that we did not use recent molecular biology tools to diagnose CMV. Indeed, false-positive results are not totally excluded, but much more important, CMV could have been underdiagnosed by limiting the investigations

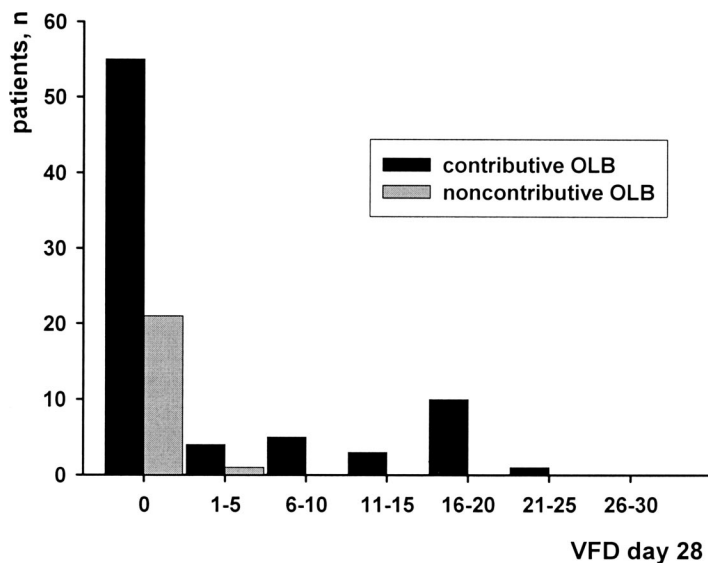


Figure 1. Ventilator-free days (VFD) and alive at day 28 (VFD day 28) according to the results of open-lung biopsy (OLB).

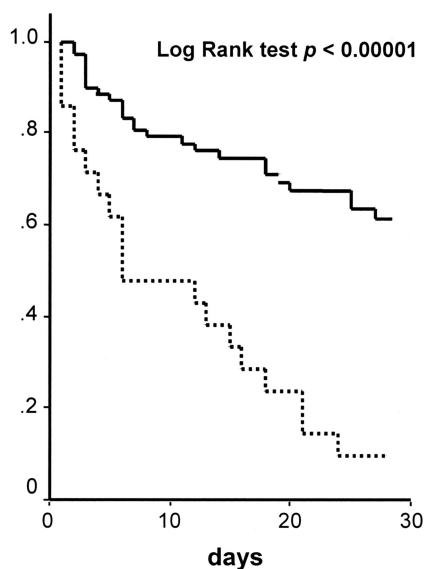


Figure 2. Kaplan-Meier survival analysis comparing patients with acute respiratory distress syndrome (ARDS) with a contributive open-lung biopsy (OLB) (solid line) with ARDS patients with a noncontributive OLB (dotted line).

to histologic evaluation and culture. In a prospective study, Heininger et al. (28) reported an incidence of 35.6% of active CMV infections in surgical ICU patients. Recently, Cook et al. (29) elegantly showed that there was a significant increase in pulmonary fibrosis in latently infected CMV mice when compared with controls after stimulation with bacterial sepsis. This is a solid argument for a pathologic role for CMV in mechanically ventilated patients, which is probably not a surrogate of severe illness. It has been

demonstrated that preemptive ganciclovir treatment reduces CMV end-organ disease and is literally life saving in bone marrow transplants (30, 31). Thus, it could be interesting to use routine blood determination of CMV pp65 antigen or polymerase chain reaction to detect CMV early and to start treatment, even if the sensitivity and the specificity of these techniques remained to be established in ICU patients. Cytomegalovirus pp65 antigen has been proposed for the diagnosis of end-organ disease. However, a sensitivity of 60% has been reported (32). Recently, Jaber et al. (33) showed that CMV is not uncommon in mechanically ventilated patients. They also found that the duration of mechanical ventilation was longer and the mortality rate higher in patients with a positive antigenemia for CMV. Negative BAL findings for CMV that we found could be explained by the lack of sensitivity of the conventional culture and the shell-vial culture techniques. Polymerase chain reaction techniques could be useful. However, these techniques could lack specificity, and the diagnostic performance of reverse transcription-polymerase chain reaction on BAL remains to be determined in ICU patients. The relatively high rate of CMV infection that we found can be explained by the fact that the high number of diagnostic tests performed on blood and BAL allowed us to eliminate a lot of infectious causes prior to performing OLB. The lack of sensitivity of the diagnostic techniques for CMV in ARDS patients explained that OLB allowed us to diagnose CMV rather

than bacterial or fungal infections. Finally, OLB was performed in a selected group of ARDS patients who had previously been submitted to an extensive infectious screening, which was negative. Ganciclovir treatment has also been associated with some success in symptomatic CMV diseases in immunocompromised patients (34–36). A recently performed meta-analysis concluded that the use of ganciclovir reduces the mortality rate of CMV disease of solid-organ transplants (37). The present study found that in patients presenting with established ARDS with a potential indication for corticosteroids, fibrosis was present in only 53% of the lung specimens obtained by OLB. Moreover, histologic signs of infectious pneumonia were present in 55% of these patients with fibrosis. Finally, only 28 patients received corticosteroids. The remaining 72 patients would have received corticosteroids if OLB had not been performed. According to the present results, the National Institutes of Health-sponsored trial should be interpreted cautiously because in our experience only 28% of the patients who should have received corticosteroids finally received this treatment when OLB was performed before the initiation of the treatment. If OLB had not been done, all these patients would have received corticosteroids. Another limitation of the study is the fact that we did not prospectively record whether steroids were used for septic shock in specific ARDS patients, and therefore we cannot analyze how the systematic use of steroids for septic shock affected our findings. However, we found that the year of admission did not influence the results. Moreover, the mortality rate was 48% for the first 50 patients and 42% for the last 50 patients, suggesting that this therapeutic intervention did not significantly alter our results.

Some studies have been devoted to the use of OLB in immunocompromised patients (38, 39). All these studies, however, showed that the procedure can be carried out with a low mortality rate even in seriously ill patients. Questions about the performance and the tolerance of OLB in ARDS patients have recently received attention (9, 10). Concerning tolerance and the morbidity related to OLB, our study favors the use of this technique in ARDS patients. Moreover, this surgical technique can be performed at bedside in the ICU when oxygenation status contraindicates any transport of the patient. We found in the present study that the rate of

Table 4. Factors associated with outcome at day 28 after open-lung biopsy (OLB): Univariate analysis

	Patients Alive at Day 28 (n = 55)	Patients Dead at Day 28 (n = 45)	<i>p</i>
Female gender, n (%)	29 (53)	4 (9)	.001
Age, yrs (range)	60 (46–67)	64 (50–72)	.13
Surgical, n (%)	13 (24)	13 (29)	.71
SAPS II at admission (range)	54 (50–61)	59.5 (52.5–65.5)	.056
Duration of ARDS prior to OLB, days (range)	9 (6–16)	7 (6–9)	.037
Duration of mechanical ventilation prior to OLB, days (range)	14 (7–24)	10 (7–21)	.04
Tidal volume, mL·kg ⁻¹ PBW (range)	7.5 (6.6–8.6)	7.8 (6.6–9.2)	.31
Plateau pressure, cm H ₂ O	30 ± 5	33 ± 6	.015
Minute ventilation, L·min ⁻¹ (range)	10.6 (9.0–12.7)	11.0 (9.5–15.5)	.23
PaCO ₂ , mm Hg	45 (38–51)	45 (40–60)	.17
PaO ₂ /FIO ₂ , mm Hg	138 ± 41	118 ± 39	.016
OLB done at the bedside, n (%)	32 (58)	32 (71)	.26
Vasopressors at the time of OLB, n (%)	26 (47)	31 (69)	.034
Lung injury score the day of OLB	2.97 ± 0.56	3.07 ± 0.57	.40
OSF the day of OLB (range)	1 (1–1)	1 (1–2)	.016
Mechanical complication of OLB, n (%)	3 (5)	7 (15)	.11
Fibrosis at histology, n (%)	28 (51)	25 (56)	.79
Corticosteroids after OLB, n (%)	18 (33)	10 (22)	.35
Gancyclovir after OLB, n (%)	18 (33)	14 (31)	.97
Contributive result of OLB, n (%)	52 (94)	26 (58)	.001

SAPS, Simplified Acute Physiology Score; ARDS, acute respiratory distress syndrome; PBW, predicted body weight; OSF, Organ System Failures score.

Table 5. Factors independently associated with survival at day 28 after open-lung biopsy (OLB)

	Odds Ratio	95% Confidence Interval for Odds Ratio		<i>p</i>
		Lower	Upper	
Contributive result of OLB	18.66	3.3	105.3	.001
Female gender	16.37	3.5	77.4	.0001
OSF the day of OLB	0.23	0.09	0.62	.004

OSF, Organ System Failures score.

mechanical complications is not enhanced by performing OLB at the bedside. We had no death from this procedure, and our only morbidities were a moderate hemothorax, two pneumothoraces, and the development of a low-grade air leak in eight patients. To minimize these complications, we disconnected the patient from the ventilator during the stapling procedure. In addition, we used two pleural chest tubes rather than one. Every effort was made to ensure complete pneumostasis before closure.

An alternative approach for invasive diagnosis, transbronchial biopsy (TBB), has commonly been limited to autonomously ventilating patients. Only a few reports (40–42) have evaluated the feasibility of TBB during mechanical ventilation. However, there are factors that may limit the utility of TBB. These factors are generally believed to be related to its small size, lack of representativeness of

the tissue specimen, or both (43). In our study, the number of samples necessary for pathologic examination and microbiological cultures underscores the need for large samples. Furthermore, hemorrhage and pneumothorax are potentially life-threatening complications of TBB. Two pneumothoraces (15%) were encountered in the study of Pincus et al. (42) and one by Fraire et al. (43) in their series of 15 patients. It was recently reported (44) that the combination of BAL and TBB was contributive in 11 of 11 ARDS patients. However, in this subgroup of patients, the authors reported an incidence of 36% pneumothoraces. Using standard postmortem histologic examination as the gold standard, the sensitivity of TBB for making a specific diagnosis was 57% in 30 patients with diffuse pulmonary infiltrates and acute respiratory failure (45).

In a retrospective study (46), it was shown that the mortality rate was 26% in patients benefiting from a therapeutic change based on OLB result, whereas the mortality rate was 62% when no change resulted from the OLB. Patel and coworkers (10) in a retrospective study of 57 ARDS patients found that a new therapy was started in 60% of their patients based on OLB results. A retrospective study performed in 63 patients with hematologic malignancies showed that survival increased when the biopsy results exhibited specific diagnosis (47). It was also recently reported that a specific diagnosis was associated with a lower mortality rate when compared with a nonspecific finding on OLB performed in patients with hematologic malignancy or hematopoietic stem cell transplantation presenting with unexplained pulmonary infiltrates (48). The present study is the first, to our knowledge, to demonstrate that a contributive OLB improved the outcome of ARDS patients.

The major strengths of the present work are that the study was prospectively performed, included 96% of immunocompetent patients, and required a negative BAL at the time of biopsy. The prospective nature of the study allowed us to determine whether the changes in therapy resulted in changes in survival. Moreover, this is the largest series of ARDS patients undergoing OLB for evaluation of fibrosis.

It is probably difficult to perform a randomized trial evaluating whether OLB alters ARDS patients' prognoses because the rate of patients who could be enrolled in such a study represents <15% of all ARDS patients. Moreover, it is highly probable that all centers should be trained to do these biopsies at the bedside. This is a prerequisite for an improved survival rate. Thus, it should probably be difficult to validate by a randomized trial the beneficial effect of OLB on the survival rate of ARDS patients. However, as the LaSRS study did not show any beneficial effect on the mortality rate of ARDS patients (8), it could be interesting to carefully select the patients who will benefit from corticosteroids. Indeed, as the present study shows, only 53% of our patients presented with a fibrosis, and identifying those ARDS patients with unrecognized opportunistic infections delayed the use of corticosteroids in ≥50% of these patients. A randomized trial should be conducted to demonstrate that patients with OLB-

proven fibrosis benefit from steroids. Moreover, it has been suggested (49) that patients thought to have ARDS on the basis of pneumonia, and those considered to have ARDS but without a defined predisposing condition, should promptly undergo a lung biopsy if the findings of BAL are negative, to exclude an acute noninfectious parenchymal lung disease (acute interstitial pneumonia, acute eosinophilic pneumonia, acute bronchiolitis obliterans organizing pneumonia, diffuse alveolar hemorrhage, acute hypersensitivity pneumonitis) and to rapidly start corticosteroids. Evaluating the ability of BAL fluid to stimulate human lung fibroblasts *in vitro* 24 hrs and 7 days after the onset of ARDS, investigators showed that fibroproliferation occurs early in the course of ARDS (50). This is why OLB should probably be undertaken sooner rather than later in ARDS. This is corroborated by the findings of Lachapelle and Morin (51), who showed that there was a significant difference in the proportion of specific diagnoses made among those who had OLB early compared with those who had it later. They also observed an improvement in survival when a new therapy was instituted as a result of early OLB compared with late OLB. If OLB is performed later rather than sooner, ARDS patients are in the final cascade of multiple organ failure that usually leads to death, and no therapy changes would alter the outcome (52). All these facts favor the early use of OLB when BAL is negative but the patients are not improving. The interpretation of the present results is that in some cases we performed OLB too late in the course of ARDS. It is now our policy to perform OLB earlier in the course of this illness.

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