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# Management of Pulmonary Alveolar Proteinosis Using Whole Lung Lavage, Recent Update

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## ABSTRACT

**Background**: Alveolar proteinosis is mainly autoimmune disease in which lipoproteins accumulate inside alveoli. In severe cases it presents with dyspnea, tachypnea and cough. Lung lavage is the treatment of choice in symptomatic cases. **Objective**: The aim of this study was to illustrate two different techniques of management of pulmonary alveolar proteinosis (PAP) whether unilateral or bilateral whole lung lavage (WLL), analysis of indications, superiority and the efficacy of the two techniques. **Patients and Methods**: This is a retrospective analytical study that included 31 patients; all were done in Kasr Alainy Teaching Hospitals in the period between 2012 and 2021. All of our patients had progressive severe respiratory symptoms. Pre-procedural, intra-procedural, and post-procedural data were recorded as well as postoperative mortality, complications, ICU stay, relapses, and the need for recurrent settings of WLL. **Results**: The median time from diagnosis of PAP to treatment was 10.6 months (range from 1 to 40 months). The median age was 39.7 years (ranging from 19 to 70 years). Male patients were 22 (71%), while female patients were 9 (29%). Unilateral WLL was utilized in 21 patients (67.7%) and bilateral WLL in 10 patients (32.3%). Marked improvement occurred in 13 patients (41.9%), 12 patients showed partial improved (38.7%), 3 patients were stationary (9.7%), and unfortunately, 3 patients (9.7%) worsened post lavage. Single relapse occurred in 9 patients, while multiple relapses occurred in 5 patients. **Conclusion**: Bilateral WLL was found to be a good alternative to unilateral WLL, which is cost-effective, less time consuming and even may decrease the incidence of relapses (single or multiple) with no significant difference in the incidence of complications.

**Keywords**: Pulmonary alveolar proteinosis PAP, Whole lung lavage WLL.

## INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare disease that is characterized by a steady decline in gas exchange due to the progressive accumulation of phospholipoproteinaceous material in the alveolar space [(1)]. Phospholipoproteins are stained by periodic acid-Schiff [(1-3)]. Patients of this disease complain of progressive respiratory symptoms in the form of cough and dyspnea which may lead to death from progressive hypoxemia and cor pulmonale [(1, 3)]. Radiologically, patient diagnosis depends on the typical appearance of the "crazy-paving" pattern by high-resolution computed tomography (HRCT) of the chest and by bronchoscopy the presence of "milky" fluid in bronchoalveolar lavage (BAL) [(3)]. It can be confirmed by staining using periodic acid-Schiff (positive staining of proteins and lipids in transbronchial, transthoracic or surgical biopsy)[(3)].

According to the etiology of PAP, it can be classified into three types autoimmune (primary, or idiopathic), secondary, and genetic [(3, 4)]. Autoimmune is the most common form characterized by anti-granulocyte macrophage colony-stimulating factor (GM-CSF) antibodies formation leads to deficient in macrophage function and accumulation of proteins and lipids in alveoli. In recent years, novel therapies were introduced for the management of PAP, such as inhaled GM-CSF, plasmapheresis, rituximab, and selective lobar lavage by fiberoptic bronchoscopy, the results of these therapies are not fully evaluated and costy [(3)].

Whole-lung lavage (WLL) is the standard level of care for the treatment of PAP that was first described in 1963 [(1-4)]. The procedure involves irrigation of the lungs with warm saline and washing out the alveolar space. The procedure is conducted under general anesthesia. Unilateral or bilateral WLL are generally tolerated but associated with some complications[(4)]. Possible complications of WLL include fever, fluid leakage, pneumothorax, pneumonia, pleural effusion, metabolic acidosis, hypoxemia, wheezes, respiratory acidosis, and transient neuropathy. Also prolonged mechanical ventilation, pulmonary thromboembolism, transient cardiac ischemia, and cardiac arrest. Some of these complications were thought to have a higher incidence with bilateral WLL especially those related to pulmonary edema and prolonged ventilation. However, all that mentioned complications are rare and the procedure generally is considered safe [(3,4)].

The aim of this study was to illustrate two different techniques of management of pulmonary alveolar proteinosis (PAP) whether unilateral or bilateral whole lung lavage (WLL), analysis of indications, superiority and the efficacy of the two techniques.

## PATIENTS AND METHODS

This is a retrospective analytical study that included 31 patients all were done in Kasr Alainy teaching hospitals in the period between 2012 and 2021. All of our patients had progressive, severe exertional dyspnea. The diagnosis depended on CT characteristics of the PAP (Crazy paving) pattern which was confirmed by bronchoalveolar lavage staining by periodic acid Schiff stain. All Patients were symptomatic (dyspnea, tachypnea) showing decline in lung function, decline in resting $PaO_2$, decline in $SpO_2$, and worsening of chest X-ray or CT (Fig. 1). However, patients with heart failure, severe cardiovascular disease, significant lung infection, sepsis, end-stage pulmonary fibrosis, and bleeding tendency were excluded.



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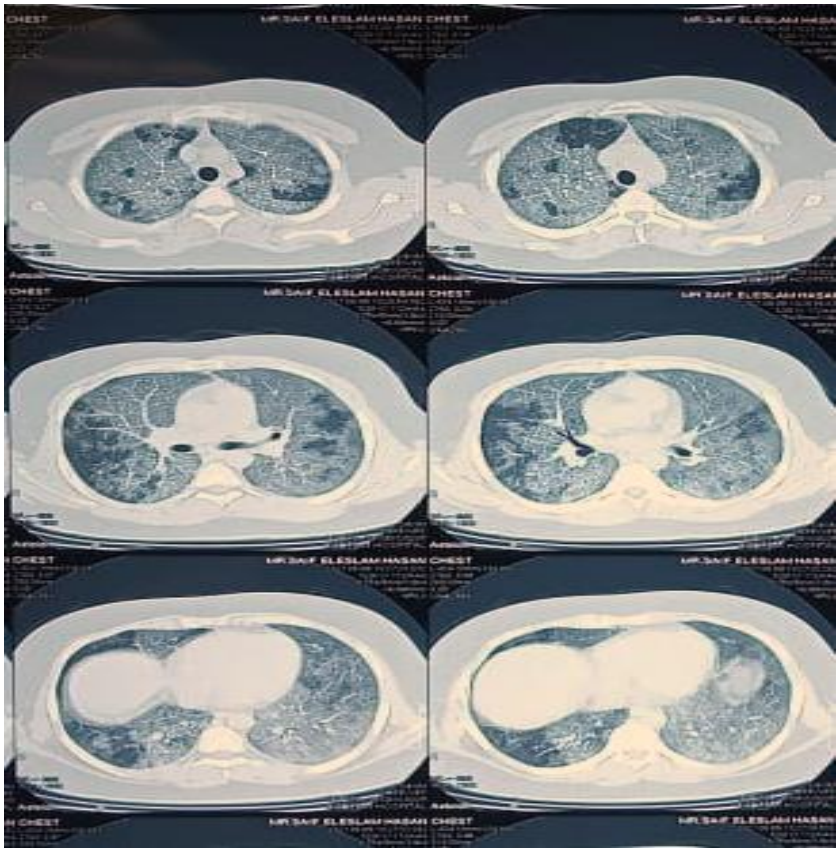

**Fig. (1):** CT chest of a patient suffers from PAP (crazy paving pattern)

In twenty-one patients unilateral WLL was adopted for PAP with severely affected lungs. Out of those patients who underwent unilateral WLL, 15 patients needed a sequential second setting WLL after 2 to 8 weeks. Ten patients underwent bilateral WLL in the same setting. After admission, full history, clinical examination, and routine laboratory investigations were done. Also, the measurement of oxygen saturation and arterial blood gases were done for all of the patients before and after WLL.

WLL was performed in the operating theatre while the patient was in a supine position under general anesthesia using a combination of propofol, opioids, and neuromuscular blockers (pancuronium) with careful monitoring of blood pressure, heart rate, ECG, oxygen saturation, blood gases, central venous pressure (CVP), urine output and capnography.

We have an experienced lavage team that includes nursing, a cardiothoracic surgeon, an anesthesiologist, a respiratory therapist, and interventional pulmonary medicine to perform this procedure. Tilting of the table was used during the maneuver for better drainage. Before starting lavage, tidal volume pressure support for each lung was measured, double lumen endotracheal tube was used with single lung ventilation. At first, before starting this maneuver, lung ventilation with 100% oxygen for 10-15 minutes was performed to ensure that patient tolerates single lung ventilation.

The endotracheal tube cuff must fit with the airway without any leak to ensure complete separation of both lungs and prevent spillage of fluid to the other lung. Baseline ABG was withdrawn to compare with the post procedural results. WLL was performed using isotonic saline at 37°C at a height of 30-50 cm above midchest sustained by gravity to prevent barotrauma and fluid leak. Initial ventilator parameters (tidal volume, pressure support) were recorded to monitor the success of lavage during the procedure by lowering the pressure support needed and increasing tidal volumes. When the lung was filled by the lavage, manual mechanical ventilation started, to help using the shearing movement of lavage to clear the distant airways helped by chest percussion until the lavage lost its clearance and became milky. At first, 250-1000 ml of warm isotonic saline was infused according to total thoracic compliance, which was previously determined by measuring the functional residual capacity (FRC).

The right lung volume was calculated by 3/5 of the FRC and the left lung by 2/5 FRC. Drainage was performed by negative suction which helps in better drainage. Saline was drained and collected in containers (Fig. 2) with careful measurement of the amount infused and drained. Fluid balance was measured by subtracting the drained amount from the infusion volume. The suction of lavage was helped by tilting the table to put the targeted side at a higher level to take advantage of the siphoning effect to clear the airways.


**Fig. (2):** Lavage fluid with a milky appearance was collected to detect the fluid balance

This part of the procedure started to get the most attention as it was noticed to have the most important effect on the prognosis of the lavage, the more time it consumes to get the most of infused fluid drained the better airway aeration and less parenchymal edema help to have better post lavage prognosis.

After achieving good results with unilateral WLL, we encountered patients with more progressive pathology that mandated bilateral WLL due to very small allowed tidal volumes after lung isolation or unsatisfactory results at the end of single lung lavage. Having good maneuvers of suction and removal of infused fluids to have a deficit of around 50-100 ml/liter encouraged us to start the bilateral simultaneous WLL with much less fear of post lavage complications such as pulmonary edema and the need for prolonged ventilation and ICU stay. Bilateral WLL was done either by starting one cycle per side to help maintain good oxygen saturation during lung isolation or by sequential, mostly starting by the right side followed by the left side.

Patients were transferred to ICU ventilated and usually extubated within 12 to 24 hours. Careful monitoring of hemodynamics, and oxygen saturation with performing chest X-rays, and blood gases were mandatory.

**Ethical consent:**

**An approval of the study was obtained from Cairo University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

***Statistical analysis***

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for the Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Qualitative data were represented as frequencies and relative percentages. Quantitative data were expressed as range and median.

**RESULTS**

The demographic data of the patients are shown in table 1. Dyspnea was the main presentation of our patients which ranged from class III to IV according to NYHA classification[(5)].

**Table (1):** Demographics and symptoms

| | | |
|---|---|---|
| **Age** | Range<br>Median | 19-70<br>39.7 |
| **Sex** | Male<br>Female | 22 (71%)<br>9 (29%) |
| **Dyspnea** | Class III<br>Class IV | 12 (38,7)<br>19 (61,3) |

General anesthesia for all patients using selective ventilation with a double-lumen endotracheal tube was used. Unilateral WLL was done for 21 patients (Right lung 13, left lung 8) and bilateral WLL was done for 10 patients. A flexible bronchoscope was needed in 3 patients to confirm the security of the airways. With good suctioning of injected warm saline under negative pressure, good results regarding the fluid balance (injected and drained) were achieved. Diuretics (furosemide) were used for protection from pulmonary edema. All patients were transferred to the ICU, and the median time of ICU stay was 2.2 days.

**Table (2):** Procedure and ICU stay

| | | |
|---|---|---|
| **Type of anesthesia** | General | 31 (100%) |
| **Use of flexible bronchoscope** | | 3 (9.7%) |
| **Site** | Unilateral<br>Bilateral | 21 (67.7%)<br>10 (32.3%) |
| **Median duration** | Unilateral<br>Bilateral | 3.2 hours<br>4.5 hours |
| **Amount of saline** | Range | 7-16 L |
| **ICU stay** | Range<br>Median | 0.5 – 23 days<br>2.2 days |

Marked improvement was achieved in 13 patients (41.9%). Unfortunately, 3 patients worsened post lavage (9.7%) depending on post-procedural symptomatology, oxygen saturation and parameters of arterial blood gases.

**Table (3):** Outcome

| Outcome | Patient number | Percentage |
|---|---|---|
| Marked improvement | 13 | 41.9% |
| Mild improvement | 12 | 38.7% |
| Stationary course | 3 | 9.7% |
| Worsened | 3 | 9.7% |

Single relapse occurred in 9 patients, while multiple relapses occurred in 5 patients.

**Table (4):** Relapse

| Number | No of patients | | Percentage |
|---|---|---|---|
| Single | 9 | 7 unilateral | 29% |
| | | 2 bilateral | |
| Multiple | 5 | 4 unilateral | 16.1 % |
| | | 1 bilateral | |

Complications occurred in 3 patients and one mortality. The unilateral WLL group had single mortality for a case of secondary infected PAP, which is known to have a worse prognosis and the patient presented with room air saturation of 50%, while on oxygen 10 liters flow per minute hardly reaches 65, the other complicated patient was discharged with below optimum oxygen saturation around 93% but with much improvement of symptoms.

The bilateral WLL group had complications for two patients. Pneumonia (1 patient) was treated with proper antibiotics and anti-inflammatory medications. Surgical emphysema occurred in one patient which needed intercostal tube insertion on the left side.

## DISCUSSION

Despite the early description of PAP, several treatment methods were used but all were deemed disappointing [(6)]. Now WLL is considered the only effective maneuver in the treatment of PAP. Despite the rarity of this disease, the clinical course is variable between patients, some patients show spontaneous regression, but others show progressive respiratory symptoms which improved after WLL, while others needed multiple repeated lavages over years [(7)]. All of our patients suffered from respiratory manifestations (progressive dyspnea affecting their daily activity). We performed bilateral sequential WLL for ten patients and unilateral WLL for twenty-one patients, starting with the most affected lung in the HRCT scan.

Continuous monitoring of lung compliance is important during the time of lavage. Hand percussion helps in emulsifying the alveolar proteinaceous substances during infusion and drainage. Temporary slight hypoxemia occurred during the infusion observed due to the increase of the intra-alveolar hydrostatic pressure which decreased the alveolocapillary flow, which returned to the normal ranges again after full drainage [(8)].

We performed the procedure in the supine position and sometimes tilting of table 30 degrees helps in more drainage to decrease the positive balance between infusion and drainage volumes, also the use of the negative suction allows us to have more perfect drainage. We concluded that there was no obvious difference in complication between unilateral and bilateral sequential WLL similar to **Lewiston and Robin**'s findings in their study [(9)]. Although some authors published and described mild improvement of clinical symptomatology after lavage [(10, 11)], most of our patients showed significant improvement after lavage regarding symptomatology and blood gases results.

Recurrence of symptoms and the need for repeated lavage were not predictable. Continuous follow-up was needed because the natural history of this disease shows a variable course [(12)]. In comparison, bilateral sequential WLL was found to be more cost-effective, more comfortable, safe, and less time-consuming than unilateral WLL.

## CONCLUSION

Bilateral WLL was found to be a good alternative to unilateral WLL which is cost-effective, less time-consuming, even may decrease the incidence of relapses (single or multiple) with the subsequent need for repeated sessions with no significant difference in the incidence of complications, especially when following all available techniques and maneuvers to minimize the fluid deficit during the procedure.

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**Author contribution:** Authors contributed equally in the study.

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