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Research Article

Haemodynamic, Biochemical and Respiratory Implications of total Bronchoalveolar Lavage in Pulmonary Alveolar Proteinosis

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Abstract

Introduction: Total bronchoalveolar lavage (BAL) continues to be the treatment of choice for alveolar proteinosis (AP), facilitating the removal of lipoprotein material. The purpose of this article is to evaluate the impact of haemodynamic, biochemical, and respiratory parameters, as well as the complications and evolution of patients undergoing this procedure.

Methods: Retrospective, observational, and descriptive study of BAL. The technique was performed in the Intensive Care Unit. Blood gases, blood pressure, central venous pressure, body temperature, and fluid balance were analyzed.

Results: Including eight patients, thirty-eight BAL were performed from 2008 to 2021.

The mean instillation of saline at each session was 13.464 ± 4.002 ml per lung. No significant changes were observed before and after BAL in heart rate and blood pressure. Mean central venous pressure increased by 2.59 cm H20. The pO2 initial was 126 mmHg with a final mean of 69.7 mmHg, with statistical significance. The pCO2, HCO3 and pH parameters remained stable.

Complications were observed during fifteen of the thirty-eight BAL (nine with arterial hypotension, three with glottic oedema, one acute pulmonary oedema, one pneumothorax, and one cardiorespiratory arrest). In terms of evolution, one case had a clinical-radiological resolution, one case of exits, one required lung transplantation, and the remaining five remained stable.

Conclusion: This study demonstrates that the procedure, is well tolerated haemodynamically and that the biochemical alterations to which the patient is subjected are not compromised. With few complications and good results in delaying the progression of AP.

More Information

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Introduction

Pulmonary alveolar proteinosis (PAP), first described by Rosen, et al. in 1958 [1], is a rare disease with an estimated incidence of 0.41 cases per million population and a prevalence of 6.87 per million population [2]. It is most common during the third or fourth decade of life and the most common presenting symptom is dyspnoea of slow and progressive onset [2]. PAP is characterized by the accumulation in the alveolar air spaces and sometimes in the peripheral airway of an excessive amount of lipid-rich proteinaceous material derived from pulmonary surfactant, which stains positive for periodic acid Schiff stain (PAS-positive) [3]. This accumulation of lipoproteinaceous material in the alveolar spaces and terminal bronchioles can lead to alterations in gas exchange [4]. The diagnosis of certainty is made by lung biopsy, although it is currently obtained by bronchoalveolar lavage by endoscopy combined with computed tomography (CT) findings [5]. The most characteristic CT findings are bilateral ground-glass opacity and thickening of the septa, resulting in the characteristic patchy paving pattern [6]. The main indication for treatment is the limitation in activities of daily living because of impaired gas exchange and the progression of the disease [7]. Bronchoalveolar lavage (BAL) can have both therapeutic and

diagnostic purposes for cellular and microbiological studies. We can differentiate between partial BAL, which is performed in only one lung segment, and total BAL, where large volumes of physiological saline are used to collect material from the entire bronchial tree. Such saline is usually the treatment of choice for PAP [8], although colony-stimulating factors (G-CSF) can also be used as a medical treatment [9], which is explained by the fact that the catabolism of surfactant in alveolar macrophages requires the presence of granulocyte colony-stimulating factor. An alteration at this level allows the alveolar accumulation of this lipoproteinaceous material, as a result of the decrease in its macrophage clearance, which would explain the pathophysiology of the disease and the justification for G-CSF as a therapeutic option. If these treatments do not prove to be successful with the patient and symptoms continue to be severe during an observation period, Rituximab [10] (anti-CD20 monoclonal antibody directed against LBs, cells involved in the synthesis of anti-G-CSF antibodies) and plasmapheresis [11] have been used. This observation period is justified as spontaneous remission can sometimes occur [3].

Total BAL can be performed simultaneously on both lungs, either in a supine or prone position, with the patient's position being modified during the test. Additionally, respiratory physiotherapy maneuvers, such as percussion and vibration can be performed during the procedure for the lavage serum to reach all lung lobes [12]. Total BAL is a safe and effective treatment [8] with clinical, physiological, and radiological improvements in more than 85% of patients. However, the impact of BAL has not been analyzed from the perspective of the haemodynamic, biochemical, and respiratory changes that occur in the patient during the treatment. Thus, the aim of this study is to assess the impact of haemodynamic, biochemical, and respiratory parameters that occur during sequential lavage of the two lungs, as well as the complications and evolution of patients with alveolarproteinosis who undergo this procedure.

Material and methods

Eight patients diagnosed with PAP were included in this study, five of them by transbronchial biopsy, two by open lung biopsy, and one by cryo biopsy. These patients underwent thirty-eight total BAL lavages between 2007 and 2021 in the Intensive Care Unit.

Total BAL was performed under general anesthesia and muscle relaxation through perfusion of propofol or midazolam, remifentanil, and cisatracurium with doses adjusted according to patient weight and age. The procedure required selective intubation with a double-lumen tube. The correct placement of the double-lumen tube was performed by direct visualization with a 3.8 mm thick Ambu® aScope™ 4 Broncho Slim video bronchoscope. Subsequently, the tightness was assessed by introducing the proximal end of the double-lumen tube into the lung to be washed to provide the saline solution. If no bubbles escape, there is airtightness between the two lungs, but if air escapes, the double-lumen tube must be positioned to achieve airtightness. As only one lung at a time is washed, selective ventilation through a volumetric ventilator is used for the lung that is not washed. The patient was placed in a supine position allowing postural changes, percussive movements, and thoracic vibration. Monitoring included bladder and nasogastric catheterization, arterial catheter, peripherally inserted arterial line and rectal thermometer.

The lung lavage technique used was that described by Ramírez J, et al. [13]. Prior to the start of lavage, intrapulmonary air was denitrogenated by ventilation with 100% FiO2 for 15-20 minutes. Physiological saline in 500-milliliter bags pre-warmed to 37 °C was used for lavage. For each lavage, a bag was instilled by gravity from a height of 75 cm in the mid-axillary line. Drainage was also performed by gravity by collecting the fluid in a container placed 70 cm below the patient's axillary midline. The infusion rate was approximately 100 ml/min. The most affected lung, according to the CT scan, was washed first, and then, after a ventilation time of both lungs, the contralateral lung was washed. The patient's position was changed when the lavage came out clear and the procedure in each lung was terminated when the lavage came out clear in all patient positions.

The parameters analyzed during the procedure were arterial saturation by pulse oximetry, arterial blood gases at baseline and every five lavages, invasive blood pressure, central venous pressure, body temperature, and hourly fluid balance. A sample was taken from each drained bag in a laboratory tube and stored in a tube rack to assess the evolution and thus finalize the technique according to the clarification of the material obtained.

At the end of the complete BAL, the double-lumen tube was replaced by a conventional orotracheal tube with standard pulmonary ventilation, to advance in the withdrawal of mechanical ventilation. Once the procedure was completed, sedorelaxation (the objective is to reduce the patient's level of consciousness. This decrease will be performed up to a limit that allows the patient to maintain the respiratory function autonomously and preserve the protective reflexes of the airway) and mechanical ventilation was withdrawn on a scheduled basis over the following hours according to clinical and blood gas data.

Data are presented as mean and standard deviation. For statistical analysis, the SPSS 16.0 statistical package was used. The p - value was considered statistically significant when it was less than 0.05.

Results

Thirty-eight total BALs were performed, with a gender distribution of three males (37%) and five females (62.5%).

The age range of the patients was 40-63 years and the mean age when diagnosing the disease was 39 years.

The average time between the PAP diagnosis and total BAL was 2 months (range 0.5-4) and the time between all lung lavages was 9 months (range 4-18). The number of total BAL performed per patient ranged from 2 to 16, with a mean of five per patient. The mean instillation for each session was 16,992 ± 3,330 ml per lung. A total of 12,940 ± 2,000 ml was drained, a positive balance of 524 ± 800 ml.

During all procedures, the heart rate (HR), central venous pressure, and systemic arterial pressures were recorded as haemodynamic parameters (Table 1). No significant changes were observed at baseline, during and after total BAL in HR (93 *vs.* 100 bpm), or blood pressure (118 *vs.* 118 mmHg). Mean central venous pressure was 4.4 cm H20 at baseline with an increase to 6.99 cm H20 at the end of lavage.

Three biochemical determinations were performed in which chlorine (Cl), sodium (Na), and potassium (K) were analyzed, with Cl (107 *vs.* 109 mEq/L), Na (137 *vs.* 138 mEq/L), and K (3.8 *vs.* 3.9 mEq/L), respectively, remaining stable during the intervention.

On the other hand, about five gasometric determinations were performed at each washout, and values of pO2, pCO2, HCO3, lactic acid, and pH were collected (Table 1). The initial pO2 was 126 mm Hg with a final mean of 69.7 mm Hg, without statistical significance. The pCO2 and pH parameters were stable at baseline, during, and at the end of the lavages: pCO2 (48.35 *vs.* 52.85 mm Hg), pH (7.3 *vs.* 7.23). Changes were detected in lactic acid from a baseline mean of 0.66 ± 0.33 to a final mean of 0.47 ± 0.20 ($p < 0.006$) and in HCO3 from 23.52 ± 2.63 to 21.70 ± 1.87 ($p < 0.001$). Complications were observed during fifteen out of the thirty-eight BAL procedures completed (Table 2). Arterial hypotension occurred in nine procedures requiring the use of vasoactive drugs to recover them. Three glottic oedema also occurred in the context of orotracheal reintubation after the procedure but had no clinical repercussions. One patient suffered acute pulmonary oedema after the procedure was completed, while another suffered from bilateral pneumothorax with recovered cardiorespiratory arrest requiring bilateral drainage. All patients were extubated without complications 24 hours after the procedure except the patient with cardiorespiratory arrest who was extubated after 48 hours and subsequently, the pleural drains were removed.

Table 1: Mean values of haemodynamic, biochemical, and respiratory parameters measured during total bronchoalveolar lavage.

	Initial value	Final value	*p*	Maximum value	Minimum value	Mean
Heart rate	93	100	NS	140	57	96
SST	118	118	NS	204	47	115
DBT	71	69	NS	137	39	65
CVP	4.4	6.99	NS	14	2	5
Chlorine	107	109	NS	116	99	108
Sodium	137	138	NS	143	133	138
Potassium	3.8	3.9	NS	5.5	3.3	3.9
The partial pressure of oxygen	126	69.7	NS	455	38	82
Carbon dioxide partial pressure	48.35	52.85	NS	110	29	51
Bicarbonate	23.53	21	NS	25	18	22
pH	7.30	7.23	NS	7.49	6.9	7.2
Lactic Acid	0.66	0.45	NS	1.7	0.1	0.53

*: between baseline and endpoint; HR: Heart Rate; SST: Systolic Blood Pressure; DBT: Diastolic Blood Pressure; CVP: Central Venous Pressure; NS: Not Significant.

Table 2: Complications of total bronchoalveolar lavage. Expressed in absolute numbers and percentages.

	n	(%)
Arterial hypotension	9	23
Glottic edema	3	7.8
Pneumothorax	1	2.6
Acute heart failure	1	2.6
Cardiorespiratory arrest[a]	1	2.6
Total complications	15	39.47
No complications	23	60.5

a: Occurred in the same patient.

Regarding the evolution of the patients with PA treated, in one case a complete clinical-radiological resolution was achieved after a single total BAL lavage without the need for further procedures. Another patient required lung transplantation due to a rapidly progressive course with no response to the various treatments and is currently stable with no recurrence of the disease. Five patients remain clinically stable after total BAL and one patient died due to severe radiological and gas exchange involvement. With this patient, other treatments such as granulocyte colony-stimulating factor (G-CSF) and Rituximab (anti-CD20) were tried and administered after total BAL. Four patients were treated with G-CSF and all patients discontinued treatment during the first month due to side effects, both clinical - such as poor general condition and myalgia - and laboratory abnormalities, such as lymphopenia and leukocytosis. Rituximab was used in two patients after G-CSF treatment and discontinued due to a lack of clinical improvement.

Discussion

Total BAL is currently the first-line treatment for PAP and the most widely treated, but despite this, there are no specific guidelines for the lavage procedure itself or standardized indications for patients. While the procedure has undergone several changes in recent years mainly in terms of its sequence, it is fair to say lavage is still performed in a standardized way [14]. It is an invasive procedure performed by selective endobronchial intubation to physically remove lipo proteinaceous material from the alveoli and flash away the material out of the lungs with saline solution at body temperature. This requires ventilation of only one lung while the other lung is washed [15]. Although total BAL is known to improve dyspnoea, gas exchange, and other functional parameters [8], the haemodynamic, biochemical,

and respiratory impact on patients during this procedure has not been published to date. The main finding of this study is that total BAL in patients with PAP, performed by a multidisciplinary team with experience in the procedure, is well tolerated by patients with different parameters analyzed.

Total BAL is effective in producing mechanical removal of excess phospholipids present in the alveolus of patients with PAP [16]. It is also the treatment of choice among other alternatives such as G-CSF administration [9,17], Rituximab [10], plasmapheresis [11], or lung transplantation. In the series presented, only one patient required a lung transplant, due to failure of total BAL and replacement therapy with G-CSF, with the transplant being successful with the clinical and functional improvement of the patient. However, recurrences have been described after bi-pulmonary transplantation for PAP that may be due to the immune alteration that is present in carriers of genetic mutations and in secondary forms of PAP [18,19]. In the remaining cases where G-CSF or Rituximab was used, they had to be withdrawn due to poor tolerance or lack of efficacy. Some authors propose that total BAL should be performed two times [20], including by flexible bronchoscopy [21], while others recommend performing lavages on both lungs on the same day [22,23]. In the series of lavages presented here, only the first procedure was performed on two consecutive days, maintaining assisted ventilation in between. Tolerance was good with no haemodynamic or biochemical changes, so it was decided to perform the sequential lavages on the same day.

During the procedure, there were no haemodynamic repercussions that could not be treated with standard measures such as antihypertensives or intravenous fluid replacement. The presence of arterial hypertension during lavage is a complication that arises from possible water overload due to the introduction of physiological saline solution for the lavage, but in the procedures we performed it did not occur even though the fluid balance was positive. The absence of arterial hypertension in our series may be related to the degree of sedorelaxation we used.

From a biochemical point of view and despite the positive fluid balance suffered by the patients, only a decrease in lactic acid and bicarbonate levels was found. It has not been possible to determine why this alteration occurred, but once the procedure was over, the values returned to normal. Biochemical parameters are altered by electrolyte absorption and changes induced by mechanical ventilation. However, in the present study, they did not affect the patients clinically and no external action was required to regulate them.

The initial increased pO2 value is driven by the need to denitrogenate the lung in order to prepare the patient prior to total BAL. The decrease in pO2 observed during total BAL is caused by changes in airway pressure, which increases or decreases depending on the saline instillation or its recovery, leading to a shunt effect during lung emptying [24]. In our series, total BAL did not have to be interrupted in any case due to hypoxaemia, a circumstance that is described as persistent hypoxaemia with saturation ≤ 80% [25]. The changes in oxygenation during BAL are explained by the fact that as fluid is infused into the washed lung, compression of the vasculature occurs, reducing the blood supply to the lung. However, during lavage fluid drainage, the shunt to the nonventilated lung increases, and hypoxaemia can occur [26]. In patients who cannot tolerate single lung ventilation, extracorporeal membrane oxygenation (ECMO) support has been used for the procedure with good results [27]. In our series, no patient required ECMO for total BAL.

Quick recovery after whole lung lavages can be explained by the proteinaceous material deposited in the alveoli, which cease to produce alveolar inflammation while the degree of fibrosis decreased [28]. This meant that patients could be extubated early without complications. An unstudied aspect during total BAL is the use of beds with vibration and perfusion possibilities. We applied this type of physiotherapy during lavage in different patient positions which may justify the small positive volume accumulated by the patients during lavage.

In a global survey in different centers with 1110 total BAL procedures in patients with PAP, the most frequent post-procedure complications were fever (18%), followed by hypoxaemia (14%), wheezing (6%), pneumonia (5%), fluid loss (4%), pleural effusion (3.1%) and pneumothorax (0.8%) [29]. The most serious complication that occurred during our series was cardiorespiratory arrest, probably caused by bilateral pneumothorax. To avoid this, it is important to have ultrasonography equipment to be able to make decisions quickly in this acute life-threatening situation.

Another aspect to note is the timing of subsequent BAL treatments. In our study, the average time between washouts was nine months and the number of total BALs per patient was five. The total number of BAL procedures is dictated by the patient's symptoms and disease severity based on lung function and CT imaging [5,13]. We observed that there is considerable variability in patient response to BAL and time between the different treatments.

For example, in one study, about 70% of patients remained free of PAP recurrence after seven years and the mean number of procedures per patient was 2.5 over a five-year period [29]. Total BAL remains the gold standard treatment for PAP, although there is a lack of data in the form of large-scale randomized controlled trials comparing this type of treatment with other modalities. In conclusion, we believe that this is a safe procedure in an experienced setting, with the potential to provide long-term benefits in patients with PAP. This study demonstrates that the procedure, performed simultaneously in both lungs in one act, is well tolerated haemodynamically

and that the biochemical alterations we subject the patient to are not compromised in a homeostatic manner. We believe that constant monitoring of haemodynamic parameters is important to be able to act on any alterations that may occur and that the drugs used for sedation should be well known to the intensivist performing the procedure. Total BAL is a safe procedure, with few complications despite being an invasive technique, with good results in preventing or delaying the progression of PAP.

Conclusion

Total bronchoalveolar lavage continues to be the treatment of choice for alveolar proteinosis, facilitating the elimination of lipoprotein material. According to the experience of our center, it is a safe procedure, with few complications despite being an invasive technique, with satisfactory results obtained, preventing or delaying the progression of alveolar proteinosis.

References

1. Rosen SH, Castleman B, Liebow AA. Pulmonary alveolar proteinosis. N Engl J Med. 1958 Jun 5;258(23):1123-42. doi: 10.1056/NEJM195806052582301. PMID: 13552931.
2. McCarthy C, Avetisyan R, Carey BC, Chalk C, Trapnell BC. Prevalence and healthcare burden of pulmonary alveolar proteinosis. Orphanet J Rare Dis. 2018 Jul 31;13(1):129. doi: 10.1186/s13023-018-0846-y. PMID: 30064481; PMCID: PMC6069872.
3. Shah PL, Hansell D, Lawson PR, Reid KB, Morgan C. Pulmonary alveolar proteinosis: clinical aspects and current concepts on pathogenesis. Thorax. 2000 Jan;55(1):67-77. doi: 10.1136/thorax.55.1.67. PMID: 10607805; PMCID: PMC1745595.
4. Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. N Engl J Med. 2003 Dec 25;349(26):2527-39. doi: 10.1056/NEJMra023226. PMID: 14695413.
5. Mazzone P, Thomassen MJ, Kavuru M. Our new understanding of pulmonary alveolar proteinosis: what an internist needs to know. Cleve Clin J Med. 2001 Dec;68(12):977-8, 981-2, 984-5 passim. doi: 10.3949/ccjm.68.12.977. PMID: 11765122.
6. Murch CR, Carr DH. Computed tomography appearances of pulmonary alveolar proteinosis. Clin Radiol. 1989 May;40(3):240-3. doi: 10.1016/s0009-9260(89)80180-1. PMID: 2752679.
7. Rodríguez Portal JA. Treatment of Adult Primary Alveolar Proteinosis. Arch Bronconeumol. 2015 Jul;51(7):344-9. English, Spanish. doi: 10.1016/j.arbres.2015.02.003. Epub 2015 Apr 17. PMID: 25896950.
8. Beccaria M, Luisetti M, Rodi G, Corsico A, Zoia MC, Colato S, Pochetti P, Braschi A, Pozzi E, Cerveri I. Long-term durable benefit after whole lung lavage in pulmonary alveolar proteinosis. Eur Respir J. 2004 Apr;23(4):526-31. doi: 10.1183/09031936.04.00102704. PMID: 15083749.
9. Kavuru MS, Sullivan EJ, Piccin R, Thomassen MJ, Stoller JK. Exogenous granulocyte-macrophage colony-stimulating factor administration for pulmonary alveolar proteinosis. Am J Respir Crit Care Med. 2000 Apr;161(4 Pt 1):1143-8. doi: 10.1164/ajrccm.161.4.9906044. PMID: 10764303.
10. Cheng SL, Chang HT, Lau HP, Lee LN, Yang PC. Pulmonary alveolar proteinosis: treatment by bronchofiberscopic lobar lavage. Chest. 2002 Oct;122(4):1480-5. doi: 10.1378/chest.122.4.1480. PMID: 12377884.
11. Soyez B, Borie R, Menard C, Cadranel J, Chavez L, Cottin V, Gomez E, Marchand-Adam S, Leroy S, Naccache JM, Nunes H, Reynaud-Gaubert M, Savale L, Tazi A, Wemeau-Stervinou L, Debray MP, Crestani B. Rituximab for auto-immune alveolar proteinosis, a real life cohort study. Respir Res. 2018 Apr 25;19(1):74. doi: 10.1186/s12931-018-0780-5. PMID: 29695229; PMCID: PMC5918901.
12. Iftikhar H, Nair GB, Kumar A. Update on Diagnosis and Treatment of Adult Pulmonary Alveolar Proteinosis. Ther Clin Risk Manag. 2021 Aug 10;17:701-710. doi: 10.2147/TCRM.S193884. PMID: 34408422; PMCID: PMC8364424.
13. Ramirez J, Schultz RB, Dutton RE. Pulmonary alveolar proteinosis: a new technique and rationale for treatment. Arch Intern Med. 1963 Sep;112:419-31. doi: 10.1001/archinte.1963.03860030173021. PMID: 14045290.
14. Garber B, Albores J, Wang T, Neville TH. A plasmapheresis protocol for refractory pulmonary alveolar proteinosis. Lung. 2015 Apr;193(2):209-11. doi: 10.1007/s00408-014-9678-2. Epub 2015 Jan 4. PMID: 25557091.
15. Diaz-Mendoza J, Celis Valdiviezo E, Patel NM, Simoff MJ. One-session bilateral sequential whole lung lavage (OSBSWLL) for the management of pulmonary alveolar proteinosis. BMC Pulm Med. 2021 Nov 9;21(1):358. doi: 10.1186/s12890-021-01734-w. PMID: 34749694; PMCID: PMC8575669.
16. Rogers RM, Levin DC, Gray BA, Moseley LW Jr. Physiologic effects of bronchopulmonary lavage in alveolar proteinosis. Am Rev Respir Dis. 1978 Aug;118(2):255-64. doi: 10.1164/arrd.1978.118.2.255. PMID: 697176.
17. Seymour JF, Presneill JJ, Schoch OD, Downie GH, Moore PE, Doyle IR, Vincent JM, Nakata K, Kitamura T, Langton D, Pain MC, Dunn AR. Therapeutic efficacy of granulocyte-macrophage colony-stimulating factor in patients with idiopathic acquired alveolar proteinosis. Am J Respir Crit Care Med. 2001 Feb;163(2):524-31. doi: 10.1164/ajrccm.163.2.2003146. PMID: 11179134.
18. Takaki M, Tanaka T, Komohara Y, Tsuchihashi Y, Mori D, Hayashi K, Fukuoka J, Yamasaki N, Nagayasu T, Ariyoshi K, Morimoto K, Nakata K. Recurrence of pulmonary alveolar proteinosis after bilateral lung transplantation in a patient with a nonsense mutation in CSF2RB. Respir Med Case Rep. 2016 Aug 13;19:89-93. doi: 10.1016/j.rmcr.2016.06.011. PMID: 27595063; PMCID: PMC4995526.
19. Gal AA, Bryan JA, Kanter KR, Lawrence EC. Cytopathology of pulmonary alveolar proteinosis complicating lung transplantation. J Heart Lung Transplant. 2004 Jan;23(1):135-8. doi: 10.1016/s1053-2498(03)00032-9. PMID: 14734139.
20. Montón C, Peña R, Marín A. Proteinosis alveolar. Tratamiento mediante lavado pulmonar completo [Alveolar proteinosis. Treatment with total lung lavage]. Arch Bronconeumol. 2000 May;36(5):291-2. Spanish. doi: 10.1016/s0300-2896(15)30172-1. PMID: 10916671.
21. Cheng SL, Chang HT, Lau HP, Lee LN, Yang PC. Pulmonary alveolar proteinosis: treatment by bronchofiberscopic lobar lavage. Chest. 2002 Oct;122(4):1480-5. doi: 10.1378/chest.122.4.1480. PMID: 12377884.
22. Murray MJ, De Ruyter ML, Harrison BA. Bilateral lung washings for pulmonary alveolar proteinosis. J Bronchol. 1998; 5: 324-6.
23. Fernández del Campo R, Lozares Sánchez A, Francisco Corral G, Prieto del Portillo I, Pérez Rodríguez E, Maudes Rodríguez A. Lavado broncoalveolar bilateral secuencial: caso clínico, método y discusión [Bilateral bronchoalveolar lavage: a clinical case, method and discussion]. Med Intensiva. 2007 Oct;31(7):407-10. Spanish. doi: 10.1016/s0210-5691(07)74846-5. PMID: 17942065.
24. Smith JD, Millen JE, Safar P, Robin ED. Intrathoracic pressure, pulmonary vascular pressures and gas exchange during pulmonary lavage. Anesthesiology. 1970 Oct;33(4):401-5. doi: 10.1097/00000542-197010000-00007. PMID: 5512328.
25. Smith BB, Torres NE, Hyder JA, Barbara DW, Gillespie SM, Wylam ME, Smith MM. Whole-lung Lavage and Pulmonary Alveolar Proteinosis: Review of Clinical and Patient-centered Outcomes. J Cardiothorac Vasc Anesth. 2019 Sep;33(9):2453-2461. doi: 10.1053/j.jvca.2019.03.047. Epub 2019 Mar 28. PMID: 31307910.
26. Hunter Guevara LR, Gillespie SM, Klompas AM, Torres NE, Barbara DW. Whole-lung lavage in a patient with pulmonary alveolar proteinosis. Ann Card Anaesth. 2018 Apr-Jun;21(2):215-217. doi: 10.4103/aca.ACA_184_17. PMID: 29652291; PMCID: PMC5914230.
27. Stokes JW, Katsis JM, Gannon WD, Rice TW, Lentz RJ, Rickman OB, Avasarala SK, Benson C, Bacchetta M, Maldonado F. Venovenous

extracorporeal membrane oxygenation during high-risk airway interventions. Interact Cardiovasc Thorac Surg. 2021 Nov 22;33(6):913-920. doi: 10.1093/icvts/ivab195. PMID: 34293146; PMCID: PMC8632782.

28. Claypool WD, Rogers RM, Matuschak GM. Update on the clinical diagnosis, management, and pathogenesis of pulmonary alveolar proteinosis (phospholipidosis). Chest. 1984 Apr;85(4):550-8. doi: 10.1378/chest.85.4.550. PMID: 6368143.

29. Campo I, Luisetti M, Griese M, Trapnell BC, Bonella F, Grutters J, Nakata K, Van Moorsel CH, Costabel U, Cottin V, Ichiwata T, Inoue Y, Braschi A, Bonizzoni G, Iotti GA, Tinelli C, Rodi G; WLL International Study Group. Whole lung lavage therapy for pulmonary alveolar proteinosis: a global survey of current practices and procedures. Orphanet J Rare Dis. 2016 Aug 31;11(1):115. doi: 10.1186/s13023-016-0497-9. PMID: 27577926; PMCID: PMC5006612.