

Review

The overview of pulmonary alveolar proteinosis treatment methods, with a proposition of a prospective multicenter randomized controlled trial

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ABSTRACT

Pulmonary alveolar proteinosis (PAP) is characterized by accumulation of surfactant in the alveoli due to impaired clearance or overproduction leading to progressive dyspnea and potentially fatal respiratory failure. This review provides a comprehensive analysis of current and emerging therapeutic strategies for PAP, evaluating their pathophysiological rationale, clinical efficacy and limitations. A structured literature review was conducted using PubMed, Google Scholar, and Cochrane Library databases to identify studies published between 01.01.2002 and 01.07.2026. Search terms included: "PAP," "whole lung lavage (WLL)," "segmental lung lavage (SLL)," "granulocyte-macrophage colony-stimulating factor (GM-CSF)," "molgramostim," "sargramostim," "rituximab," and "statin therapy." WLL removes accumulated surfactant, but it remains hindered by its invasive nature, procedural risks, and recurrence rates requiring repeated sessions. To overcome these limitations, less invasive techniques, such as mini-WLL and bronchoscopic SLL, achieve targeted surfactant clearance with reduced volume load, making them valuable alternatives for high-risk patients or bridging therapies. Targeted pharmacotherapies including inhaled recombinant GM-CSF which restores alveolar macrophage clearance functions, improves gas exchange and reduces the reliance on WLL. Statin therapy may reduce macrophage lipid accumulation. Despite these interventions rituximab, extracorporeal membrane oxygenation (ECMO) support, or lung transplantation may be useful in selected cases. Innovations, including gene therapy and gene-corrected macrophage transplantation, aiming to permanently restore cellular function are also being tested. The management of PAP is shifting from global mechanical surfactant removal towards personalized, local lavage or pathogenetically driven pharmacological algorithms, however WLL remains essential for acute rescue in severe hypoxemia.

KEYWORDS

pulmonary alveolar proteinosis, whole lung lavage, bronchofiberscopy, therapeutic lung lavage, segmental lung lavage, molgramostim, rituximab, granulocyte-macrophage colony-stimulating factor, sargramostim, statin therapy

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare respiratory syndrome characterized by the excessive accumulation of surfactant lipoproteins within the alveoli, classifying it fundamentally as an alveolar filling disorder. First documented in 1958 by Rosen et al. [1], PAP is increasingly recognized as a heterogeneous clinical syndrome driven by distinct underlying pathophysiological mechanisms rather than a single disease entity. The relentless accumulation of proteinaceous material within the alveolar spaces compromises normal pulmonary gas transfer, leading to

progressive dyspnea, severe hypoxemia, and a variable impairment of diffusion capacity. If left untreated, the condition carries a profound risk of secondary infections, progressive pulmonary fibrosis, respiratory failure, and early mortality.

Epidemiology

PAP is an exceptionally rare condition, with a global prevalence estimated at 7 cases per million individuals in the general population. Autoimmune PAP is the most common form, accounting for an overwhelming 90–95% of adult cases, while secondary PAP represents only 5–10%. Although global epidemiological data is limited, a Japanese registry estimates the incidence of autoimmune PAP to be between 0.24 and 0.49 per million, with a prevalence ranging from 2.04 to 6.2 cases per million [2].

Pathophysiology and rationale for treatment

Overview of pulmonary alveolar proteinosis

Patients can present with a wide array of clinical signs, varying from diminished exercise capacity to fatal hypoxemic respiratory failure [2,3].

Surfactant biology and function

In order to understand the pathogenesis of PAP, it is crucial to consider the role of surfactant. Synthesized by type II alveolar epithelial cells, normal surfactant is composed primarily of phospholipids (90%) and proteins (10%). Once secreted into the alveolar space, the phospholipids reduce surface tension at the air-liquid interface, which prevents the alveoli from collapsing during exhalation, stabilizes their size, and decreases lung elastic recoil. Meanwhile, surfactant proteins (A, B, C, and D) organize the surfactant structure and serve as key mediators in the lung's innate immune system. Under normal conditions, surfactant is continuously cleared and recycled by type II epithelial cells and alveolar macrophages [4,5].

Pathophysiology and epidemiology

In adult PAP, the core issue lies in the impaired maturation of alveolar macrophages, which disrupts this normal surfactant clearance. Proper granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling is essential for these macrophages to develop their full range of metabolic and immune functions.

Pathophysiology overview and classification

Based on these mechanistically distinct pathways, PAP is classified into three major clinical categories:

- Primary PAP: Characterized by the direct disruption of GM-CSF signaling, impairing the function of both macrophages and neutrophils.
 - Autoimmune PAP (aPAP): Driven by high-affinity, neutralizing anti-GM-CSF autoantibodies detectable in serum or bronchoalveolar lavage (BAL) fluid.
 - Hereditary PAP: A non-autoimmune variant driven by inactivating mutations in the GM-CSF receptor alpha or beta chains (*CSF2RA* or *CSF2RB*).
- Secondary PAP (sPAP): Occurs when surfactant clearance is compromised due to a functional or quantitative reduction of alveolar macrophages secondary to an underlying medical condition, such as hematological malignancies, chronic infections, or heavy occupational dust inhalation (e.g., silica).
- Disorders of surfactant production: A distinct congenital category manifesting primarily in neonates, driven by genetic mutations (e.g., *ABCA3* lipid transporter deficiency or surfactant protein mutations) that alter surfactant synthesis or disrupt lung embryogenesis, typically precipitating rapid-onset pulmonary fibrosis [2].

Rationale and strategy for the treatment of pulmonary alveolar proteinosis

The primary goals of PAP management are to induce disease regression or achieve long-term clinical stabilization, thereby minimizing symptom burden and reducing reliance on repeated, highly invasive interventions. The decision to initiate active therapy, as well as the selection of specific modalities, should be guided by disease severity, rate of progression, and the underlying pathogenetic mechanism [4].

Clinical management is categorized into two primary strategies based on patient status:

- The "watch and wait" strategy: A conservative, observational approach is fully justified and recommended for asymptomatic or mildly symptomatic patients who do not present with severe respiratory impairment or life-threatening complications, provided they maintain a stable and acceptable quality of life. Spontaneous remission can occur in a subset of autoimmune PAP cases, further supporting initial close observation rather than immediate intervention [6].
- Indications for active treatment: Therapeutic intervention is warranted in cases of active, symptomatic, or progressively worsening disease. Key objective indicators necessitating the initiation of active therapy include significant symptoms such as dyspnea or failing physical activity followed by a meaningful decline in pulmonary function tests (specifically Forced Vital Capacity [FVC] and Diffusing Capacity of the Lung for Carbon Monoxide

[DLCO]), worsening hypoxemia either at rest or induced by exertion, radiological progression on high-resolution computed tomography (HRCT) [7].

Rationale for specific therapeutic modalities

- Whole lung lavage (WLL): WLL acts as a primary rescue or bridging therapy for patients with autoimmune PAP who exhibit significant symptoms and impaired gas exchange. The procedure physically washes out the excessive, accumulated lipoproteinaceous material from the alveoli. This mechanical clearance is justified by its proven ability to improve pulmonary function, enhance exercise capacity, and relieve respiratory symptoms, with benefits that generally outweigh the procedural risks for hypoxic patients [4].
- Inhaled exogenous GM-CSF: This non-invasive therapy directly targets the fundamental mechanism of autoimmune PAP (aPAP). By delivering GM-CSF directly to the airways, it overrides the neutralizing effects of endogenous GM-CSF autoantibodies, effectively restoring normal alveolar macrophage function and surfactant clearance. Its use is strongly justified by sustained physiological and radiological improvements, as well as its potential to prevent or significantly delay the need for recurrent, costly, and invasive WLL [8].
- Immunosuppressive and extracorporeal therapies (rituximab and plasmapheresis): Rituximab and plasmapheresis are conditional therapies reserved for severe, refractory cases of aPAP where patients remain symptomatic and oxygen-dependent despite treatment with WLL and inhaled GM-CSF. The rationale lies in directly targeting the autoimmune source: plasmapheresis physically filters and removes the pathogenic GM-CSF autoantibodies from the bloodstream, while rituximab (a B-cell depleting agent) is utilized to suppress the ongoing production of these autoantibodies [9].
- Lung transplantation: Lung transplantation is considered as a definitive, last-resort option for patients with end-stage, fibrotic, or relentless PAP that progresses despite all other pharmacological and lavage treatments. Patients facing progressing hypoxic respiratory failure with a disease related high mortality risk, transplantation is justified, as it can successfully reverse hypoxemia and restore QoL. This outweighs the lifelong need for immunosuppression and the potential risk of disease recurrence in the donor organ [7].

Standard of care: whole lung lavage

Technique and mechanism of action

Whole lung lavage (WLL) remains the foundational reference therapy for symptomatic PAP, aimed at the immediate mechanical clearance of accumulated intra-alveolar lipoproteinaceous material. The procedure is performed under general anesthesia and requires isolating the lungs using a

double-lumen endotracheal tube [10]. While one lung undergoes continuous mechanical ventilation, the contralateral lung is sequentially flooded with warmed isotonic saline (typically in aliquots of 0.5 to 1 liter) and subsequently drained by gravity. To optimize surfactant detachment from the alveolar walls, physical chest percussion or manual hyperinflation is systematically applied during the drainage phase [10,11].

Clinical efficacy and functional outcomes

WLL provides profound and immediate physiological benefits by reducing alveolar filling and restoring gas exchange:

- **Oxygenation and blood gas:** Clinical data demonstrate that WLL significantly reverses hypoxemia. In a 20-year retrospective analysis by Kaenmuang and Navasakulpong [12], the mean partial pressure of oxygen (PaO_2) improved significantly from 49.3 mmHg to 66.1 mmHg post-procedure. Similarly, a multicenter study by the French GELF group reported a statistically significant mean improvement in PaO_2 of 6.38 mmHg under standard protocols [13].
- **Diffusion capacity:** Diffusing capacity for carbon monoxide (DLCO) recovers concurrently. Following WLL, the mean DLCO predicted value increased from 44.8% to 59.5% in specialized cohorts, with a strong positive correlation noted between PaO_2 recovery and the transfer coefficient (K_{CO}) [12].
- **Symptomatic relief:** The primary indication for WLL is the management of progressive dyspnea. Following mechanical clearance, patients experience a rapid reduction in breathlessness, with median modified Medical Research Council (mMRC) dyspnea scores dropping from 3 to 2, directly translating into enhanced exercise capacity [12].

Procedural complications and limitations

Despite its established clinical efficacy, WLL is hindered by high invasiveness and significant technical limitations:

- **Perioperative risks:** Flooding one lung while ventilating the other induces a massive ventilation/perfusion (V/Q) mismatch and intrapulmonary shunting. This can precipitate severe, life-threatening peri-procedural hypoxemia, occasionally requiring emergency extracorporeal membrane oxygenation (ECMO) rescue. Additional complications include airway trauma from double-lumen tube placement, fluid leakage into the ventilated lung, and barotrauma [10].
- **High recurrence rates:** Because WLL merely removes the accumulated sediment without correcting the underlying macrophage dysfunction, it is inherently non-curative. Large-scale multi-center data indicate that 56.2% of patients experience disease recurrence, with

a median time to symptom return of 16.9 months, necessitating lifelong, repeated lavage sessions [13].

- Resource consumption: As highlighted by Awab et al. [10], WLL is a highly exhausting and time-consuming procedure, often requiring 5 to 10 hours of operating room time, a highly specialized multidisciplinary team, and mandatory post-operative intensive care unit (ICU) monitoring.

Therapeutic lung lavage – segmental, partial, and less invasive approaches

Definition, technique, and resource efficiency

To mitigate the severe systemic burdens associated with standard whole lung lavage (WLL), less invasive and targeted technical modifications have been integrated into clinical practice.

Segmental lung lavage (SLL) is performed via a flexible bronchoscope wedged directly into a specific segmental or subsegmental bronchus, allowing for targeted surfactant clearance [14].

Unlike standard WLL, which requires full general anesthesia, double-lumen intubation, and intensive care unit (ICU) monitoring, SLL and other partial approaches—such as therapeutic lavage supported by non-invasive ventilation (NIV)—can be safely executed under mild or conscious sedation. By completely eliminating the risks of airway trauma from rigid double-lumen tubes and systemic anesthetics, these procedures significantly reduce operative time (e.g., from up to 10 hours down to approximately 4 hours) and allow patients to bypass ICU recovery entirely, enhancing healthcare resource efficiency [15].

Indications and strategic advantages

Partial techniques are primarily indicated for patients presenting with milder disease severity, pediatric cohorts, or individuals burdened by severe cardiac and respiratory comorbidities that preclude the safe induction of deep general anesthesia [16]. A key physiological benefit of targeted techniques is the prevention of severe, procedure-induced hypoxemia and ventilation/perfusion (V/Q) mismatching. Traditional WLL requires total unilateral pulmonary flooding while the single contralateral lung supports gas exchange, a process that risks critical intrapulmonary shunting. In contrast, segmental and partial approaches leave the surrounding, non-flooded alveoli. This localized strategy significantly limits physical trauma to the airway walls, minimizes the local inflammatory response, and virtually eliminates the risks of systemic fluid overload, pulmonary edema, or pleural effusions [11].

Clinical efficacy and evidence review

The clinical efficacy of these modified and less invasive techniques is supported by recent cohorts and technical comparative trials:

- Segmental lung lavage (SLL): Clinical registries show that SLL provides significant physiological recovery. Targeted clearance leads to distinct improvements in arterial oxygenation (PaO₂), carbon monoxide diffusing capacity (DLCO), and chest high-resolution computed tomography (HRCT) clearance scores, demonstrating cross-over functional benefits even in non-lavaged lung regions [14].
- Mini-WLL: In a direct technical comparison, Mariani et al. [11] evaluated standard WLL (using a 14-liter volume) against a modified "mini-WLL" protocol utilizing a reduced volume of 9 liters combined with early chest percussion. Over an 18-month observation period, both approaches yielded comparable, statistically significant long-term improvements in the alveolar-arterial oxygen gradient (A-aDO₂) and DLCO percentage ($p < 0.001$). Strikingly, mini-WLL was significantly more effective than standard WLL at recovering restricted lung volumes (Vital Capacity and Total Lung Capacity), a benefit attributed to the reduced mechanical and volume-induced insult to the alveolar framework.

Limitations and technical comparison vs. standard WLL

Despite their procedural convenience, partial and segmental approaches are bounded by distinct operational drawbacks:

- Lower relative surfactant clearance: Because SLL utilizes much smaller quantities of irrigation fluid, it clears a significantly lower absolute mass of accumulated lipoproteinaceous sediment per session compared to standard WLL [3]. Consequently, SLL is often clinically positioned as a temporary bridge to stabilize highly unstable, profoundly hypoxic patients rather than a definitive long-term maintenance treatment [17].
- Lack of standardization and need for repetition: Like standard WLL, partial techniques suffer from a profound lack of international protocol standardization. Total saline volumes, optimal instillation temperatures, and the implementation of manual or mechanical chest percussion vary extensively across institutions. Furthermore, because mechanical washing does not target the causative macrophage maturation defect, recurrence rates remain high across all modalities, frequently necessitating multiple repeat sessions to maintain baseline functional stability [3,13].

Pharmacological and emerging pathogenetically driven therapies

Recombinant GM-CSF therapy (inhaled vs. subcutaneous)

Targeted pharmacotherapies represent a paradigm shift in aPAP by directly addressing the underlying pathogenetic mechanism. Recombinant GM-CSF formulations – primarily sargramostim and molgramostim – aim to restore alveolar macrophage function by delivering sufficient exogenous growth factor to neutralize endogenous anti-GM-CSF autoantibodies [7].

A comprehensive meta-analysis of 10 observational studies involving 115 patients established that the inhaled (nebulized) route is vastly superior to subcutaneous administration across all primary physiological outcomes:

- Gas exchange and oxygenation: Inhaled GM-CSF improved arterial oxygenation (PaO_2) by an average of 21.02 mmHg and reduced the alveolar-arterial oxygen gradient (A-aDO_2) by 19.63 mmHg, whereas subcutaneous delivery yielded modest improvements of only 8.28 mmHg for PaO_2 and 9.15 mmHg for A-aDO_2 [8].
- Diffusion capacity and symptoms: Nebulized therapy led to a pooled clinical response rate of 89% (compared to 71% for subcutaneous) and achieved an overall improvement in carbon monoxide diffusing capacity (DLCO) of up to 8.49% [8]. Furthermore, in a landmark phase II prospective trial using a high-to-low dose inhaled molgramostim regimen, categorical resolution of dyspnea was achieved in 54.3% of subjects [18].
- Strategic position: Initiating inhaled sargramostim as a maintenance regimen or immediately following a baseline WLL procedure significantly lowers serum disease biomarkers and dramatically delays or permanently prevents the need for recurrent, highly invasive mechanical lavages [19].

Statin therapy and cholesterol homeostasis

Oral statin therapy (such as atorvastatin or rosuvastatin) has emerged as a groundbreaking, inexpensive, and non-invasive alternative that targets intracellular lipid homeostasis within the lungs. In PAP patients, alveolar macrophages demonstrate a marked intracellular accumulation of cholesterol due to defective ABCG1 transporter expression [9].

Statins directly induce upregulation of ABCG1 expression, promoting dramatic cholesterol efflux from explanted alveolar macrophages and accelerating natural surfactant clearance without procedural intervention [9]. Clinical data from a detailed case report by Shi et al. [20] demonstrate that oral atorvastatin can induce complete radiological clearing of lung opacities and eliminate the need for supplemental oxygen, even in patients who are entirely refractory to recurrent WLL and GM-CSF therapies and who do not exhibit baseline systemic hypercholesterolemia. In long-term follow-ups, statins have successfully doubled DLCO values from critically low baseline levels (e.g., from 41% to 80% predicted), providing profound symptomatic relief and total resolution of severe resting dyspnea [17].

Immunosuppressive and extracorporeal rescue modalities

For severe, highly refractory cases of aPAP where patients remain dangerously hypoxemic despite standard WLL and optimal inhaled GM-CSF, conditional rescue therapies target the autoimmune source directly:

- Rituximab: This monoclonal antibody targets the CD20 antigen on B-cells to suppress the ongoing production of pathogenic anti-GM-CSF autoantibodies. In a French real-life cohort of 13 refractory patients, rituximab induced significant objective improvements in 30% of subjects; among these responders, mean PaO₂ surged from 64.3 mmHg to 82.8 mmHg, and mean A-aDO₂ decreased from 42.4 mmHg to 24.3 mmHg over a 12-month period. Because its therapeutic effects develop slowly, rituximab is strictly positioned as a second- or third-line rescue modality rather than a replacement for immediate mechanical clearance [21].
- Plasmapheresis: Extracorporeal plasmapheresis is reserved as a conditional bridging therapy designed to physically filter and remove circulating high-affinity anti-GM-CSF autoantibodies from the bloodstream, temporarily restoring peripheral clearance mechanisms in critically ill individuals [6].

Advanced curative frontiers for hereditary PAP

Therapies currently being investigated for hereditary/congenital PAP—which is driven by permanent genetic mutations in the CSF2RA or CSF2RB receptor genes- cannot be treated with standard pharmacotherapies or GM-CSF supplementation. These cutting-edge approaches display true groundbreaking innovative potential:

- Gene-corrected pulmonary macrophage transplantation: This intervention involves the direct intra-airway transplantation of functional, gene-corrected macrophages [22]. Progenitor cells are harvested, corrected ex vivo via viral vectors to express functional GM-CSF receptors, and instilled into the lungs, providing a permanent, self-renewing cellular cure that successfully reverses alveolar filling without systemic toxicity [22].
- Human-induced pluripotent stem cell (iPSC)-derived macrophages: Modern research shifts toward utilizing iPSC-derived macrophages to replace defective native alveolar cells, aiming to permanently restore cellular metabolic pathways and physiological surfactant recycling [9].

Limitations

Although treatments for Pulmonary Alveolar Proteinosis (PAP) have improved, there are a number of important issues related to the current therapy options, including the standardization, length and comparative effectiveness of the treatments:

- Lack of standardization: Although historically the standard approach to treatment is Whole Lung Lavage (WLL), there are no internationally standardized guidelines or consensus documents outlining a specific protocol, indications or outcome criteria for the procedure [11,13]. WLL is a technically sophisticated method therefore its use is not uniform, there are only a few centers that are specialized in the technique [11,13]. Saline used for total

volume, for instance, may vary from 5 to 40 liters per lung, and whether manual or mechanical chest percussion is used, this varies widely from institution to institution [10].

- Multiple sessions required: WLL does not improve the underlying macrophage defect, but instead removes accumulated surfactant, it is not a cure in itself and the proteinaceous material may replenish [3,19].

As a result, the recurrence rate is high (between 30% to 70%) [11]. The majority of patients who receive an initial WLL and TLL will need repeated lavages for clinical stability > 60% [18]. In a global survey, patients received an average of 2.5 WLL procedures in a 5-year period with a median time between therapeutic sessions of 15 - 35 - 60 weeks [23].

- Lower efficacy of less invasive treatments vs WLL: There are some risks to less invasive treatments compared to general anaesthetic and intensive care, but they can also present lower or delayed efficacy when compared to immediate physical clearance provided by WLL:
 - Segmental lung lavage (SLL): SLL via flexible bronchoscopy is much less invasive and does not worsen the hypoxia and is performed segmentally. It is regarded as less effective than WLL, however, because it requires a much smaller quantity of lavage fluid to be washed out, and hence, wash out a much lower amount of the accumulated lipoproteins [13,14,18].
 - Pharmacotherapies (e.g., GM-CSF): WLL offers a quick, positive physiological and symptomatic result in more than 90% of patients [11]. Conversely, therapies such as inhaled GM-CSF which target the disease mechanism do not act immediately and can have inconsistent effects with an alveolar-arterial oxygen gradient which is generally moderate [3]. However, response rates to GM-CSF treatments may also be less than to WLL, and there are no head-to-head randomized trials of GM-CSF being shown to be as effective as WLL [3,8]. Hence, WLL is the basic rescue treatment in moderate and severe hypoxemic patients [3].

Treatment algorithms and personalization

The treatment of PAP relies on the physical elimination of accumulated surfactant and the implementation of pathogenetically targeted therapies. WLL remains the gold standard for symptomatic patients, significantly alleviating dyspnea (an improvement from 3 to 2 on the mMRC scale), increasing the diffusing capacity of the lungs for carbon monoxide (DLCO), and raising oxygen saturation from an average of 86% to 94% [12]. However, the long-term efficacy of WLL as a monotherapy is often limited—multicenter studies show that 56.2% of patients experience disease recurrence at a median of 16.9 months post-procedure [13].

To minimize the burden associated with repeated WLL procedures, modifications to treatment protocols are systematically implemented [11,24]. Retrospective analyses demonstrate that one-session bilateral WLL is as safe as the standard two separate sessions, while significantly reducing the patient's length of hospital stay [24]. The "mini-WLL" variant, with the instillation volume reduced to 9 liters per lung, is also increasingly used; this method effectively evacuates surfactant while simultaneously reducing mechanical insult to the alveoli [11]. A highly innovative technique is the new modified lavage technique (nMLT), in which repeated manual hyperinflation and chest percussion after every three washes allow for the removal of up to 91% of the accumulated protein with minimal fluid consumption [25].

For patients with milder disease or those burdened with high anesthetic risk, segmental lung lavage (SLL) or lobar lavage (TLL) performed via a bronchoscope serves as a safer alternative [16]. This procedure improves gas exchange and radiological findings not only in the directly lavaged segment but also in the non-lavaged lung areas [14]. SLL is also a key component of the intervention for patients with severe, life-threatening respiratory failure [17].

In the autoimmune form of the disease (aPAP), granulocyte-macrophage colony-stimulating factor (GM-CSF) is the key pharmacological support, with inhaled administration providing a higher response rate and better improvement in oxygenation parameters compared to subcutaneous injections [26]. Initiating inhaled sargramostim immediately after a baseline WLL procedure significantly reduces the need for rescue lavages and effectively lowers the levels of disease biomarkers [27]. A modern, non-invasive option is also oral statin therapy (e.g., atorvastatin), which corrects intracellular lipid clearance in macrophages [17]. This therapy can lead to the regression of dyspnea and lung opacities after 18 months of treatment, even in patients without baseline hypercholesterolemia and with clinical resistance to WLL procedures and GM-CSF therapy [20].

Special populations

Special populations of patients with pulmonary alveolar proteinosis (PAP) require highly individualized diagnostic and therapeutic strategies due to profound differences in age, clinical comorbidities, or extreme disease severity.

Pediatric population

Congenital PAP in newborns represents a rare and severe disorder that may mimic neonatal respiratory distress syndrome but typically remains refractory to mechanical ventilation and exogenous surfactant therapy. Without definitive treatment, the prognosis is poor, and lung transplantation may be the only life-saving option in selected patients. Hereditary forms are

frequently associated with pathogenic variants affecting surfactant metabolism or GM-CSF signaling and may occur more commonly in populations with parental consanguinity [2]. Conversely, in infants developing PAP secondary to primary immunodeficiencies (PID) – such as hypogammaglobulinemia presenting with monocytopenia – standard WLL procedures provide only transient, symptomatic benefit. The definitive, causal treatment in this subgroup involves allogeneic hematopoietic stem cell transplantation (HSCT), which successfully leads to the complete resolution of pulmonary lesions and permanent independence from oxygen therapy [28].

Secondary PAP (sPAP) and environmental exposures

In patients with secondary PAP, the overall clinical prognosis is strictly dictated by the nature of the underlying disease. Pulmonary lesions developing secondary to myelodysplastic syndrome (MDS) are associated with drastically poor survival rates, demonstrating a median survival of just 14.95 months. In contrast, secondary forms triggered by *Mycobacterium tuberculosis* infections carry a highly favorable prognosis following the timely initiation of targeted anti-tuberculosis therapy.

On high-resolution computed tomography (HRCT), the classic "crazy-paving" pattern is significantly less frequent in sPAP compared to the autoimmune form, occurring in only 33.3% of patients [29]. Furthermore, toxic environmental and occupational exposures heavily impact the disease course; epidemiological data indicates that 53% of PAP patients are tobacco smokers (with a median exposure history of 22 pack-years), and 48% present with a distinct history of occupational dust exposure, most frequently to metal dust (26.5%) or stone and sand (20.6%) [30].

Critically ill patients in the intensive care unit (ICU)

The highest-risk clinical cohort comprises critically ill patients admitted to the ICU. In the presence of severe acute respiratory failure and refractory hypoxemia, the baseline intrapulmonary shunting may entirely preclude the safe induction and performance of conventional WLL due to the risk of fatal procedure-induced hypoxia.

A critical, life-saving strategy in these clinical scenarios is the preemptive implementation of veno-venous extracorporeal membrane oxygenation (VV-ECMO) [31]. VV-ECMO ensures stable, continuous systemic gas exchange, which directly enables the application of lung-protective mechanical ventilation strategies and permits the clinician to perform a completely safe, concurrent lavage of both lungs during a single procedural session [31].

Discussion

The clinical management of pulmonary alveolar proteinosis (PAP) has reached a critical historical juncture. For decades, the therapeutic paradigm was strictly reactive and mechanical, relying

almost exclusively on the brute-force clearance of accumulated surfactant via large-volume whole lung lavage (WLL) [10]. As detailed in this review, the treatment landscape is rapidly transitioning toward a dual-axis framework that balances localized mechanical surfactant evacuation, with non-invasive, pathogenetically driven pharmacotherapies [4]. Despite these insights, several profound systemic challenges remain unaddressed, limiting the global reproducibility, equity, and evidence base of PAP therapy.

A prominent issue identified across the literature is that current management protocols are fundamentally built upon an unstable scaffolding of empirical practice rather than high-tier evidence. The vast majority of technical benchmarks – ranging from the total volume of irrigation saline to the specific scheduling of sequential sessions – are dictated primarily by the retrospective experiences and historical legacy of individual reference centers rather than prospective, randomized validation [13]. This deep-seated lack of procedural standardization introduces significant clinical heterogeneity, where patient outcomes may vary drastically based on the structural expertise of the localized therapeutic team.

Furthermore, the real-world utility of emerging pharmacological interventions remains heavily bounded by macroeconomic healthcare disparities and national regulatory frameworks. While nebulized recombinant GM-CSF therapies and oral statins target the biomolecular root causes of surfactant accumulation, their practical availability is highly dependent on national reimbursement models and regional healthcare budgets [7]. In resource-limited or highly centralized healthcare systems, patients are frequently denied access to specialized home-based pharmacotherapy, forcing them to remain fully dependent on recurring, high-risk, and costly hospitalizations for invasive WLL.

Areas of future research

To address these critical evidence gaps and dismantle the empirical biases dominating current treatment practice, there is an need to establish direct, head-to-head comparative data between standard and modified mechanical interventions. Based on our comprehensive analysis of the existing literature, we firmly propose the initiation of a Prospective, Multicenter Randomized Controlled Trial (RCT) titled: "PAP – therapeutic lung lavage RCT (PAP-TLL)".

- Target population: The study will enroll adult patients with a definitively confirmed diagnosis of PAP (autoimmune or secondary) presenting with significant clinical impairment, defined as a modified Medical Research Council (mMRC) dyspnea score and/or objective respiratory failure consisting of resting hypoxemia or significant exertional desaturation.

- Proposed sample size: The final sample size should be determined using an a priori power analysis based on the expected between-group difference in the selected primary endpoint and estimates derived from previously published PAP studies.
- Study arms: Eligible participants will be randomized into four distinct, parallel procedural arms:
 - standard large-volume whole lung lavage (WLL) under general anesthesia [10]
 - bronchoscopic segmental lung lavage (SLL) under conscious sedation [16]
 - therapeutic lung lavage (TLL) / noninvasive ventilation-supported therapeutic lung lavage (NIV-TLL) [15]
 - modified volume-reduced lavage (Mini-WLL, utilizing a strict 9-liter protocol per lung) [11].
- Study outcomes:
 - Primary endpoint: The primary endpoint would be the change in pulmonary gas exchange and lung function six months after intervention, assessed by: PaO₂, DLCO, mMRC dyspnea score
 - Secondary endpoints: Secondary outcomes would include: duration of hospitalization, changes in HRCT findings, capacity (6MWT), quality of life.

Call for collaboration

Centers, clinics, and research institutions specialized in interstitial lung diseases or interventional pulmonology that are interested in co-authoring and participating in this landmark multicenter trial are warmly invited to coordinate directly with our department via email at: ftpulmza@sum.edu.pl.

Conclusions

1. PAP is a rare respiratory syndrome that relies on two primary therapeutic axes: mechanical clearance to physically evacuate intra-alveolar lipoproteins and targeted pharmacotherapy to address underlying metabolic defects.
2. Mechanical intervention remains strictly reserved as an immediate rescue strategy for patients presenting with overt respiratory failure, profound hypoxemia, or high symptomatic burden (mMRC dyspnea score ≥ 2).
3. Pharmacological options – specifically nebulized recombinant GM-CSF and oral statins – act as critical maintenance or bridging therapies aimed at downregulating the clinical course, alleviating long-term symptoms, reducing patient reliance on repetitive, invasive procedural sessions.

4. The current evidence base for both mechanical and pharmacological modalities is heavily limited by a reliance on retrospective analyses, un-randomized cohorts, or small case series, leaving the standard of care driven by localized institutional experience rather than international consensus.
5. Future breakthroughs mandate the transition toward large-scale, prospective multicenter RCTs to establish optimal, standardized protocols, balance clinical safety with procedural efficacy, and guarantee global equity in PAP patient management.

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Conflict of interest

The authors declare no conflicts of interest.

Authors' contribution

Study design – M. Rycerski, P. Piekarz, A. Gajda, A. Kudłacz, A. Kmak, D. Karadoğan, S. Skoczyński

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