

# Pulmonary Alveolar Proteinosis in Children: Diagnosis and Treatment Outcomes

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## INTRODUCTION

Pulmonary Alveolar Proteinosis (PAP) is an uncommon pulmonary disease characterized by the accumulation of surfactant composed of proteins and lipids due to disruption of surfactant clearance by alveolar

**Background:** Pulmonary Alveolar Proteinosis (PAP) is an uncommon pulmonary disease characterized by the accumulation of surfactant composed of proteins and lipids due to disruption of surfactant clearance by alveolar macrophages. The current standard treatment is lung lavage. There are no specific criteria for lavage, but in case of observing these signs it is recommended to perform lavage for the patient: progressive respiratory failure, no labored breathing at rest, and drop in oxygen level during activity (>5%).

**Materials and Methods:** In this study, patients with PAP admitted to Pediatric ward of Masih Daneshvari Hospital were studied. The required data were collected including the patient's demographic data, clinical signs and radiographic data, the number of admissions, the age of diagnosis, detection and treatment methods, number of lavage, current condition of the patient, and in case of death, the cause of death.

**Results:** In this study, 17 patients with PAP who were admitted during the past 15 years were examined; among which 7 patients were boys (41.2%) and 10 were girls (58.8%). The mean age of population was 11.79±7.21 years. Transbronchial Lung Biopsy (TBLB) (47.1%) and open lung biopsy (52.9%) were used for diagnosis of patients. Lung lavage was used to treat patients, 15 of whom were treated by this method. Five of the patients died because of their serious conditions.

**Conclusion:** Therapy method in the present study was lavage for both lungs, and it was performed for all patients except for two patients due to their anatomical complications. This method is still considered as the gold standard for PAP. Considering the findings from previous studies and the present study, it seems that Whole Lung Lavage (WLL) was fruitful for patients who had the indication for using this therapy and it played a significant role in improving the prognosis of patients. Besides, it is recommended to do follow-up regularly in order to have more therapeutic efficacy and increased patient longevity.

**Key words:** Pulmonary alveolar Proteinosis; Diagnosis; Outcome

macrophages; but a reliable estimation of its incidence is not available. This disease is more common in the third and fourth decades of life and the ratio of male to female in its incidence is 2: 1, which can be due to the higher prevalence of smoking in men (1).

Animal models suggest that alveolar proteinosis is not an independent disease and it appears as a clinical syndrome. Based on the etiology, three different categories of the disease are defined: 1) autoimmune (mostly seen in adults, which is either associated with the presence of anti-GM-CSF antibodies or secondary to inhalation of toxic substances or hematologic defects without anti-GM-CSF antibodies); 2) secondary; 3) genetic (children). In genetic form, especially in children, radiological and clinical signs vary depending on the mutated gene (1).

Autoimmune PAP is the most common form (about 90% of the cases), but it is rarely associated with other autoimmune diseases (2).

The gold standard for detecting PAP is open-lung biopsy (3). In this method there is likelihood of pneumothorax, hemorrhage, and complications associated with surgery. Diagnosis of PAP begins with CT scan, following the onset of clinical symptoms and is mostly confirmed by staining bronchoalveolar lavage fluid (4). The current standard treatment is lung lavage. This method also has the potential for hypoxemia, especially at the time of lavage fluid evacuation due to low blood pressure and lung perfusion, pneumothorax, and hemorrhage; and death can occur due to progressive respiratory failure and secondary opportunistic infections (2).

In the congenital or genetic form, the treatment mostly includes supportive care, but cases of successful lung transplantation have also been reported.

Clinical symptoms are not specific, but the most common symptoms of progressive shortness of breath on exertion are sudden onset and coughing. Fever, chest pain, and weight loss are rarely seen. Respiratory crackles are the most common abnormal findings heard. In addition, cyanosis or finger clubbing may be seen (1). For infection detection in these patients PCR based assays and BAL for galactomannan for the detection of mycobacterium disease, viral and fungal germs can be performed (5-7).

Chest X-ray shows symmetry bilateral patchy opacities in the base of the lung. In CT scan there are ground glass opacities, septum reticulation and parenchymal opacities. Reticulations are often located on ground glass opacities, so forming crazy paving pattern for PAP is diagnostic

(Figure 1). However, lipid pneumonia and bronchoalveolar cell carcinoma can mimic the symptoms of CT features associated with alveolar proteinosis (1,8). Chest imaging and CT scan can be helpful in pulmonary diseases diagnosis (9).

In the acquired form of the disease, CBC, diff and biochemical tests are normal. Serum levels of lactate dehydrogenase are commonly reported high in these patients (3,10).

Restrictive ventilator defects, along with a mild decrease in forced vital capacity and total lung capacity and also a significant reduction in carbon monoxide emission capacity, are indirectly observed in the patients' respiratory test. Due to ventilation-perfusion inequality and intrapulmonary shunt, hypoxia results in elevated arterial-alveolar gradient (1,8).

Bronchoalveolar lavage is performed in the operating room; the patient becomes anesthetized and intubated by double-lumen endotracheal tube. Fiber optic bronchoscopy is done to confirm the correct location of tracheal tube. The patient is lying in lateral decubitus position, and while mechanical one-lung ventilation is performed, another lung undergoes the lavage. In each session, 500-600 ml of warm saline (37 °C) is injected into the lungs and is collected by gravity drainage after opening the draining tube. The lavage fluid of these patients has a milky and opaque color. Lavage continues until the liquid becomes completely clear (1,11,12).

In laboratory studies on lavage fluid, large foamy macrophages, or monocyte-derived alveolar macrophages along with increased lymphocyte count, and significant reduction in other inflammatory cells have been seen. The main components of lavage fluid are phospholipids, especially lecithin (the major component of surfactant). This liquid also contains serum proteins and surfactant-specific proteins including proteins A (SP-A), and D8.

There are no specific criteria for lavage, but in cases of observing these signs it is recommended to perform lavage for the patient: progressive respiratory failure, no labored breathing at rest, and drop in oxygen level during activity (>5%). Contraindications for lavage include uncorrectable blood dyscrasias, seizure, fever (indicating an infection), and cardiopulmonary instability (13).

This study aimed to investigate the diagnosis and treatment outcomes of patients with pulmonary alveolar proteinosis.

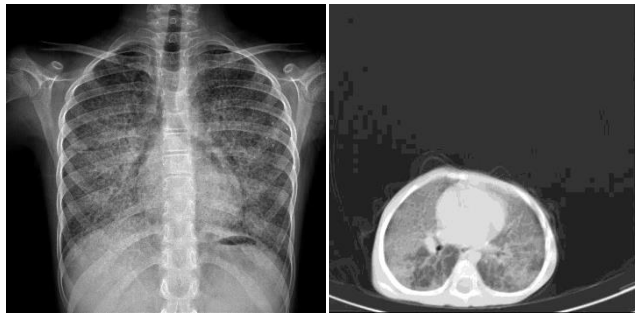


Figure 1. Chest x.ray and CT-Scan of patients with PAP.

**MATERIALS AND METHODS**

In this study, patients with PAP admitted to Pediatric ward of Masih Daneshvari Hospital since 2002 were studied. Medical history of these patients in different hospitalizations was studied through their medical records; and the required data were collected including the patient's demographic data, clinical signs and radiographic data, the number of admissions, the age of diagnosis, detection and treatment methods, number of lavage, current condition of the patient, and in case of death, the cause of death. The data were filled in a pre-designed questionnaire. Finally, data were analyzed statistically by SPSS software version 16.

**RESULTS**

In this study, 17 patients with PAP who were admitted during the past 15 years (2002-17) were examined; among which 7 patients were boys (41.2%) and 10 were girls (58.8%). The mean age of population was 11.79 ± 7.21 years. The mean height and weight of patients were 109 cm (79-157 cm) and 16.71 kg (9-41.8 kg), respectively. In 22.2% of patients, the height to age ratio was less than the 5th percentile and in 11.1% it was greater than the 50th percentile. The weight to age ratio in 66.7% of patients was less than the 5th percentile and in 22.2% it was greater than the 25th percentile. The mean age of the diagnosis was 7.37 years (2-17 years). The median number of admissions was 3 times (1-10 times). 90.9% of patients were the result of consanguinity marriage (Table 1).

Table 1. Patients' basic data

	Age	Height (cm)	Weight (Kg)	Age of Diagnosis (Y)	Birth Weight (gr)	Admission (No.)	Consanguinity
Mean	11.79	109	16.71	7.37	3170	3.65	90.9
Median	12	101	14.25	5.5	3500	3	-

Based on the frequency, the symptoms of patients were shortness of breath 88.2%, coughing 82.4%, crackles 47.4%, cyanosis 35.3%, tachypnea 29.4%, increased mucus 17.6%, weight loss 17.6%, and clubbing 17.6% (Figure 2).

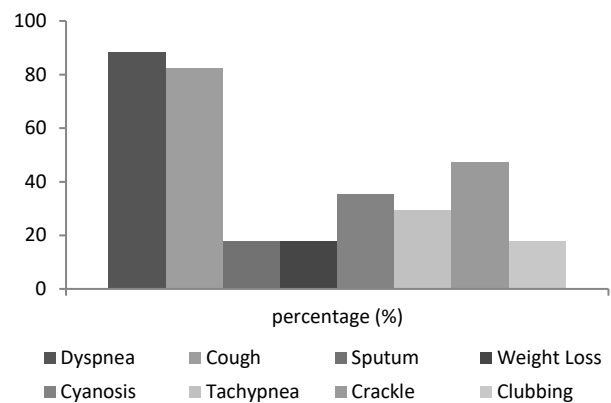


Figure 2. Clinical findings of understudy patients

The ABG findings of patients were as follows: hypoxia 46.7%, respiratory acidosis 40%, metabolic acidosis 13.3%, metabolic alkalosis 7.1%. In all the population, LDH was reported to be higher than normal, while just in 3.6% of patients, the ESR was abnormal.

In review of radiology and CT scan, 100% of patients had pulmonary opacity. Other radiological findings were as follows: alveolar infiltration 61.5%, consolidation 100%, reticulonodular pattern 7.7%, ground glass 76.9%, honey combing 7.7%, and crazy paving 45.5% (Figure 3).

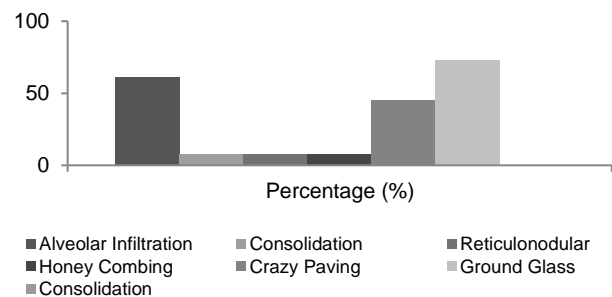


Figure 3. Radiologic findings of Patients with PAP.

Transbronchial Lung Biopsy (TBLB) (47.1%) and open lung biopsy (52.9%) were used for diagnosis of patients referred to Masih Daneshvari Hospital. Lung lavage was used to treat patients, 15 of whom were treated by this method. Lavage was not performed for 2 patients due to their conditions, one of whom died in PICU after open lung biopsy, and for the other one lavage was not performed due to respiratory problems during the operation. For 4 patients (35.3%), only one lavage was performed, of which 2 are currently in good condition, but unfortunately 1 died due to the severity of the disease and respiratory distress. The other one also died due to immunodeficiency. Due to relapses, 11 patients (64.7%) underwent lung lavage for several times, two of whom, unfortunately, died due to critical conditions and lack of response to treatment. All these 5 patients who died were girls; however, there was not enough evidence to confirm the relationship between the gender of the patients and their mortality. Out of these 11 patients, 3 children less than 30 kg were treated by Extracorporeal Membrane Oxygenation (ECMO) during lavage.

In the present study, the significant relationship between gender and number of necessary lavages was studied through T-test, but there was not enough evidence to prove any relationship between these two factors. Moreover, gender had no significant relationship with the frequency of admissions and severity of disease.

In addition, Pearson correlation coefficient was used to assess the relationship between the age of the patients, the frequency of admissions, and the frequency of lavage, in which no significant relationship was found.

In this study, the diagnostic method for patients had no relationship with the gender and Fisher's test was used to confirm this issue. Besides, T-test showed that the election of diagnostic method had no relationship with age. On the other hand, there was not any evidence that electing diagnostic method had any effect on the disease procedure, the treatment, and frequency of performed lavage.

## DISCUSSION

PAP is an uncommon pulmonary disease that is found following the accumulation of surfactant composed of proteins and lipids due to disruption of surfactant

clearance by alveolar macrophages. However, there is no reliable estimation of its incidence.

In a study done by Enaud et al., the most common clinical symptoms of patients at the time of diagnosis were respectively dyspnea, coughing, decreased oxygen level, and finger clubbing. The present study also found that dyspnea was the most common and coughing was the second most common clinical symptom of the disease. CT scan findings from the Enaud et al.'s study were slightly different from those of our study. In his study, the most common radiographic finding from CT scan was ground glass opacity, and consolidation was in second place of abundance. However, in the present study, the most pulmonary involvement reported in CT scan of patients was consolidation, and ground glass opacity was in the third place of abundance. In the aforesaid study, about 50% of patients below 14 years old suffered from lung fibrosis, while in none of our patients, lung fibrosis was reported (4).

Therapy method in the present study was lavage for both lungs, and it was performed for all patients except for two patients due to their anatomical complications. This method is still considered as the gold standard for PAP. According to the two studies conducted in 2011 and 2015, Whole Lung Lavage (WLL) was the standard therapy and the best treatment for alveolar proteinosis; and the use of new therapies such as GM-CSF and antibodies with specific aims alone or associated with lung lavage was just suggested as a proposal. Besides, few studies have been conducted with large sample size and in a long-term period. Unfortunately, this method has not been investigated in our country due to the high cost of GM-CSF and the lack of this medication in the market (1,11).

Furthermore, in another study, WLL was used for treatment of 9 children with PAP. In 8 subjects, in order to prevent the hypoxemia, ECMO was used. In this therapy, peripheral arterial bypass is used. Likewise, in the present study, for 3 patients with PAP who were less than 30 kg, ECMO was used during lavage (13).

In another study conducted in 2016, 27 centers that performed lung lavage for PAP patients were examined. The results showed that all of the centers used double-lumen endotracheal tube, warm saline (37 °C) for lavage,

gravity drainage of lavage fluid, and separate lavage of lungs with intervals of several weeks. In our study, also the lavage was performed for patients, but lavage was performed on both lungs in a single session (14).

In a survey done on 23 children with PAP, it was found that most of the subjects, depending on the severity of the disease, required multiple lung lavages, and especially in severe forms of disease, increased number of lavage promoted the prognosis of the patients. In the present study, due to relapsed disease 64.7% of patients were treated by multiple lavages (10).

## CONCLUSION

Considering the findings from previous studies and the present study, it seems that WLL was fruitful for patients who had the indication for using this therapy and it played a significant role in improving the prognosis of patients. Besides, it is recommended to do follow-up regularly in order to have more therapeutic efficacy and increased patient longevity.

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