

# Corrigenda

## Erratum

Por questões alheias à nossa vontade a versão em inglês do artigo “Biópsia pulmonar cirúrgica em doentes sob ventilação invasiva e com suspeita de doença difusa do parênquima pulmonar/*Open lung biopsy in patients on mechanical ventilation with suspected diffuse lung disease*” (Natália Melo, Sandra Figueiredo, António Morais, Conceição Souto Moura, Paulo Pinho, Pedro Bastos, Teresa Oliveira) publicado na Rev Port Pneumol 2009; XV(4):597-611, veio acompanhada de erros importantes que desvirtuaram significativamente o original, pelo que optamos pela sua nova publicação. Pelo ocorrido, as nossas desculpas aos autores.

Regrettably, the english version of the article “Biópsia pulmonar cirúrgica em doentes sob ventilação invasiva e com suspeita de doença difusa do parênquima pulmonar/*Open lung biopsy in patients on mechanical ventilation with suspected diffuse lung disease*” (Natália Melo, Sandra Figueiredo, António Morais, Conceição Souto Moura, Paulo Pinho, Pedro Bastos, Teresa Oliveira) published in the Rev Port Pneumol 2009; XV(4):597-611, appeared in a form which contained a number of errors that detracted significantly from the original, and due to the nature of this mistake we have decided to re-publish the article. We offer our sincere apologies to the authors for this unfortunate lapse.

O editor

The editor

Natália Melo  
Sandra Figueiredo  
António Morais  
Conceição Souto Moura  
Paulo Pinho  
Pedro Bastos  
Teresa Oliveira

### Biópsia pulmonar cirúrgica em doentes sob ventilação invasiva e com suspeita de doença difusa do parênquima pulmonar

### *Open lung biopsy in patients on mechanical ventilation with suspected diffuse lung disease*

Rev Port Pneumol 2009; XV(4):597-611

#### Introduction

Open lung biopsy (OLB) is the gold standard test for many lung diseases which present with acute respiratory failure and diffuse pulmo-

nary infiltrates<sup>1</sup>. It is, however, an invasive procedure, and thus employed only when other, less invasive, methods have been tried or when a precise diagnosis is needed quickly<sup>1</sup>.

The available evidence on the safety and diagnostic yield of OLB in critically ill patients on mechanical ventilation (MV) is scarce; therefore, the correct indication of OLB is difficult to establish in such patients, and the available studies disagree about whether it is beneficial. Some authors<sup>2,3</sup> consider OLB both safe and diagnostically useful, and believe that it influences therapeutic decisions, while others<sup>4,5</sup> argue that it confers no survival benefit and entails additional morbidity and mortality. Because of these potential drawbacks, many clinicians are reluctant to perform OLB in patients on MV. However, cases of lung disease of unknown aetiology and refractory to empirical treatment require an accurate histological diagnosis so that specific therapy can be started.

We aimed to determine the diagnostic yield, changes to diagnosis and therapy, complications, and mortality of OLB performed in patients with suspected diffuse lung disease on MV.

### Material and methods

We performed a retrospective study of the clinical files of patients admitted to the adult Multidisciplinary Intensive Care Units of S. João Hospital between January 1999 and July 2007 (8.5 years). The inclusion criteria were respiratory failure requiring MV and diffuse lung infiltrates for which OLB was indicated. Patients who were placed on MV after OLB or were biopsied during a thoracotomy performed for therapeutic purposes were excluded.

The data obtained on the subjects included demographic data, comorbidities, suspected diagnosis on ICU admission, diagnostic tests

performed before OLB (including computed tomography (CT) of the chest and bronchoscopy), treatment administered prior to OLB, PaO<sub>2</sub>/FiO<sub>2</sub> and PEEP levels before and after OLB, the histological diagnoses obtained and their influence on patient management, and complications and mortality associated with the surgical procedure. All biopsies were performed via thoracotomy (mostly minithoracotomy) on sites selected based on imaging abnormalities. A maximum of 3 lung tissue samples were taken for histological analysis. After lung tissue was obtained, all patients had their pleural spaces drained using 2 pleural drains, which were removed as early as possible if there were no air leaks.

Statistical analysis was performed using SPSS 14.0., with  $p < 0.05$  considered significant.

### Results

#### Pre-OLB demographic and clinical data

OLB is seldom performed in our institution, with an annual rate of 0.2%-0.6% of patients admitted to the ICU at S. João Hospital. Nineteen patients met our inclusion criteria. Mean patient age was  $58 \pm 16.3$  years, 10 (53%) were male, 5 (26.3%) were immunodepressed, and 12 (63.2%) had previously diagnosed comorbidities. Before the biopsy, all patients underwent CT of the chest and 15 (79%) patients had had fiberoptic bronchoscopy. When OLB was performed, 12 (63.2%) patients were on antibiotic therapy, 14 (73.7%) were receiving steroids, 4 (21.1%) were on inotropic support, PEEP ( $n=16$ ) and PaO<sub>2</sub>/FiO<sub>2</sub> ( $n=18$ ) levels were, on average, 9 cmH<sub>2</sub>O and 171 mmHg, respectively. At the time of the OLB, patients had stayed on

average  $13 \pm 7$  days in the ICU. Duration of MV before the procedure was 11.8 days for survivors and 14.9 days for non survivors, a difference that was not statistically significant ( $p=0.6$ ).

### **Intra- and peri-operative complications and physiological abnormalities**

There were no intra-operative complications. Four patients (21%) developed complications, all of which consisted of persistent air leak lasting 4 to 27 days, and one patient required inotropic support after OLB. Mean post-OLB  $\text{PaO}_2/\text{FiO}_2$  and PEEP were 202 mmHg and 8 mmHg, respectively. The levels of these parameters were not significantly different before and after the biopsy.

### **Histological diagnoses**

The diagnostic yield was 95%. Only one patient had an inconclusive diagnosis because of small sample size. Table I shows the histological diagnoses. Diffuse alveolar damage (DAD) (Fig. 1) was the most common diagnosis, found in 7 patients, 6 of which were in the disease's fibroproliferative stage and 1 in the exudative stage. Two patients with no known prior lung pathology had abnormalities compatible with DAD on histology, as well as features compatible with usual interstitial pneumonia. Given these findings, acute exacerbation of idiopathic pulmonary fibrosis (IPF) was diagnosed after other causes of IPF decompensation were ruled out (Fig. 2).

One female patient, admitted to hospital with respiratory insufficiency and pulmonary thromboembolism (PTE), was admit-

ted to the ICU following cardiorespiratory arrest (CRA). Imaging abnormalities suggested diffuse lung disease, and an OLB was performed because her clinical presentation was suspected to be caused by another underlying disease. The biopsy revealed no abnormalities other than recent, organised thrombus.

The 2 cases of organising pneumonia (OP) were associated with *Pseudomonas aeruginosa* infection (1 case) and *Legionella* infection (1 case) (Fig. 3). Two patients were diagnosed with eosinophilic pneumonia, and one of them underwent a bronchoscopy. However, a total and differential cell count could not be performed in the bronchoalveolar lavage (BAL) because the sample's yield was insufficient. BAL cell counting was not performed in the other patient because the diagnosis was not suspected.

One patient was admitted to the ICU after suffering CRA during a fiberoptic bronchoscopy performed for DLD workup. Since the patient still did not have a definitive diagnosis, an OLB was performed and the histological findings were compatible with sarcoidosis. Viral pneumonia was diagnosed by histological analysis in one patient and by molecular biology techniques (positive test for *Cytomegalovirus* (CMV) DNA in a lung biopsy fragment) in another. Fungal pneumonia with *Candida spp.* characteristics was diagnosed by visualisation of fungal structures and confirmed by histochemical methods using PAS, PAS-D and Grocott methods.

### **The impact of the histological diagnosis on management and outcomes**

The OLB results led to review of the initial diagnosis in 14 patients (74%) and influ-

Table I – Patients enrolled in the study

	Diagnosis on admission	Diagnosis after OLB	Changes to diagnosis	Changes to management	Clinical course
1	Bilateral pneumonia + septic shock	Diffuse alveolar damage	Yes	Yes	Died
2	Diffuse lung disease of unknown aetiology	Acute exacerbation of IPF	Yes	No*	Died
3	Lung-kidney syndrome	Diffuse alveolar damage	Yes	No	Discharged
4	Vasculitis with lung involvement	Diffuse alveolar damage	Yes	Yes	Died
5	PTE + diffuse interstitial infiltrates	PTE	No	No	Discharged
6	Bilateral pneumonia	OP	Yes	Yes	Discharged
7	Bilateral pneumonia	OP	Yes	Yes	Discharged
8	ARDS	Diffuse alveolar damage	No	No	Discharged
9	Severe sepsis + suspected lung-kidney syndrome	Unspecific abnormalities (small sample)	No	No	Discharged
10	Bilateral pneumonia	CMV pneumonia	Yes	Yes	Discharged
11	Severe CAP	Acute eosinophilic pneumonia	Yes	No*	Died
12	Severe CAP	Eosinophilic pneumonia	Yes	Yes	Discharged
13	Diffuse lung disease of unknown aetiology	Acute exacerbation of IPF	Yes	No*	Died
14	Bilateral pneumonia	Viral pneumonia	Yes	Yes	Died
15	ARDS	Diffuse alveolar damage	No	No	Discharged
16	Post CRA + DLD undergoing a workup	Sarcoidosis	Yes	No	Discharged
17	ARDS	Diffuse alveolar damage	No	No	Died
18	CAP + bilateral pulmonary nodules	Fungal pneumonia	Yes	Yes	Died
19	CAP	Diffuse alveolar damage	Yes	No	Died
	TOTAL	18 (95%)	14 (74%)	8 (42%)	9 (47%)

IPF – idiopathic pulmonary fibrosis; PTE – pulmonary thromboembolism; OP – organising pneumonia; ARDS – acute respiratory distress syndrome; CRA – cardiorespiratory arrest; CAP – community acquired pneumonia

\* Died before histologic result of OLB was known

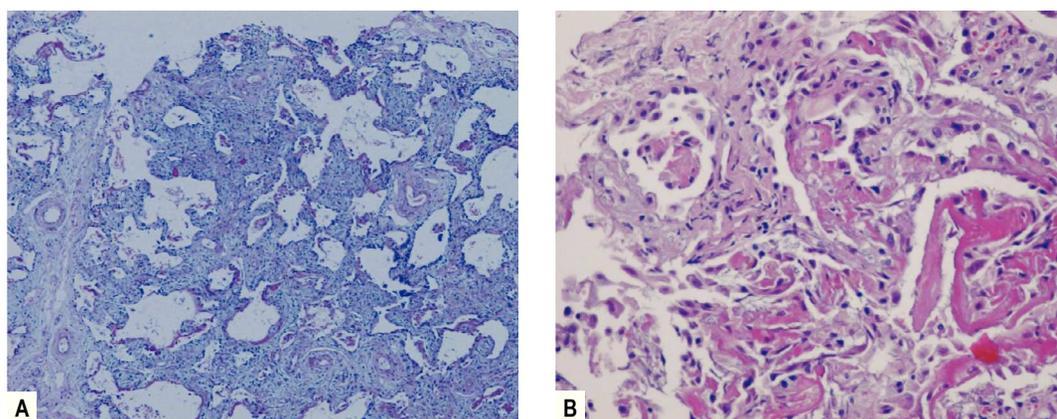
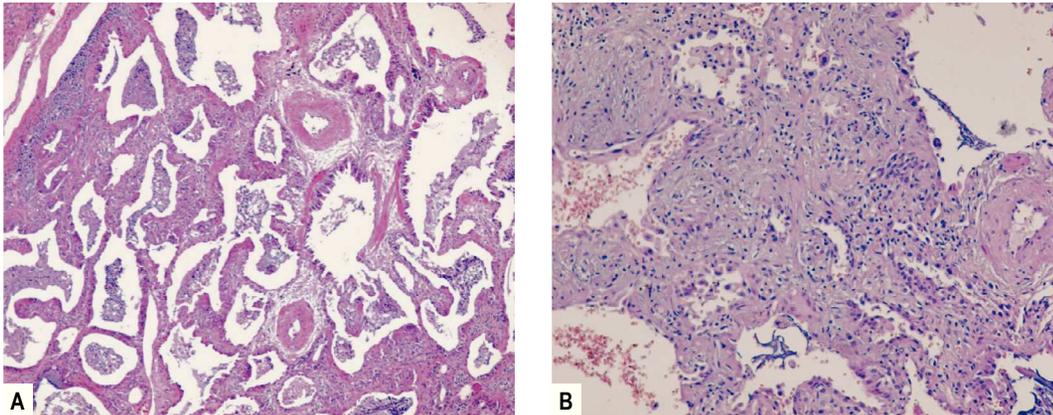
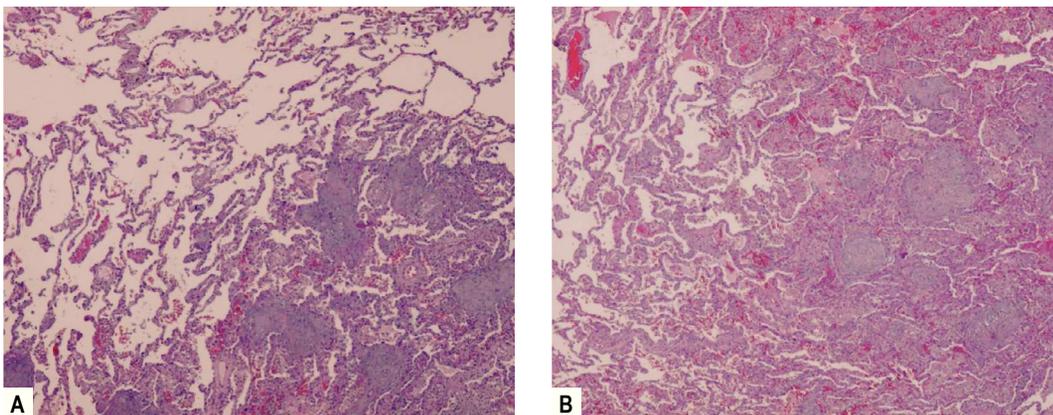


Fig. 1 – Diffuse alveolar damage. A – Marked interstitial thickening from fibroblast proliferation and a mild mononuclear inflammatory infiltrate with distortion of the alveolar spaces (HE 40X). B – Hyaline membranes (HE 400X)



**Fig. 2** – Diffuse alveolar damage superimposed on usual interstitial pneumonia. A – Irregular spaces, cystic dilatation and mucous content, on a fibrotic background (HE 40X). B – Interalveolar septa show marked thickening due to fibroblast proliferation, which is evidence of an exacerbation (HE 400X)



**Fig. 3** – Organising pneumonia. A and B – Intra-luminal fibrosis involving a respiratory bronchiolus and the adjacent alveolar spaces. The process is well delimited in relation to the adjacent pulmonary parenchyma (A– HE 40X; B– HE 400X)

enced management in 8 patients (42%). It is important to note that 3 patients died before the biopsy results became available. Overall mortality was 47% (9 patients). Of the 10 patients who survived to discharge, 4 (40%) had their management influenced by the biopsy results; of the 9 patients who died, 4 (44.4%), had their treatment influenced by the histological diagnosis. Three of the 4 patients who developed complications

died and 1 was discharged from hospital. Their deaths were caused by acute exacerbation of IPF, cardiac and pulmonary thrombi (autopsy finding) and sepsis with multiorgan dysfunction.

### Discussion

OLB is rarely performed in the ICU. In the USA, the annual rate is 0-0.9%<sup>6</sup>. The deci-

sion to perform the procedure in patients on MV depends on the need for an accurate diagnosis, which is a prerequisite for starting specific therapy, avoiding the side effects of ineffective empirical treatment, and obtaining prognostic information<sup>6</sup>.

In our study, OLB had a diagnostic yield of 95%, and only one patient remained without a diagnosis because the sample was too small. This rate is comparable to that reported in the literature<sup>7,8</sup> (> 92%), but it is important to point out that an ideal sample must have at least 3 cm in its greatest dimension and originate from more than one lobe<sup>9</sup>. Despite the similar diagnostic yield<sup>10</sup>, we preferred thoracotomy to videothorascopy for biopsy because the former takes less time and requires neither replacement of the orotracheal tube with a double-lumen tube, nor selective ventilation of one lung. In addition, the diagnostic yield of OLB in patients on MV was similar to that observed in a study of outpatients with diffuse lung disease referred for OLB, which did not require prior ventilatory support<sup>3,10-13</sup>.

While the OLB results led to review of the initial diagnosis in 14 patients (74%), it only affected the management of 8 (42%) cases. This rate is lower than that seen in other studies<sup>6,11-13</sup> (64 – 75%) and can be explained in part by 3 patients having died before the biopsy result was known, (2 were later diagnosed with acute exacerbation of IPF and 1 with eosinophilic pneumonia). These diagnoses could have influenced treatment and prognosis in all these cases, particularly the last one.

Seven patients were diagnosed with DAD. In these cases, knowing the DAD stage had an important influence on treatment, even though histology did not reveal the under-

lying cause, because, as Meduri *et al.*<sup>14</sup> have shown, steroids can improve survival in patients in the fibroproliferative stage. When the clinical picture is compatible and there is no known predisposing factor to DAD, a diagnosis of acute interstitial pneumonia<sup>15</sup> (AIP) is made. Some patients in this study could have AIP, but infectious causes could not be definitely ruled out because the biopsy fragments were not subjected to exhaustive microbiology studies, particularly virology assays.

The time interval between ICU admission on MV and the OLB (mean 13 days) was greater than in other similar studies<sup>13,16,17</sup> (3 – 8 days). The impact of the duration of MV before lung biopsy on clinical outcomes has not been established. Some authors, however, suggest that early OLB is advantageous. Warner *et al.*<sup>5</sup> reported that time interval between the onset of respiratory failure and performance of OLB was significantly shorter in survivors (4.4±2.9 days) than in non survivors (6.1±3.6 days). In the study by Lim *et al.*<sup>16</sup>, patients who underwent OLB within a week of starting MV had a greater chance of survival (63% *vs.* 11%; *p*=0.018), even though there were no differences in MV time between the survivors and non survivors group. Araby *et al.*<sup>18</sup>, however, found no difference in time on MV before biopsy in survivors and non survivors. We found no significant difference in time on MV prior to biopsy in survivors and non survivors either (11.8 days *vs.* 14.9 days; *p*=0.6).

There were no significant differences in the levels of PEEP and PaO<sub>2</sub>/FiO<sub>2</sub> before and after OLB, and only one patient needed OLB inotropic support after OLB. Therefore, we concluded that this surgical proce-

cedure did not cause any significant ventilatory or haemodynamic disturbances.

The complications associated with this procedure in patients on MV vary considerably from study to study, probably because the populations studied are heterogeneous. The most common complication is persistent air leak<sup>6,11,12,17</sup>, with rates as high as 42%<sup>18</sup>. Other, less common, complications include haemothorax<sup>11,17</sup>, empyema<sup>2,11</sup>, wound infection<sup>2</sup> and intra-operative hypotension<sup>6,16</sup>. In the present study, 4 (21%) patients developed complications. All of them were treated for persistent air leakage. Cho *et al.*<sup>19</sup> studied the risk factors for persistent air leak in patients on MV with ARDS who underwent OLB. Peak airway pressure (Ppeak) was the only predictive factor identified (risk of persistent air leak was reduced by 42% for each 5 cmH<sub>2</sub>O reduction in Ppeak); therefore, protective ventilatory strategies which limit the Ppeak are strongly associated with a lower risk of persistent air leak in the post-operative period. Since our study had a small patient population and few complications, the effects of Ppeak on the risk of air leak could not be determined.

Overall mortality was 47%, similar to that reported in other studies<sup>3,6,11-13,16-18</sup> (46% – 67%). Procedure-related mortality is extremely low, even in patients on MV<sup>3,6,11-13,16-18</sup>. Fatalities caused by cardiac arrest<sup>17</sup>, haemorrhage<sup>6</sup> and hypertensive pneumothorax<sup>6</sup> have been described. There were no biopsy-related deaths in our study.

This study has several limitations, such as its retrospective methodology, small sample size and sample heterogeneity, as well as selection bias. While a prospective, randomised trial could supply more feasible conclusions, such studies are difficult to perform in critical patients.

An analysis of this sample suggests that OLB is useful in patients on MV with DLD of unknown aetiology because of its high diagnostic yield and low incidence of ventilatory and haemodynamic complications. Moreover, early OLB may improve outcomes further in some patients.

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