EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Task Force Report

European Respiratory Society guidelines for the Diagnosis and Management of Pulmonary Alveolar Proteinosis

Cormac McCarthy, Francesco Bonella, Marissa O'Callaghan, Clairelyne Dupin, Tiago Alfaro, Markus Fally, Raphael Borie, Ilaria Campo, Vincent Cottin, Aurelie Fabre, Matthias Griese, Alice Hadchouel, Stephane Jouneau, Maria Kokosi, Effrosyni Manali, Helmut Prosch, Bruce Trapnell, Marcel Veltkamp, Tisha Wang, Ingrid Toews, Alexander Mathioudakis, Elisabeth Bendstrup

Please cite this article as: McCarthy C, Bonella F, O'Callaghan M, *et al*. European Respiratory Society guidelines for the Diagnosis and Management of Pulmonary Alveolar Proteinosis. *Eur Respir J* 2024; in press (https://doi.org/10.1183/13993003.00725-2024).

Journal European Respiratory Journal

Manuscript Type: Guideline

ID: ERJ-00725-2024.R1.Clean

Date June 4th 2024

Title: European Respiratory Society guidelines for the Diagnosis and Management of Pulmonary Alveolar Proteinosis.

Authors: *Cormac McCarthy[1], *Francesco Bonella[2], Marissa O'Callaghan[1], Clairelyne Dupin[3], Tiago Alfaro[4], Markus Fally[5], Raphael Borie[6], Ilaria Campo[7], Vincent Cottin[8], Aurelie Fabre[9], Matthias Griese[10], Alice Hadchouel[11], Stephane Jouneau[12], Maria Kokosi[13], Effrosyni Manali[14], Helmut Prosch[15], Bruce Trapnell[16], Marcel Veltkamp[17, 18], Tisha Wang[18], Ingrid Toews[20], **Alexander Mathioudakis[21,22], **Elisabeth Bendstrup[23, 24]

*Shared first authorship **Shared senior authorship

Institutions: [1]School of Medicine, University College Dublin, Dublin 4, Ireland. ORCID: 0000-0003-2896-5210. [2]Center for interstitial and rare lung diseases, Pneumology Department, Ruhrlandklinik University Hospital, University of Duisburg-Essen, Essen, Germany. ORCID 0000-0001-7579-9767. [3]Service de Pneumologie A Hôpital Bichat, APHP, Université Paris Cité, Inserm UMR-S 1152 PHERE, 75018 Paris, France, ORCID 0000-0001-7957-8195. [4]Pneumologia Unit, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; ORCID: 0000-0001-6490-0620. [5]Department of Respiratory Medicine and Infectious Diseases, Copenhagen University Hospital – Bispebjerg and Frederiksberg, Copenhagen, Denmark. ORCID 0000-0002-1339-2918. [6]Service de Pneumologie A Hôpital Bichat, APHP, Université Paris Cité, Inserm UMR-S 1152 PHERE, 75018 Paris, France. [7]Pneumology Unit, Fondazione IRCCS Policlinico San Matteo, viale Golgi 19, 27100, Pavia, Italy. ORCID 0000-0002-4423-2482. [8]Reference center for rare pulmonary diseases, Department of respiratory medicine, Louis Pradel hospital, Hospices Civils de Lyon; UMR 754, Claude Bernard University Lyon 1, Lyon, France, ORCID 0000-0002-5591-0955. [7]Histopathology Department, St. Vincent's University Hospital, Dublin 4, Ireland. [10]Department of Pediatric Pneumology, Dr von Hauner Children's Hospital, Ludwig-Maximilians-University, German Center for Lung Research, Munich, Germany. ORCID 0000-0003-0113-912X. [11]AP-HP, Hôpital Universitaire Necker-Enfants Malades, Service de Pneumologie Pédiatrique, Centre de Référence pour les Maladies Respiratoires Rares de l'Enfant, INSERM U1151 INEM, Université Paris Cité, Paris, France. [12]Respiratory Disease Department, Reference Center for Rare Pulmonary Diseases, Pontchaillou Hospital, IRSET UMR 1085, EHESP, Univ Rennes, Rennes, France. ORCID 0000-0002-1949-3461. [13]Interstitial Lung Disease Unit, Royal Brompton Hospital, Guy's & St Thomas' NHS Foundation Trust, London, UK. [14]2nd Pulmonary Medicine Department, General University Hospital "Attikon", Athens Medical School, National and Kapodistrian University of Athens, Athens, Greece. [15]Dept. of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Austria. ORCID: orcid.org/0000-0002-6119-6364. [16]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, and Department of Pediatrics, University of Cincinnati, Translational Pulmonary Science Center, Cincinnati Children's Hospital, Cincinnati, OH, USA ORCID: 0000-0003-2817-

6254. [17]ILD Center of Excellence, Department of Pulmonology, St. Antonius Hospital, Nieuwegein, The Netherlands. [18]Division of Heart and Lungs, University Medical Center, Utrecht, The Netherlands ORCID: 0000-0001-7973-1604. [19]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, UCLA David Geffen School of Medicine, Los Angeles, California, USA. ORCID 0000-0002-4452-2148. [20]Institute for Evidence in Medicine, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany. [21]Division of Immunology, Immunity to Infection and Respiratory Medicine, School of Biological Sciences, The University of Manchester, Manchester, UK. ORCID 0000-0002-4675-9616. [22]North West Lung Centre, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK. [23]Center for Rare Lung Diseases, Department of Respiratory Disease and Allergy, Aarhus University Hospital, Aarhus, Denmark. ORCID 0000-0002-4238-6963 [24]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark.

Key Words: PAP, alveolar proteinosis, GM-CSF, whole lung lavage, pulmonary alveolar proteinosis, lipoproteinosis, surfactant, practice guidelines, diagnosis, treatment, systematic review, GRADE

Correspondence: Cormac McCarthy: cormac.mccarthy@ucd.ie
Francesco Bonella: francesco.bonella@rlk.uk-essen.de
Elisabeth Bendstrup: karbends@rm.dk

Author contribution:

Conflicts of interest: CMcC, FB, BCT report membership of scientific advisory board of Savara Inc. TW reports membership of scientific advisory board of Partner Therapeutics and Savara Inc. These members did not vote on PICO question 4. CMcC reports consultancy fees from Theravance Inc., Savara Inc. FB reports consultancy fees from Boehringer Ingelheim, Sanofi, Bristol Meyers Squibb, Savara Inc. MO'C, TA, CD, MF, VC, AF, MG, MK, AH, SJ, IT and AM report no potential conflicts. RB reports honoraria from Boehringer Ingelheim, Sanofi, Ferrer. IC reports fees from Partner's Therapeutics. EM reports consulting fees from Boehringer Ingelheim, CLS Behring and Hoffman la Roche. HP reports speaker honoraria from AstraZeneca, BMS, Boehringer Ingelheim, Bracco, Daiichi Sankyo, Janssen, MSD, Novartis, Roche, Sanofi, Siemens Healthineers, and Takeda, and research support from Boehringer Ingelheim, AstraZeneca, Siemens Healthineers and the Christian Doppler Research Association. MV reports consulting fees from Boehringer Ingelheim and Chiesi.EB reports honorari from Boehringer Ingelheim, Astra Zeneca and Daichii Sankyo.

Funding: European Respiratory Society Taskforce: TF-2021-16

Acknowledgements: Librarian Valeria Scotti, Center for Scientific Documentation-Fondazione IRCCS Policlinico San Matteo of Pavia, Italy. Patient representatives KM Bjelland and S Dhir. AGM was supported by the NIHR Manchester Biomedical Research Centre (NIHR203308) and by an NIHR Clinical Lectureship in Respiratory Medicine.

ABSTRACT

Background

Pulmonary alveolar proteinosis (PAP) is a rare syndrome caused by several distinct diseases leading to progressive dyspnoea, hypoxemia, risk of respiratory failure and early death due to accumulation of proteinaceous material in the lungs. Diagnostic strategies may include computed tomography (CT) of the lungs, bronchoalveolar lavage, evaluation of antibodies against granulocyte macrophage colony stimulating factor (GM-CSF), genetic testing, and, eventually, lung biopsy. The management options are focused at removing the proteinaceous material by whole lung lavage (WLL), augmentation therapy with GM-CSF, rituximab, plasmapheresis, and lung transplantation. The presented diagnostic and management guideline aim to provide guidance to physicians managing patients with PAP.

Methods

A European Respiratory Society Task Force committee composed of clinicians, methodologists, and patients with experience in PAP developed recommendations in accordance with the ERS Handbook for Clinical Practice Guidelines and the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach. This included a systematic review of the literature and application of the GRADE approach to assess the certainty of the evidence and strength of recommendations. The committee formulated five PICO (Patients, Intervention, Comparison, Outcomes) questions, and two narrative questions to develop specific evidence-based recommendations.

Results

The Task Force committee developed recommendations for five PICOs. These included management of PAP with WLL, GM-CSF augmentation therapy, rituximab, plasmapheresis, and lung transplantation. Also, the committee made recommendations regarding the use of GM-CSF antibody testing, diagnostic bronchoalveolar lavage (BAL) and biopsy based on narrative questions.

In addition to the recommendations, the committee provided information on the hierarchy of diagnostic interventions and therapy.

Conclusions

The diagnosis of PAP is based on CT and BAL cytology or lung histology, whereas diagnosis of specific PAP-causing diseases requires GM-CSF antibody testing or genetic analysis. There are several therapies including WLL and augmentation therapy with GM-CSF available to treat PAP, but supporting evidence is still limited.

Take home message:

The diagnosis of PAP is based on CT and BAL cytology or histology, whereas the diagnosis of a specific PAP-causing disease requires GM-CSF antibody testing and/or genetic analysis. WLL is considered the main management for many, but not all, PAP-causing diseases, and inhaled GM-CSF appears to be a promising option for autoimmune PAP.

SCOPE AND OBJECTIVES

This European Respiratory Society (ERS) guideline provides evidence-based recommendations for managing patients with pulmonary alveolar proteinosis (PAP). Since PAP is caused by clinically and mechanistically distinct diseases, we focused on key diagnostic and management questions. The target audience are those involved in the care of children/adolescents and adults with PAP, including specialists in respiratory medicine, paediatricians, radiologists, pathologists, regulatory authorities, pharmaceutical companies, and policy makers. This guideline is not intended to substitute for sound clinical judgement and requires interpretation or adaptation to the specific clinical context regarding access to diagnostic tools and treatment options (e.g., GM-CSF antibody testing and GM-CSF augmentation therapy). Further, these recommendations should be considered in accordance with patient perceptions, values and preferences, available expertise and the nature and severity of the clinical problem.

INTRODUCTION

PAP is characterised by accumulation of surfactant in pulmonary alveoli resulting in progressive hypoxemic respiratory insufficiency or failure, and an increased risk of secondary infections and/or pulmonary fibrosis [1]. **(Figure 1)** PAP can occur due to a variety of mechanistically distinct diseases that result from impaired surfactant clearance or from abnormal surfactant production (**Table 1**).

Primary PAP is driven by disruption of signalling by granulocyte/macrophage-colony stimulating factor (GM-CSF) resulting in dysfunction of alveolar macrophages and neutrophils while secondary PAP occurs because of an underlying disease or condition that reduces the numbers and/or functions of alveolar macrophages. Disorders of surfactant production or pulmonary surfactant metabolic dysfunction disorders are caused by mutations in genes encoding surfactant proteins or genes involved in surfactant production or lung development[1]. The prevalence of autoimmune PAP (aPAP) is estimated at 6.7-6.9 per million in the general population [2, 3]. Advances over the last 20

years have improved the understanding of PAP and resulted in novel methods for diagnosis and treatment. With established and emerging therapies and better understanding of the underlying pathogenesis, clinical practice guidelines are needed [1, 4].

METHODOLOGY

The ERS Pulmonary Alveolar Proteinosis Clinical Practice Guidelines were developed by an ERS Task Force (TF) following methodology proposed by the ERS guidance for developing Clinical Practice Guidelines[5] and the GRADE (Grading of Recommendations, Assessment, Development and Evaluation)[6] approach. The TF was chaired by C. McCarthy (Ireland), F. Bonella (Germany) and E. Bendstrup (Denmark). The TF included 17 respiratory medicine specialists, two paediatricians, a radiologist, a pathologist, two guideline methodologists (who were also respiratory medicine specialists) and two lay representatives living with PAP (details in the online appendix). The two lay representatives were full members of the TF and contributed to all recommendations. Conflicts of interest were disclosed by all panel members and were managed in line with the ERS policy. The TF met virtually and during physical meetings to define and discuss the methodological details of the guideline, to discuss the evidence and develop recommendations.

Questions and outcomes

This Guideline addressed seven clinically pertinent questions on the diagnosis, and management of PAP that were selected by consensus. Following ERS processes [5], we formulated five questions using the ‘Patient, Intervention, Comparison, Outcome’ (PICO) format, and two narrative questions (NQ). For every question, relevant outcomes were selected based on their importance for clinical practice, in line with the GRADE approach. Only outcomes that were rated critical or important by a majority of panel members were considered for the development of recommendations (See supplementary appendix). PICO questions were informed by formal systematic reviews, meta-

analyses and appraisal of the available evidence, while narrative questions were informed by systematic literature searches.

Literature searches and systematic literature review

An independent librarian designed systematic searches for all questions in collaboration with the chairs and methodologists of the TF (See supplementary appendix). Each question was informed by systematic searches of three online databases, PubMed, EMBASE, and Cochrane Central. Searches were carried out 13th-19th May 2022 and subsequently updated on 9th August 2022. We considered interventional and observational studies addressing any of the PICO and narrative questions. We included all comparative studies and single arm studies including at least five participants. In addition, in anticipation of a weaker evidence-base for children and for PICO questions 5-7, we included case series irrespective of their study populations and case reports. Additional studies such as informative case reports or mechanistic studies that the panel members considered relevant for any of the PICO, and narrative questions but did not fulfil the eligibility criteria are described in the "additional considerations" sections of the Evidence-to-Decision Frameworks (online supplement).

Study screening at a title-abstract and full-text level was independently conducted in Rayyan [7] by at least two members of the TF using predefined inclusion and exclusion criteria. Relevant information about study design, baseline characteristics of the participants, characteristics of interventions, or index tests of interest, as well as the outcomes of interest were extracted in a prospectively designed data extraction form by one and cross-checked by a second panel member for accuracy. Risk of bias of randomised controlled trials (RCTs) was appraised using the Cochrane Risk of Bias tool [8] while the Risk of bias in non-randomised studies of interventions (ROBINS-I) tool was used for observational and non-comparative interventional studies [9], and for case series or reports we used the Joanna Brigg's institute's risk of bias tool for case reports[10]. In line with a protocol that had been prospectively submitted to the ERS guidelines working group, meta-analyses

were performed using random effects models when it was considered meaningful, for PICO questions. The random effects model was selected because of the expected heterogeneity among the included studies. Data from RCTs or quasi-RCTs, comparative observational studies and non-comparative studies were not pooled. Data for the narrative questions were described, in line with the ERS Handbook for Clinical Practice Guidelines[5].

Assessing the certainty of evidence and strength of recommendations

GRADE Evidence profiles were generated for PICO questions informed by comparative studies and Evidence-to-decision (EtD) frameworks were generated for all PICO question, whilst only EtDs were generated for NQs (See supplementary appendix). For PICO questions, the certainty of the body of evidence informing each outcome was appraised using GRADE methodology as very low, low, moderate, or high certainty. Judgements around certainty were informed by the assessment of the risk of bias of the included studies, inconsistency, indirectness, imprecision, and publication bias across the included studies. For NQs, in accordance with the updated ERS guidelines, the approach was narrative. EtD frameworks were used by the panel to formulate recommendations and strength by consensus and/or voting. The recommendations were graded as strong or conditional with key considerations summarised in **Table 2.** In line with GRADE terminology [6], the term "we recommend" was used for strong recommendations and "we suggest" for conditional ones.

A strong recommendation was made for an intervention when the panel was certain that the desirable consequences of the intervention outweighed the undesirable consequences and a strong recommendation against an intervention was made when the opposite was observed in the evidence. A strong recommendation indicates that most patients and healthcare providers would choose to recommend, or not to recommend, the intervention. A conditional recommendation for an intervention was made when the panel was uncertain that the desirable consequences of an intervention outweighed the undesirable consequences in most patients and a conditional recommendation against an intervention was made when the opposite was observed in the

evidence. A conditional recommendation indicates that different patients and healthcare providers may make different choices regarding an intervention. In addition to the recommendations, specific considerations were made regarding individual PICOs. These considerations reflect the TF members current practice and describe their clinical experience. Evidence supporting these comments were provided for each PICO. All recommendations, comments and algorithms were reviewed and approved by the full panel.

Recommendation development

GRADE and EtD frameworks were used for aggregating relevant evidence and considerations around potential benefits and harms of the interventions, certainty of the available evidence, patients' values and preferences, required resources, and considerations around equity, acceptability, feasibility and cost-effectiveness. These frameworks were shared in advance of consensus meetings for panel members to review and the evidence was also presented and discussed during these meetings. Once all panel members, including patient representatives, were satisfied that the information was adequately interpreted, discussed, and reported, recommendations were developed by open voting. A majority vote was sufficient for issuing a conditional recommendation, while an agreement of at least 70% of the participants was required for issuing a strong recommendation.

Panel meetings

For developing this clinical practice guideline, the panel organised four face-to-face meetings (Barcelona, ERS Congress 2022; Essen, October 2022; Paris, July 2023; Milan, ERS Congress 2023) and four videoconferences. The first two meetings were focused on finalising the methodology, PICO questions, outcomes selection, and search strategies. During the latter meetings, the results of systematic reviews and EtD frameworks were discussed, and recommendations were finalised. These meetings were complemented by several online meetings of groups focusing on specific

questions or tasks. Teams consisting of at least two PAP experts, one methodologist and one patient representative were assigned to each clinical question. Teams met virtually and during physical meetings to address the topics At all meetings detailed minutes/notes were kept and shared with all TF members after.

DEFINITIONS OF DISEASE ACTIVITY, SEVERITY AND PROGRESSION

General considerations

To provide structured management recommendations, the TF panel has summarised clinical definitions for the benefit of the reader, based on the available literature and the experience of PAP reference centres.

Disease activity

PAP is characterised by progressive accumulation of surfactant in pulmonary alveoli resulting in hypoxemic respiratory insufficiency or failure. PAP is considered active in the presence of (a) continuous or progressive symptom(s) such as dyspnea, cough, sputum production, chest pain, weight loss, and/or (b) lung function decline in forced vital capacity (FVC) or diffusing capacity of carbon monoxide (DLco), and/or (c) hypoxaemia measured by arterial blood gas (PaO_2, SaO_2, $AaDO_2$), and/or (d) new or worsening PAP-characteristic infiltrates on high resolution CT (HRCT), including but not limited to ground glass and crazy paving. Alternative causes or complications like respiratory infections, pulmonary embolism, pulmonary hypertension, and congestive cardiac failure should be excluded.

Disease severity

A disease severity score was proposed in 2008 [2] and is based on symptoms and PaO2 levels. [11]. This score is easy to calculate and has been used to stratify patients in clinical trials [12, 13]. Further scores which include smoking status and HRCT findings have been proposed and showed good

correlation with prognosis[14]. It remains unclear whether opportunistic infections should be considered an indicator of disease severity or simply a complication [1]. A second opinion from a PAP reference centre can be of assistance in patient assessment, determining if the disease is active, and to ascertain management options.

Disease progression

There is no standard definition of disease progression for PAP, however it is widely considered to be the worsening of respiratory symptoms, decline in lung function tests (FVC, DLco), onset or worsening of respiratory failure including need for oxygen treatment, and worsening of PAP-related CT findings after careful exclusions of other causes. Based on previous observational studies [15-17] and clinical trials [12, 13], DLco and $AaDO_2$ maybe the most sensitive markers of disease progression [1, 18]. Due to the paucity of data, specific thresholds for decline in lung function tests or blood gas parameters to define disease progression are not available. The reduction of time interval between subsequent whole lung lavage (WLL) procedures has also been used as an indicator of disease progression in PAP (10, 12). Disease progression should always be confirmed by HRCT and to ensure no alternative processes are ongoing. Pulmonary fibrosis, which occurs at varying frequency but can affect up to 20% of PAP patients [19], should be considered as a sign of progressive disease. In this case, disease progression can tentatively be further assessed by using the progressive pulmonary fibrosis (PPF) definition from the 2022 ATS/ERS guidelines [20], however the use of these criteria for PAP awaits validation.

RECOMMENDATIONS

The search strategies, PRISMA flow diagrams, included studies, risk of bias assessments, meta-analyses, evidence profiles, and evidence-to-decision frameworks for all questions are available in the online appendix. Recommendations around individual interventions and the evidence supporting

these are presented first, followed by a proposed algorithm for the differential diagnosis of PAP (Figure 2) and a hierarchy of treatment in aPAP (Figure 3).

Question 1a (NQ)

When should patients with clinical and radiological features consistent with a diagnosis of PAP undergo bronchoalveolar lavage (BAL)?

Recommendation

We recommend that BAL be performed as part of the diagnostic work up of patients with suspected PAP. BAL should include differential cell count, periodic-acid-Schiff (*PAS*)*-staining, and microbiology (strong recommendation, very low certainty).*

Justification of recommendations

The justification for the strong recommendation for BAL is based on the perceived benefit of a clear diagnosis on PAS staining without the need for more invasive tests and the low risk of complications. BAL is a low-risk technique that allows for the direct sampling of the cellular and acellular components in the distal airways and alveoli. The usefulness of BAL for identifying the presence of PAP has been reported in several studies. Ilkovich reported 68 patients with idiopathic PAP where BAL fluid (BALF) was reported as milky white, opalescent, with white material after sedimentation. Cytology revealed amorphous and granular eosinophilic masses mixed with alveolar macrophages [21]. BALF cellularity in PAP patients is often increased with a predominance of lymphocytes and cytological examination of the BALF shows foamy macrophages which contain eosinophilic granules and amorphic material that stains PAS-positive; tubular myelin like lamellar bodies are seen on electron microscopy [22]. Bonella *et al* reported on 70 patients where BAL was performed in 83%. [23]. In a study of 150 patients (86 with aPAP), Azuma *et al* report diagnostic yields of 90.7% (78/86) for BAL, 81.4% (70/86) for transbronchial biopsy (TBB) and 98.8% (85/86) for the combination. [24]

In children, the yield of BAL to diagnose PAP is good; Enaud *et al* reported that the diagnosis was made by BALF examination for 15 children [25].

BAL is decisive to exclude pulmonary infections, which, along with systemic infections, can complicate PAP of all forms, accounting for approximately 20% of mortality [26]. Opportunistic infections (particularly *Nocardia* spp., Mycobacteria, and fungi) are associated with worse prognosis and higher risk of mortality [27]. Most adverse events of BAL are closely related to endoscopic technique, location, and extent of lavaged lung area, volume and temperature of instilled fluid [28].

Practical considerations

BAL including PAS staining and microbiology is a simple technique that can be done in most centres performing bronchoscopy. Patient representatives expressed preference for a test that allowed for a quick diagnosis without the need of more aggressive interventions like a biopsy.

Question 1b (NQ)

When should patients with clinical and radiological features consistent with a diagnosis of PAP undergo lung biopsy for histologic analysis?

Recommendation:

We suggest to not routinely perform lung biopsy as part of the diagnostic work up of patients with suspected PAP (conditional recommendation, moderate certainty).

Justification of recommendations

The justification for the conditional recommendations is based on the known risk of side-effects and the perceived low benefit of a clear diagnosis from this invasive test. Rosen *et al* first described the lung histology in PAP, and found preserved interalveolar septa with lipoproteinaceous material filling the alveoli and some bronchioles [29]. Examination of surgical lung biopsies demonstrated preserved

lung parenchyma with peribronchial lymphocytic infiltrations and alveoli filled with macrophages and amorphic eosinophilic PAS-positive material [30, 31]. Immunohistochemical staining of this material confirmed surfactant protein [30]. Lung biopsy was previously routinely used for diagnosis of PAP, although is not necessary in every patient. [30] Inoue *et al* reported that lung biopsy confirmed the diagnosis of PAP in 102/223 cases [2]. Where biopsy is needed, some case series have shown increasing use of TBB [32-35] with a diagnostic yield of 81.4% [35]. Other studies report higher use of surgical biopsy [21, 36, 37] and there are limited reports on the use of transbronchial cryobiopsy for diagnosing PAP [38].

While biopsy was previously considered the gold standard for diagnosing PAP, histological examination may also fail to identify the presence of PAP syndrome as seen in a study from the US National PAP Registry where histology was non-diagnostic in 28% of cases because of patchy involvement [36]. The authors conclude that any lung biopsy should only be performed in the rare situations in which the cause of PAP remains uncertain after completing BAL, non-invasive serologic, blood-based, and genetic tests [36].

Practical considerations

Lung biopsy is an invasive technique that may fail to diagnose PAP due to sampling error, has known risk of complications and a mortality risk [39]. Some hospitals do not have access to services providing lung biopsies. Patient representatives expressed preference for a test that allowed for a quick diagnosis without the need of more invasive interventions. If lung biopsy is considered, benefits and limitations of the least invasive procedure should be discussed with patients, based on benefit/risk assessment and an expert PAP centre.

Question 2 (NQ)

When should patients with clinical and radiological features consistent with PAP undergo GM-CSF antibody testing for diagnosing autoimmune PAP?

Recommendation

We recommend GM-CSF antibody testing for diagnosing autoimmune PAP for all patients with suspected or confirmed PAP syndrome (strong recommendation, moderate certainty).

Summary of evidence

A systematic search of the available evidence revealed a large observational study comprising 248 patients [2], three methodology papers [40-42], and multiple real-world observational studies [4, 30, 36, 43, 44] focused on the use of GM-CSF autoantibody testing in PAP. Taken together, these studies established that GM-CSF autoantibodies can be measured in an objective and reproducible manner with a high accuracy for a diagnosis of aPAP with a level of 10.2µg/ml or above the threshold of individual laboratory references (see supplement Pg.148) [4, 40, 42]. The largest study describes the use of GM-CSF autoantibody testing in 248 patients with a lung biopsy confirming a diagnosis of PAP [2]. Of this cohort, 89.9% of the patients had no underlying condition or cause to explain why they developed PAP and subsequently all these patients had elevated GM-CSF autoantibody levels [2]. In another observational study [43], GM-CSF autoantibody levels were described in 70 patients with PAP and was positive in the 64 individuals who had “idiopathic” PAP.

Justification of recommendations

The certainty of the available evidence has been ranked moderate despite the high sensitivity, specificity, and reproducibility of the GM-CSF autoantibody testing and its successful use in real-world cohorts [2, 4, 36, 40, 42, 43].

GM-CSF autoantibodies have been determined to be pathogenic of aPAP. Early data showed that GM-CSF deficient mice were found to accumulate surfactant in the lungs and cause a PAP-like disease [45, 46] and GM-CSF autoantibodies were found in BALF from patients with what was known at the time as “idiopathic” PAP [41, 47]. It was also demonstrated that GM-CSF autoantibodies reproduced the molecular, cellular, and histopathologic features of PAP in healthy primates, demonstrating that GM-CSF autoantibodies directly cause PAP [48, 49]. GM-CSF autoantibody

testing in the form of a simple blood test is pathognomonic for the diagnosis of aPAP, which accounts for almost 90% of all cases of PAP. More recently, studies have shown that a combination of GM-CSF antibody testing and genetic testing for hereditary causes can achieve a diagnosis in 95% of patients without a biopsy [42, 50, 51]. In these scenarios, this testing precludes the need for invasive lung biopsy. As further evidence of GM-CSF autoantibodies being the main mechanism of disease in aPAP, treatments acting on this specific mechanism such as inhaled GM-CSF and rituximab have successfully been used to treat this disease. This supports the testing of GM-CSF autoantibodies in all suspected patients with PAP. This non-invasive test with minimal risk outweighs the risk of not testing for aPAP.

Practical considerations

It is important to ensure that the appropriate test is performed to assess levels of GM-CSF antibody titres, and not just the presence of antibodies alone. A positive or negative antibody test is insufficient to diagnose aPAP. Concentration should be reported, and this is best performed in experienced laboratories (See supplementary appendix). All cases should be referred or discussed with a recognised PAP centre to get advice on which laboratory to test in and appropriate interpretation of results, especially before proceeding to more invasive procedures.

Question 3 (PICO)

In patients with clinical symptoms and/or functional impairment due to PAP should whole lung lavage be used versus to no whole lung lavage?

Recommendation

We recommend performing bilateral whole lung lavage in patients with autoimmune PAP with evidence of gas exchange impairment and either symptoms, or functional impairment (strong recommendation, very low certainty of evidence).

No recommendation for or against whole lung lavage in other PAP types can be made due to lack of evidence. We suggest seeking advice from an expert centre on an individual case basis.

Summary of evidence

Since WLL was first performed in 1964, it has been the most common treatment for patients with PAP [52]. There are no specific guidelines for the procedure itself and indications to perform a WLL vary between centres [53]. Briefly, WLL is done under general anaesthesia and intubation is performed using a double lumen endotracheal tube to ventilate one lung while washing the other with several litres of saline (See supplementary appendix) [53-55]. The main indications for WLL were decline in lung function and/or resting PaO2, and an increase in respiratory symptoms or parenchymal abnormalities on CT. The most common complications reported were fever (18%), pneumonia (5%), fluid leakage (4%) and pneumothorax (0.8%). Extracorporeal membrane oxygenation (ECMO) can be used to support severely ill PAP patients undergoing WLL, as anecdotally reported [56].

Systematic searches identified 26 retrospective case series each describing 5 or more patients who had at least one unilateral or bilateral WLL (See supplementary appendix). The median study population in the 26 selected studies was 14 patients (IQR: 8-21). Twenty series included adults only, five included both children and adults and one study described the experience in children alone. Effects in children seemed similar to those observed in adults.

There was low certainty evidence suggesting that WLL improves respiratory symptoms when compared to pre-WLL symptom burden. While we were not able to pool data from all of the included studies due to limitations, six of the ten studies reporting on symptoms showed a moderate or significant symptomatic improvement in all participants [57-62], while the remaining four studies reported symptomatic improvement in 68-90% of participants [16, 17, 63, 64]. Two studies measuring exercise capacity reported increases in walking distance of 101m in the 6MWT (95% CI 66.35, 136.05) and 417m using a treadmill (95% CI 235, 598). The certainty of evidence was low and very low, respectively. There was low certainty evidence to suggest an improvement in PaO2

within a month of WLL (20.07mmHg [95% CI 9.54, 30.60], I2=92%) and within months to years of WLL (13.98mmHg [95% CI 10.15, 17.80], I2= 35%). Moreover, a trend towards improved $AaDO_2$was observed post-WLL (-14.87mmHg [-32.44, 2.70], I2=16%, very low certainty), with a clear improvement at longer follow-up (-21.33 mmHg [-26.99, -15.66], I2=11%, low certainty). No clear improvement was observed in FVC at short (8.54% [-8.22, 25.29], I2 = 96%), or longer follow-up (5.43% [-0.67, 11.53]), low certainty of evidence.

Justification of recommendations

There is a lack of RCTs to define the exact effect of WLL on symptoms or pulmonary function tests in patients with a diagnosis of PAP. However, there is moderate certainty of evidence that WLL improves pulmonary function and low certainty evidence that it improves symptoms and exercise capacity over time and, reassuringly, minimal serious short term adverse events or mortality issues reported in the post WLL period. The clinical practice guidelines development group, based on their clinical experience and input from patient representatives consider that most patients would consider that the potential benefits of WLL as a rescue therapy in case of symptoms and hypoxia that are refractory to other treatments or as a bridging therapy to other treatments outweigh the potential risks. Bilateral WLL is suggested as both lungs are affected almost universally.

Practical considerations

It is important to state that possible treatment indications for PAP should be discussed with a recognised PAP centre with experience in performing WLL as there is no standardised protocol for WLL at now. From a patient perspective, the main advantage of WLL, if clinically indicated, is the fact that it can be a stand-alone treatment with reasonably quick recovery and there is no need for daily medication. Some disadvantages reported include the need for hospitalisation, costs, and the need to travel, sometimes long distances, when there is no nearby expert centre. WLL is not available in all countries hampering accessibility for some patients. WLL is an invasive procedure, with a risk of complications such as fever, pneumonia, or pneumothorax.

Question 4 (PICO)

In patients with confirmed autoimmune PAP should exogenous GM-CSF be used versus no exogenous GM-CSF?

Recommendation

We recommend inhaled GM-CSF for symptomatic patients with confirmed autoimmune PAP. (Strong recommendation for the intervention; very low certainty of evidence).

Summary of evidence

Systematic searches revealed three RCTs [12, 13, 65], one comparative observational study and seven observational, non-comparative studies on exogenous GM-CSF for patients with confirmed aPAP [15, 66-72]. All studies included adult patients with aPAP confirmed by the presence of high GM-CSF autoantibody titres. In the PAGE trial [12], 64 patients with mild to moderate aPAP were randomised to intermittent inhaled GM-CSF [sargramostim 125µg BD every other week] or placebo for 25 weeks. Patients who underwent WLL within the previous six months or those who had severe disease (PaO2 <50mmHg) were excluded. In the IMPALA trial [13], 138 patients were randomised to continuous inhaled GM-CSF [molgramostim 300µg OD], or intermittent GM-CSF [300µg OD every other week] or placebo for 24 weeks. The 24-week intervention period was followed by an open-label treatment-extension period with intermittent treatment. Patients who underwent WLL within the previous month were excluded. In an open-label RCT [65], 36 patients were randomised to intermittent inhaled GM-CSF [sargramostim 150µg BD every other week for 3 months, then 150µg OD every other week for 3 months] or placebo for 26 weeks. Patients who had undergone a WLL in the three months prior were excluded. The above mentioned RCTs were the main source of evidence, and data were pooled for intermittent, inhaled GM-CSF at approximately six months after treatment initiation. Evidence suggests that compared to placebo, intermittent, inhaled GM-CSF reduces $AaDO_2$with a (MD) of -4.36 mmHg (95% [95%CI] -7.71; 1.01), improves the PaO2 with a

MD of 4.47 mmHg (95%CI 1.16; 7.78) and the DLCO with an absolute change (MD) of 4.05% (95%CI 0.23; 7.88). Further evidence is provided for either beneficial or no beneficial effects regarding 6MWT distance in metres (MD 14.53 m (95%CI -17.5; 46.6)), VC or FVC (MD 2.08% (95%CI -0.6; 4.8)), lung density in HRCT (MD -20.82 HU (95%CI -48.7; 7.0)), and symptoms when measured by SGRQ symptoms domain (MD -6.94 points (95%CI -19.2; 5.3)). The PAGE trial also assessed symptoms by measuring CAT and mMRC [15]. CAT was estimated to be higher in those treated with GM-CSF (MD 3.91 points, 95% CI 0.44; 7.38) and mMRC was estimated to be lower (MD -0.4 points, 95% CI -0.7; -0.2). Trivial, adverse events were reported [12, 13, 65]. No mortality events were observed in any of the trials.

Eight observational studies with a total of 156 included patients evaluating either inhaled [15, 67, 69, 71, 72] or subcutaneous GM-CSF were included [66, 68, 70]. In 2010, the first prospective, multicentre, phase II trial was published, examining 39 aPAP patients with a PaO2 of <75mmHg. The patients sequentially received a 12-week high-dose therapy with inhaled GM-CSF (sargramostin 250μg for 8 days, no treatment for 6 days), followed by a 12-week low-dose therapy (125μg for 4 days, no treatment for 10 days), and a follow-up period of 52 weeks [15]. Individuals were excluded if they had undergone WLL within 6 months prior to enrolment. The study demonstrated that the overall response rate was 62% at 6 months, response being defined as reduction in $AaDO_2$ by at least 10mmHg at the end of the low-dose period; the response was maintained in 83% of patients for 1 year without the need for additional therapy and treatment was safe [15]. Four years later, the long-term effects of intermittent inhaled GM-CSF during a 30-month observation period were reported in the same population [15, 72], There was sustained remission of PAP in >50% of cases [72]. In 2014, a case series of six patients with PAP also showed promising long-term results by the application of the “as far as it takes protocol”, minimizing both disease burden and treatment costs in safety [69]. Finally, an observational study compared WLL alone with a combination of WLL followed by inhaled GM-CSF for 3 months in a total of 33 patients with severe aPAP [71]. The GM-CSF/WLL group had significantly faster functional, exercise capacity and radiological improvement

as well as reduction in the need for WLL compared with the WLL alone group [71]. Additional studies include two case series in adult patients [73, 74] as well as four case series in children and young adolescents with documented aPAP [75-78] (See supplementary appendix). Paediatric studies reported beneficial effects in 5/7 children and young adolescents treated with inhaled GM-CSF either alone (n=1) or in combination with WLL (n=4).

Justification of recommendations

The beneficial outcomes of inhaled GM-CSF treatment reported in all clinical trials regarding physiological, functional, clinical, and radiological outcomes in combination with the safety and non-invasiveness of this treatment modality justify the strong recommendation for inhaled GM-CSF for symptomatic patients with confirmed aPAP despite a very low certainty of evidence. The very low certainty of evidence relates mostly to the limited number of patients related to the rarity of the disease and the very limited number of recently published RCTs, most studies being observational, retrospective studies and case reports/series.

Practical considerations

GM-CSF administration may prevent or delay the next WLL, an expensive intervention that requires hospital admission and general anaesthesia. Patients with PAP often require regular WLL, sometimes monthly. The sustained benefits of inhaled GM-CSF for longer periods might minimize the need for repeated WLL, and the costs related to this procedure [65, 69, 72]. Serious adverse events (SAE) were not more common in the GM-CSF arms as compared to the placebo arms in the included RCTs. Treatment can therefore be considered safe and non-invasive, and we believe that acceptability will be high. Treatment with inhaled GM-CSF can potentially be administered at home or at local health institutions, which increases equity.

Question 5 (PICO)

In patients with confirmed autoimmune PAP should rituximab be used versus no immunosuppressive treatment?

Recommendation

We suggest the use of rituximab for patients with confirmed autoimmune PAP who remain symptomatic, requiring supplemental oxygen, despite whole lung lavage therapy or exogenous GM-CSF treatment (conditional recommendation, very low certainty).

Summary of evidence.

A systematic search revealed a single arm interventional study involving ten patients [79], a retrospective case series of 13 patients [80] and seven case reports. [81-87]. All studies and case reports evaluated adults with aPAP. Most patients included in the studies had undergone WLL and/or GM-CSF treatment prior to recruitment. Studies by both Kavuru and Soyez compared the clinical status of patients 6-12 months after rituximab treatment to baseline [79, 80], hence, the data were pooled together. Participants in both studies received two doses of rituximab 1,000 mg, administered 15 days apart. One patient in the observational study only received a single dose, while three received an additional, maintenance dose. There was very low certainty evidence suggesting that rituximab may reduce the $AaDO_2$ (MD -11.83 mmHg [-23.76, 0.10 mmHg]) and improve the partial concentration of oxygen measured on room air (MD 11.94 [-4.17, 28.05] mmHg). In addition, very low certainty evidence suggests no substantial impact of rituximab on DLCO, (MD 15.64% [9.08%, 22.21%] predicted, I2 =0%), FVC (MD 2.65% [-4.17%, 9.48%] predicted) or 6MWT (MD 19 [-93.47, 131.47] meters) [91][92]. Kavuru *et al* reported that 4/7 patients that were observed for a mean of 32 (±6) months did not require WLL [79]. The remaining three patients required one WLL each during follow-up. Soyez *et al* 2018 report 4/11 patients exerted significant improvement at 12 months [80], compared to baseline. Improvement was defined as a decrease in the $AaDO_2$ by at least 10mmHg. Kavuru *et al* also reported a significant improvement in the HRCT scores ($p = 0.027$) [79], which was, however, not observed by Soyez [80]. No deaths or serious adverse events were observed in these studies. However, the results should be interpreted carefully, as the sample size of the included studies was limited, and they were not controlled. Five of seven case reports documented a clinically relevant improvement at various timepoints after rituximab initiation (3-12 months). Benefits included

better oxygenation, improved exercise capacity, reduction in frequency of WLL, and/or improvement in pulmonary function. Only one of the case reports addressed safety and it did not report any serious adverse events. Two of seven cases (28.6%) did not gain any benefits from rituximab.

Justification of recommendation

The certainty of the available evidence is very low for all outcomes. There was very low certainty evidence suggesting that rituximab may reduce $AaDO_2$, DLCO or 6MWT There are serious concerns around the methodological limitations of these small single-arm uncontrolled studies.

Practical considerations

While the safety of rituximab has not been adequately assessed in patients with aPAP, ample data are available from other disease areas. More specifically, the safety profile of rituximab at a similar dose (two doses of 1,000 mg) in adults has been evaluated in more detail in a Cochrane review evaluating rituximab in rheumatoid arthritis [88]. (See supplementary appendix for details of dosing) The addition of rituximab was not associated with increased risk of serious adverse events, at 48-56 weeks follow-up, or at 104 weeks follow-up. Rituximab was associated with a trend of increased discontinuation due to adverse events during the first six months, this trend disappeared at 1 year follow-up and was reverted at longer follow-up. In children, the safety of rituximab at a dose of 1-4 infusions of 375mg/m^2 has been assessed in more detail in a meta-analysis evaluating rituximab for childhood steroid-dependent nephrotic syndrome. This meta-analysis did not reveal any increase in the risk of infections, or cardiovascular disease events, but found a trend for increased risk of infusion reactions. The authors reported that the rate of severe allergic reactions in children was very low [89].

Question 6 (PICO)

In patients with confirmed autoimmune PAP should plasmapheresis be used versus no plasmapheresis?

Recommendation

We suggest the use of plasmapheresis for patients with confirmed autoimmune PAP who remain symptomatic, requiring high flow of supplemental oxygen (≥4L /min) or two or more WLL over a period of a year, despite receiving exogenous GM-CSF and rituximab, or having previously failed these treatments (conditional recommendation, very low certainty).

Summary of evidence

The systematic search included only nine case reports [77, 85, 86, 90-95] and no RCTs or observational studies on the role of plasmapheresis in aPAP. Only one case report described the use of plasmapheresis in an adolescent with aPAP, while all other cases were adults. The duration of the disease was variable; from 4 to 120 months (median 12 months). One of the patients was not tested for GM-CSF autoantibodies [94]. Patients all presented with severe disease: all but one was receiving supplemental oxygen therapy up to 8L/minute, and one patient was intubated receiving 60-75% FiO2. All had persisting symptoms and had undergone several WLL prior to treatment with plasmapheresis. Four of nine patients had WLL and exogenous GM-CSF and one had WLL, exogenous GM-CSF and Rituximab prior to plasmapheresis. Thus, plasmapheresis was used in patients with severe PAP, refractory to other treatments. No relevant clinical benefits were observed in three of the reported cases [85, 91, 95]. Yu *et al* [94] reported improved clinical symptoms and radiological findings, which were however short-lived, as relapse was observed five months later. Luisetti *et al* [93] reported a reduced frequency of WLL after plasmapheresis, but no clear improvement in the symptoms after plasmapheresis. Finally, four cases reported clear improvement in the symptoms [77, 86, 90, 92], oxygenation, radiological findings and/or pulmonary function [77, 91]. A clear reduction in the GM-CSF antibody titres was reported in 5/9 cases [79, 86, 90, 93]. Rituximab was also administered after completion of plasmapheresis in two case reports, that only reported effects after both treatments were administered [77, 86]. It appears that higher intensity

plasmapheresis regimens successfully suppress GM-CSF autoantibodies and may offer clinical benefit.

Justification of recommendation

The certainty of evidence is very low arising from case reports only. Spontaneous remission is observed in some patients with PAP and therefore, a treatment effect cannot confidently be established based on the available case reports. In addition, the reported outcomes were mostly subjective and not based on a validated measurement instrument.

Practical considerations

The safety of plasmapheresis was evaluated in detail in a Cochrane review of the effectiveness of plasmapheresis for Guillain-Barre disease [96]. Based on data from three trials totalling 556 participants, plasmapheresis did not increase the risk of infection (RR 0.91 [0.73, 1.13]), of blood pressure instability (RR 0.88 [0.64, 1.22]), cardiac arrhythmias (RR 0.75 [0.56, 1.00]), or pulmonary embolism (RR 1.01 [0.26, 4.00]). However, it should be noted that the included studies employed 2-6 sessions of plasmapheresis, a lower number compared to those proposed for aPAP. The mortality associated with plasmapheresis has been estimated to be 0.05%, based on a systematic review meta-analysis of >15,500 patients, mainly adults [97]. The complications of >4,500 sessions of plasmapheresis in 593 children with neurological disease have been summarised in a narrative review [98], that concluded that the intervention is well-tolerated and associated with adverse events that can be anticipated and avoided. Complications were reported in 15% of plasmapheresis sessions and 70% of children. However, life-threatening complications were limited to 0.4% of treatment sessions and 2.4% of children. The patient representatives consider that potential prevention of WLL and improvement in the hypoxia may be considered important by patients with aPAP that is refractory to treatment and associated with a significant disease burden.

Question 7 (PICO)

In patients with PAP progressing despite whole lung lavage or pharmacological treatment should lung transplantation be considered versus no lung transplantation?

Recommendation

We suggest lung transplantation for patients with PAP progressing despite whole lung lavage and/or pharmacological treatment, who fulfil the International Society for Heart and Lung Transplantation (ISHLT) criteria for patients with interstitial lung disease (conditional recommendation, very low certainty of evidence).

Summary of evidence

Data regarding lung transplantation in patients with PAP is derived from 14 individual case reports, 9 adults and 5 children. Causes of PAP included graft vs host disease (2 cases [99, 100]), aPAP (4 cases [101-104]), hereditary PAP (2 cases [105, 106]) and lysinuric protein intolerance (*SLC7A7* mutation, 1 case [107]). Causes were not reported in 5 cases [108-111]. Median duration of follow-up was 3 years [range 0.2 to 7]. Two patients died, one 4 years after lung transplantation in the context of recurrence of PAP, fungal infection and bronchiolitis obliterans syndrome (BOS) [106], and one 2 years after lung transplantation in the context of recurrence of PAP [107]. For the remaining patients with outcome data (n=11), the desirable effects of lung transplantation were quantified based on durable wean from oxygen, lung function and quality of life (QoL) at last follow-up. Nine patients were weaned from oxygen after transplantation, one was still on home oxygen and data was missing for one. Lung function among patients alive at last follow-up was reported to be improved in five, stable in one, and not available in five. The reported QoL among alive patients was good in 10/11. Among the 13 patients with post-lung transplantation data available, adverse events were mainly infections (9/13), post-transplant lymphoproliferative disease (PTLD) was observed in two cases [103, 110] and BOS in two cases [106, 109]. Graft rejection was not reported. Recurrence of PAP on the transplant was reported in 3 cases. In these patients, the cause of the PAP was *CSF2RB* mutation in one, *SLC7A7* mutations in one and unknown in the last case. Twelve additional

paediatric cases were recorded in a report on the outcome of 190 children after lung transplantation; no causes of PAP and individual patient data were available. Survival and complications were not different from transplant for other diseases [112]. A query was made at the registry of the ISHLT. Of 101 patients reported by ISHLT with different forms of PAP and lung transplant, 43 had died at the end of the observation period. In none of the patients the diagnosis “Graft Failure: Recurrent Disease” was noted. Thus, no relapses of PAP in the transplanted patients were noted leading to graft failure.

Justification of recommendation

Available data favour the conditional recommendation of lung transplantation in end-stage and refractory PAP, i.e. progressive PAP despite all treatments, because lung transplantation reversed chronic hypoxic respiratory failure in all but one reported case.

Practical considerations

In treatment-refractory PAP, with or without pulmonary fibrosis and likely death within a few years, lung transplant, associated with life-long medication and medical treatment/surveillance is an alternative that can improve QoL [113]. Indeed, many patients consider lung transplantation for palliation of symptoms and improvement of QoL even when extended survival is not assured [113]. However, there are always few people who reject an offer of transplantation and wish palliative care [114]. A scoping review identified 28 studies in adults and made cost-utility estimates of lung transplantation versus waitlist, from the healthcare payer perspective. For a time-horizon of at least 10-years costs ranged between $42,459 and $154,051 per quality-adjusted life year [115]. The costs of care for patients with end-stage lung disease and chronic respiratory insufficiency should be balanced with the costs of care of hospitalisation for lung transplantation including stays in surgery and ICU and lifelong costs for medications and care [115].

In patients with PAP progressing despite WLL and/or pharmacological treatment, an important issue is to estimate the risk of recurrence of the PAP in the donor lung(s). However, it is not yet known if there is a correlation between the risk of disease recurrence and cause of PAP. In aPAP, the risk of recurrence exists as the production of GM-CSF autoantibodies may persist after lung transplantation. This might be balanced with the possible effect of immunosuppressive treatments required after organ transplantation on autoimmune processes. In genetically caused PAP, the replacement of donor macrophages in the transplanted lung by the host macrophages of patients with genetically caused PAP may increase recurrence risk of PAP in the donor lungs. Fortunately, the persistence of donor macrophages within the lungs has been reported in several cases with follow-up durations of up to 3.5 years post-lung transplantation [116]. Currently, the risk of recurrence of PAP on the graft is a difficult issue to address and not a contra-indication for lung transplantation. Some rare genetically caused PAP (*CSF2RA* or *CSF2RB* defects, *OAS1* defects, etc.) may be treated with bone marrow transplant (BMT), if the lung has no fibrotic non-reversible damages (see supplementary appendix for specific details). In hereditary PAP due to mutations in the *CSF2RA or CSF2RB* genes and progressive PAP progressing despite all treatments, another theoretical possibility would be to consider the combination of lung transplantation and BMT.

Treatment Hierarchy

Treatment is indicated in patients with active or worsening disease, as defined earlier. The appropriateness of treatment should be based on the degree of impairment of lung function, CT imaging changes, blood oxygenation and QoL. If no respiratory failure or life-threatening complications are present, and the patient still has an acceptable QoL, a *wait and see* strategy can be justified. In a survey of 20 PAP centres practising WLL, indications for WLL varied among centres [53]. Specific indications included an unspecified decline in lung function, a decline in resting PaO2, worsening of lung disease severity based on a comparison of serial chest imaging, decline in DLco, decline in FVC, decline in resting oxygen saturation on pulse oximetry (SpO2) or an increase in

respiratory symptoms. The inclusion criteria in the RCTs of inhaled GM-CSF for aPAP were variable in terms of disease activity. In the PAGE trial, patients were eligible to receive treatment if PaO2 was <70 mm Hg after 5 minutes in the supine position while breathing ambient air, or <75 mm Hg, and at least one symptom (cough, sputum production, or exertional dyspnea) was present [12]. In the IMPALA trial, inclusion criteria were stable or progressive aPAP during a minimum period of two months prior to the baseline visit, PaO2 <75 mmHg at rest, or desaturation of >4% in a 6MWT, and an $AaDO_2$ of ≥25 mmHg [13]. The TF panel recognises the need for more research in this field and of an international consensus on treatment indication criteria. The proposed hierarchy of treatment in aPAP, illustrated in Figure 3, is based on consensus among the panel members that was informed by (a) the strength of recommendations in PICOs 3-7, with a focus on the potential benefits, risks and resources required for the corresponding interventions, (b) the certainty of evidence supporting those PICOs, and (c) current clinical practice.

Treatment response

There are no standard criteria defining treatment response. Treatment goals in PAP are to achieve either disease regression or long-term disease stabilisation, without the need for repeated WLL. In the reports on the efficacy of WLL, changes in blood gas parameters and radiological improvement have been used to assess response [53, 117]. In RCTs of GM-CSF, $AaDO_2$ while breathing room air was chosen as the primary outcome, whereas improvements in DLco and HRCT infiltrates were secondary outcomes [12, 13] The magnitude of improvement in these, and other, RCT outcomes has been reviewed by our TF and is outlined in the summary of evidence in PICO 2 above. Changes in QoL and/or symptoms of patients with a diagnosis of PAP have been anecdotally reported in retrospective studies and RCTs of inhaled GM-CSF [12, 13], although these studies rely on respiratory questionnaires which are nonspecific for PAP. Although several circulating biomarkers, like KL-6, SP-D, LDH, YKL-40, tumor tissue antigens [43, 66, 118-123], seem to be promising for assessing treatment response, validation studies are needed. The TF panel recognises the usefulness of lung function tests and blood gas parameters to define treatment response but does

not indicate specific thresholds of decline or improvement. Beside functional assessment, a careful evaluation of symptoms and radiological changes over an appropriate follow-up (at least 6 months) is suggested.

Refractory disease

Refractory PAP can be defined by persistence or worsening of respiratory symptoms, lung function or gas exchange impairment, and HRCT infiltrates despite adequate treatment and after appropriate follow-up (~6 months). Post interventional complications should be excluded as a reason of treatment failure. The need of repeated WLL over time and the reduction of the time interval between two consecutive WLLs has been used as indicators of unresponsiveness to treatment [13, 124], but the studies are too heterogeneous to draw conclusions. The same is true for circulating and genetic biomarkers [125]. The TF panel suggests a careful and close evaluation of the patients after treatment, aimed at assessing disease activity, and to exclude immediate or long-term treatment complications or concomitant diseases as causes of treatment failure.

Discussion

The diagnosis and management of PAP are challenging. The prerequisite of an appropriate treatment is the differentiation of each PAP causing disease through a standardised diagnostic approach, which is still lacking. In this guideline we recommend using BAL, but not lung biopsy, to confirm clinical and radiological suspected PAP (**Figure 2**). GM-CSF autoantibody testing has been recognised by the authors as the most sensitive and specific test for diagnosing aPAP. If GM-CSF autoantibodies are not present at sufficient concentration to cause PAP, further diagnostic tests to assess GM-CSF signalling, like those using neutrophils flow cytometry, or the presence of underlying genetic mutations are needed [1]. Due to the heterogeneity of causes of PAP apart from aPAP, it was out of the scope of the current guideline to make specific recommendations on single diagnostic tests for the other forms. Nonetheless, this guideline suggests the timely referral of patients with unclassified PAP to reference centers to avoid further delay in diagnosis and access to care.

In terms of disease outcome, ~7% of patients diagnosed with PAP have spontaneous remission and never require treatment[1]. In this guideline, we propose that patients are treated in cases of respiratory failure, lung function impairment or symptoms leading to disrupted QoL. Despite increasing evidence for DLco, HRCT infiltrates and blood gas parameters as treatment indicators, the authors strongly suggest considering multiple aspects at once, including patient needs. This concept has become readily accepted in clinical practice of expert centres [125]. For most PAP patients, treatment with WLL translates into rapid improvement of symptoms, gas exchange and radiology[126]. However, the paucity of data does not allow conclusions to be drawn regarding the long term effects of WLL [127]. Similarly, the evidence for effectiveness of treatment, especially in relation to QoL is weak, since no validated instruments for PAP patients exist [125]. The authors were able to provide a positive recommendation for WLL in adult patients with aPAP, since most studies have focused on adult disease [53, 128, 129]. Nonetheless, the authors included special considerations for the management of PAP in children, based on small and mostly single centre observational studies, or case series.

Inhaled GM-CSF, the only treatment investigated in RCTs of adult patients aPAP, received a strong recommendation, whereas the certainty of evidence was graded as very low. Due to the heterogeneous endpoints and trial design, a *head to head* comparison of molgramostim and sargramostim is currently not feasible[12, 13]. For completeness' sake, we mention that sargramostim for inhalation 250 mcg has recently been approved in Japan to treat aPAP [130]. Beside the need of further long-term data on efficacy of inhaled GM-CSF, the authors underscore the unmet need of PAP-specific endpoints and more standardized administration protocols for the clinical routine and future clinical trials. Despite the results of a recent trial [128] examining whether WLL and inhaled GM-CSF should be combined into specific protocols with *add on* or sequential administration, this remains a question relevant to futures studies.

The committee emphasise that strong recommendations are made on several questions despite low certainty of evidence, however this is based on the observed effects and feasibility of the intervention

studied. This guideline has several limitations. Firstly, the diagnostic recommendations provided by this guideline refer to an ideal situation in which all procedures or tests are available. Few centres offer GM-CSF antibody measurement, GM-CSF signalling assessment or genetic testing, and early referral to a PAP expertise centre or network is mandatory. Secondly, despite the authors´ efforts to provide definitions of disease severity and progression, as well as treatment indications, they mostly remain based on a case-by-case approach and expert opinion. Thirdly, measurements of response to treatments are still too heterogeneous across observational studies and RCTs, so that a consensus on clinically meaningful outcomes and best endpoints is urgently needed. Fourthly, the hierarchy of treatments provided in this guideline (**Figure 3**) should be considered at individual level, and treatment decision depends on several factors, including local availability and reimbursement policies. Finally, this guideline does not make specific recommendations regarding supportive treatments such as oxygen supplementation or pulmonary rehabilitation. In conclusion, the committee identified areas where there is sufficient information to make informed recommendations based on current evidence and clinical experience. While great progress has been made in understanding the pathogenesis and clinical progression of PAP syndrome, many questions remain unanswered, several recommendations for future research were proposed by the TF (**Table 3**). Obviously, many of the research topics require international collaboration such as consensus reports and international registries.

The guidelines published by the ERS incorporate data obtained from a comprehensive and systematic literature review of the relevant, published evidence available at the time. Health professionals are encouraged to take the guideline into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with the patient and the patient's caregiver where appropriate and/or necessary, and

to verify local or national rules and regulations applicable to drugs and devices at the time of prescription. This document was endorsed by the ERS Executive Committee on 16th April 2024.

Tables

Table 1: Classification of PAP Causing Diseases

Disorders of Surfactant Clearance	
Primary PAP (GM-CSF signalling disruption)	
Autoimmune PAP	Mediated by autoantibodies to GM-CSF
Hereditary PAP	GM-CSF signalling disruption due to GM-CSF receptor mutations (CSF2RA or CSF2RB) or STAT5B mutations.
Secondary PAP (Reduced alveolar macrophage function or number)	
Haematological Conditions	Acute lymphocytic leukaemia, acute myeloid leukaemia, aplastic anaemia, chronic lymphocytic leukaemia, chronic myeloid leukaemia, myelodysplastic syndromes, multiple myeloma, lymphoma, Waldenstrom's macroglobulinaemia, GATA2 deficiency
Non-Haematological Malignancies	Adenocarcinoma, glioblastoma, melanoma
Immune Deficiency and Chronic Inflammatory Conditions	Acquired immunodeficiency syndrome, amyloidosis, Fanconi's syndrome, agammaglobulinaemia, juvenile dermatomyositis, renal tubular acidosis, severe combined immunodeficiency disease
Occupational and Environmental Exposures	aluminium, cement, silica, titanium, indium, flour, fertilizer, sawdust, chlorine fumes, cleaning products, gasoline/petroleum fume, nitrogen dioxide, paint fumes, synthetic plastic fumes, varnish
Chronic Infections	Cytomegalovirus, mycobacterium tuberculosis, nocardia, pneumocystis jirovecii
Others including mutations affecting mononuclear phagocytes	Lysinuric protein intolerance, mutations in methionyl-tRNA synthetase (MARS)
Disorders of Surfactant Production	
Pulmonary Surfactant Metabolic Dysfunction Disorders	
Mutations in SFTPB, SFTPC, ABCA3, *NKX*2.1	Surfactant homeostasis affected due to mutations causing surfactant protein deficiency, lipid transporter deficiency or mutations that affecting lung development

Table 2: PICO Questions and Recommendations

Question	Recommendation
Narrative question 1a. When should patients with clinical and radiological features consistent with a diagnosis of PAP undergo bronchoalveolar lavage (BAL)?	We recommend that BAL be performed as part of the diagnostic work up of patients with suspected PAP. BAL should include differential cell count, periodic-acid-Schiff (PAS)-staining, and microbiology **(strong recommendation, very low certainty).**
Narrative question 1b. When should patients with clinical and radiological features consistent with a diagnosis of PAP undergo lung biopsy for histologic analysis?	We suggest to not routinely perform lung biopsy as part of the diagnostic work up of patients with suspected PAP **(conditional recommendation, moderate certainty).**
Narrative question 2. When should patients with clinical and radiological features consistent with PAP undergo GM-CSF antibody testing for diagnosing autoimmune PAP?	We recommend GM-CSF antibody testing for diagnosing autoimmune PAP for all patients with suspected or confirmed PAP syndrome **(strong recommendation, moderate certainty).**
PICO 3. In patients with clinical symptoms and/or functional impairment due to PAP should whole lung lavage be used versus to no whole lung lavage?	We recommend performing bilateral whole lung lavage in patients with autoimmune PAP with evidence of gas exchange impairment and either symptoms, or functional impairment **(strong recommendation, very low certainty).** No recommendation for or against whole lung lavage in other PAP types can be made due to lack of evidence. We suggest seeking advice from an expert centre on an individual case basis.
PICO 4. In patients with confirmed autoimmune PAP should exogenous GM-CSF be used versus no exogenous GM-CSF?	We recommend inhaled GM-CSF for symptomatic patients with confirmed autoimmune PAP **(strong recommendation, very low certainty) .**
PICO 5. In patients with confirmed autoimmune PAP should rituximab be used versus no immunosuppressive treatment?	We suggest the use of rituximab for patients with confirmed autoimmune PAP who remain significantly symptomatic, requiring supplemental oxygen, despite whole lung lavage therapy or exogenous GM-CSF treatment **(conditional recommendation, very low certainty,).**

PICO 6. In patients with confirmed autoimmune PAP should plasmapheresis be used versus no plasmapheresis?	We suggest the use of plasmapheresis for patients with confirmed autoimmune PAP who remain significantly symptomatic, requiring high flow of supplemental oxygen (≥4L /min) or two or more WLL over a period of a year, despite receiving exogenous GM-CSF and rituximab, or having previously failed these treatments **(conditional recommendation, very low certainty).**
PICO 7. In patients with PAP progressing despite whole lung lavage or pharmacological treatment should lung transplantation be considered versus no lung transplantation?	We suggest lung transplantation for patients with PAP progressing despite whole lung lavage and/or pharmacological treatment, who fulfil the International Society for Heart and Lung Transplantation (ISHLT) criteria for patients with interstitial lung disease **(conditional recommendation, very low certainty).**

Table 3: Future Research Needs

• Biomarkers (molecular, inflammatory, cytokines) in BAL and serum for disease progression, treatment response and prognosis
• Definition of core outcome set
• Development of PAP disease specific patient reported outcome measures
• Establish minimum clinically important differences (MCID) in current and new outcomes
• Establishment of criteria to categorize the severity of disease (mild, moderate, severe)
• Definition and diagnostic criteria of fibrotic PAP
• Clarify the role of opportunistic infections as an indicator of disease severity or a complication
• Explore/use new trial designs that consider the severity of disease of the patients (mild, moderate, severe)
• Compare WLL procedures (technique, concomitant physiotherapy etc.)
• Homogenisation of WLL standard protocol to allow better comparison across populations and therapies
• Definition on WLL indications, contraindications, and parameters to define treatment responsiveness
• Comparison of sequential or combination therapy with WLL and inhaled GM-CSF
• Comparison of continuous vs. intermittent GM-CSF treatment regimens
• Evaluate individualised dose and treatment duration of GM-CSF therapy
• Evaluate the role of GM-CSF therapy as rescue therapy
• Evaluate the role of inhaled GM-CSF in children with aPAP
• Evaluate safety and clinical effectiveness of combination therapy with GM-CSF substitution and rituximab
• Systematic evaluation of the effectiveness rituximab therapy for aPAP
• Evaluate of the effectiveness of plasmapheresis and standardisation of technique
• Outcome of lung transplantation in patients with different types of PAP
• Development of a specific registry for patients with PAP who undergo lung transplantation
• Development of a registry for patients with PAP

Figure Legends.

Figure 1: Radiological findings in PAP. Representative images from chest radiograph (A) and CT of the thorax demonstrating the diversity of radiographic findings in PAP (B-G). (B) Ground-glass infiltrates in a mild case of aPAP without interlobular septal thickening. (C-F) CT images demonstrating varying degrees of involvement with the distinctive pattern of interlobular septal thickening superimposed on ground-glass opacification, referred to as "crazy-paving." (C, E, F) Clearly demarcated differences in the degree of involvement between adjacent lobes. (G) aPAP complicated by pulmonary fibrosis 15 years after initial diagnosis of aPAP: CT demonstrates parenchymal distortion, honeycombing and traction bronchiectasis.

Figure 2: Algorithm for the differential diagnosis of PAP. The presence of PAP is suspected when typical radiological findings and compatible history with or without bronchoalveolar lavage findings. GM-CSF autoantibody test should be performed first: a positive test confirms the diagnosis of aPAP. Patients with anormal GM-CSF autoantibody titres who have a disease known to cause PAP can often be diagnosed with secondary PAP. If an underlying causative condition is not identified, and serum GM-CSF levels can be checked; high concentrations of serum GM-CSF and no or reduced GM-CSF signalling should prompt further tests for *CSF2RA* and *CSF2RB* mutations to identify hereditary PAP. Patients with physiological levels of serum GM-CSF and appropriate GM-CSF signalling can undergo further tests for other gene mutations to diagnose congenital PAP. If no PAP-causing mutation can be found, the patient is diagnosed with unclassified PAP and a transbronchial or surgical lung biopsy for lung parenchymal histopathological examination may be needed to confirm diagnosis. This diagnostic algorithm reflects an ideal setting in which physicians have access to the appropriate diagnostic tests. Adapted from Trapnell *et al* 2019[1]. The evidence supporting each step of the diagnostic algorithm is colour coded (see legend).

Figure 3: Hierarchy of Treatments in autoimmune PAP. Treatment is indicated in patients with active or worsening disease. The appropriateness of treatment should be based on the degree of impairment of lung function, CT imaging changes, blood oxygenation and symptoms. Treatment hierarchy was developed based on consensus among the panel members that was informed by (a) the strength of recommendations in PICOs 3-7, with a focus on the potential benefits, risks and resources required for the corresponding interventions, (b) the certainty of evidence supporting those PICOs, and (c) current clinical practice. Depending on immediacy of treatment need either WLL or inhaled GM-CSF should be offered as first line therapy (Strong Recommendation). If these fail to show sustained benefit or in life threatening respiratory failure, rituximab or plasmapheresis may be considered (Conditional Recommendations). Lung transplantation remains an option for refractory cases (Conditional Recommendation). The hierarchy algorithm is colour coded based on the evidence supporting each step (see legend).

References

1. Trapnell BC, Nakata K, Bonella F, Campo I, Griese M, Hamilton J, Wang T, Morgan C, Cottin V, McCarthy C. Pulmonary alveolar proteinosis. *Nat Rev Dis Primers* 2019: 5(1): 16.
2. Inoue Y, Trapnell BC, Tazawa R, Arai T, Takada T, Hizawa N, Kasahara Y, Tatsumi K, Hojo M, Ichiwata T, Tanaka N, Yamaguchi E, Eda R, Oishi K, Tsuchihashi Y, Kaneko C, Nukiwa T, Sakatani M, Krischer JP, Nakata K. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. *American journal of respiratory and critical care medicine* 2008: 177(7): 752-762.
3. McCarthy C, Avetisyan R, Carey BC, Chalk C, Trapnell BC. Prevalence and healthcare burden of pulmonary alveolar proteinosis. *Orphanet J Rare Dis* 2018: 13(1): 129.
4. McCarthy C, Carey BC, Trapnell BC. Autoimmune Pulmonary Alveolar Proteinosis. *American journal of respiratory and critical care medicine* 2022: 205(9): 1016-1035.
5. Nagavci B, Thomy T, Bush A, Roche N, Vaccaro V, Genton C, Humbert M, Coleman C, Williams C, Boyd J. ERS Handbook for Clinical Practice Guidelines: Methodological guidance for developing ERS Clinical Practice Guidelines. 2021 [cited; Available from: https://ers.app.box.com/s/fwaabkr604oakr1zfs4egx9suasqzmdu
6. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ, Group GW. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008: 336(7650): 924-926.
7. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Systematic reviews* 2016: 5(1): 210.
8. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011: 343: d5928.
9. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *Bmj* 2016: 355: i4919.
10. Barker TH, Stone JC, Sears K, Klugar M, Leonardi-Bee J, Tufanaru C, Aromataris E, Munn Z. Revising the JBI quantitative critical appraisal tools to improve their applicability: an overview of methods and the development process. *JBI evidence synthesis* 2023: 21(3): 478-493.
11. Leth S, Bendstrup E, Vestergaard H, Hilberg O. Autoimmune pulmonary alveolar proteinosis: treatment options in year 2013. *Respirology* 2013: 18(1): 82-91.
12. Tazawa R, Ueda T, Abe M, Tatsumi K, Eda R, Kondoh S, Morimoto K, Tanaka T, Yamaguchi E, Takahashi A, Oda M, Ishii H, Izumi S, Sugiyama H, Nakagawa A, Tomii K, Suzuki M, Konno S, Ohkouchi S, Tode N, Handa T, Hirai T, Inoue Y, Arai T, Asakawa K, Sakagami T, Hashimoto A, Tanaka T, Takada T, Mikami A, Kitamura N, Nakata K. Inhaled GM-CSF for Pulmonary Alveolar Proteinosis. *N Engl J Med* 2019: 381(10): 923-932.
13. Trapnell BC, Inoue Y, Bonella F, Morgan C, Jouneau S, Bendstrup E, Campo I, Papiris SA, Yamaguchi E, Cetinkaya E, Ilkovich MM, Kramer MR, Veltkamp M, Kreuter M, Baba T, Ganslandt C, Tarnow I, Waterer G, Jouhikainen T. Inhaled Molgramostim Therapy in Autoimmune Pulmonary Alveolar Proteinosis. *New England Journal of Medicine* 2020: 383(17): 1635-1644.
14. Bai JW, Huang JN, Shi SY, Ge A, Lu HW, Sun XL, Gu SY, Liang S, Cheng KB, Tian XL, Xiao YL, Xu KF, Xu JF. Updated severity and prognosis score of pulmonary alveolar proteinosis: A multi-center cohort study in China. *Frontiers in medicine* 2023: 10: 1058001.
15. Tazawa R, Trapnell BC, Inoue Y, Arai T, Takada T, Nasuhara Y, Hizawa N, Kasahara Y, Tatsumi K, Hojo M, Ishii H, Yokoba M, Tanaka N, Yamaguchi E, Eda R, Tsuchihashi Y, Morimoto K, Akira M, Terada M, Otsuka J, Ebina M, Kaneko C, Nukiwa T, Krischer JP, Akazawa K, Nakata K. Inhaled granulocyte/macrophage-colony

stimulating factor as therapy for pulmonary alveolar proteinosis. *American journal of respiratory and critical care medicine* 2010: 181(12): 1345-1354.
16. 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. *The European respiratory journal* 2004: 23(4): 526-531.
17. Kaenmuang P, Navasakulpong A. Efficacy of whole lung lavage in pulmonary alveolar proteinosis: a 20-year experience at a reference center in Thailand. *Journal of thoracic disease* 2021: 13(6): 3539-3548.
18. McCarthy C, Kokosi M, Bonella F. Shaping the future of an ultra-rare disease: unmet needs in the diagnosis and treatment of pulmonary alveolar proteinosis. *Current opinion in pulmonary medicine* 2019: 25(5): 450-458.
19. Akira M, Inoue Y, Arai T, Sugimoto C, Tokura S, Nakata K, Kitaichi M, Osaka Respiratory Diseases Symposia G. Pulmonary Fibrosis on High-Resolution CT of Patients With Pulmonary Alveolar Proteinosis. *AJR American journal of roentgenology* 2016: 207(3): 544-551.
20. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, Kreuter M, Lynch DA, Maher TM, Martinez FJ, Molina-Molina M, Myers JL, Nicholson AG, Ryerson CJ, Strek ME, Troy LK, Wijsenbeek M, Mammen MJ, Hossain T, Bissell BD, Herman DD, Hon SM, Kheir F, Khor YH, Macrea M, Antoniou KM, Bouros D, Buendia-Roldan I, Caro F, Crestani B, Ho L, Morisset J, Olson AL, Podolanczuk A, Poletti V, Selman M, Ewing T, Jones S, Knight SL, Ghazipura M, Wilson KC. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *American journal of respiratory and critical care medicine* 2022: 205(9): e18-e47.
21. Ilkovich YM, Ariel BM, Novikova LN, Bazhanov AA, Dvorakovskaya IV, Ilkovich MM. Pulmonary alveolar proteinosis: a long way to correct diagnosis: problems of diagnostics and therapy in routine practice. *Ann Clin Lab Sci* 2014: 44(4): 405-409.
22. Borie R, Danel C, Debray MP, Taille C, Dombret MC, Aubier M, Epaud R, Crestani B. Pulmonary alveolar proteinosis. *Eur Respir Rev* 2011: 20(120): 98-107.
23. Bonella F, Bauer PC, Griese M, Ohshimo S, Guzman J, Costabel U. Pulmonary alveolar proteinosis: new insights from a single-center cohort of 70 patients. *Respiratory medicine* 2011: 105(12): 1908-1916.
24. Azuma K, Takimoto T, Kasai T, Hirose M, Hatsuda K, Sugimoto C, Arai T, Akira M, Inoue Y. Diagnostic yield and safety of bronchofiberscopy for pulmonary alveolar proteinosis. *Respir Investig* 2021: 59(6): 757-765.
25. Enaud L, Hadchouel A, Coulomb A, Berteloot L, Lacaille F, Boccon-Gibod L, Boulay V, Darcel F, Griese M, Linard M, Louha M, Renouil M, Rivière JP, Toupance B, Verkarre V, Delacourt C, de Blic J. Pulmonary alveolar proteinosis in children on La Réunion Island: a new inherited disorder? *Orphanet J Rare Dis* 2014: 9: 85.
26. Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: progress in the first 44 years. *American journal of respiratory and critical care medicine* 2002: 166(2): 215-235.
27. Punatar AD, Kusne S, Blair JE, Seville MT, Vikram HR. Opportunistic infections in patients with pulmonary alveolar proteinosis. *The Journal of infection* 2012: 65(2): 173-179.
28. Danel C, Israel-Biet D, Costabel U, Rossi GA, Wallaert B. The clinical role of BAL in alveolar proteinosis. *The European respiratory journal* 1990: 3(8): 950-951, 961-959.
29. Rosen SH, Castleman B, Liebow AA. Pulmonary alveolar proteinosis. *The New England journal of medicine* 1958: 258(23): 1123-1142.
30. Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. *N Engl J Med* 2003: 349(26): 2527-2539.
31. McElvaney OJ, Horan D, Franciosi AN, Gunaratnam C, McElvaney NG. Pulmonary alveolar proteinosis. *QJM: An International Journal of Medicine* 2018: 111(3): 185-186.
32. Prakash UBS, Barham SS, Carpenter HA. Pulmonary alveolar phospholipoproteinosis: Experience with 34 cases and a review. *Mayo Clinic proceedings* 1987: 62(6): 499-518.
33. Rubinstein I, Mullen JB, Hoffstein V. Morphologic diagnosis of idiopathic pulmonary alveolar lipoproteinosis-revisited. *Arch Intern Med* 1988: 148(4): 813-816.

34. Han Q, Luo Q, Chen X, Xie J, Wu L, Chen R. The evaluation of clinical usefulness of transbrochoscopic lung biopsy in undefined interstitial lung diseases: a retrospective study. *Clin Respir J* 2017: 11(2): 168-175.
35. Azuma K, Takimoto T, Kasai T, Hirose M, Hatsuda K, Sugimoto C, Arai T, Akira M, Inoue Y. Diagnostic yield and safety of bronchofiberscopy for pulmonary alveolar proteinosis. *Respiratory investigation* 2021: 59(6): 757-765.
36. McCarthy C, Carey B, Trapnell BC. Blood Testing for Differential Diagnosis of Pulmonary Alveolar Proteinosis Syndrome. *Chest* 2019: 155(2): 450-452.
37. Han Q, Chen X, Xu X, Qian W, Zhao G, Mao M, Guo B, Xia S, Peng G, He J, Gu Y, Li S, Luo Q. The Application of Transbronchial Lung Cryobiopsy and Uniportal and Tubeless Video-Assisted Thoracic Surgery in the Multidisciplinary Diagnosis of Interstitial Lung disease-A Real-World Prospective Study. *Frontiers in molecular biosciences* 2021: 8: 681669.
38. Ussavarungsi K, Kern RM, Roden AC, Ryu JH, Edell ES. Transbronchial Cryobiopsy in Diffuse Parenchymal Lung Disease: Retrospective Analysis of 74 Cases. *Chest* 2017: 151(2): 400-408.
39. Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-Hospital Mortality after Surgical Lung Biopsy for Interstitial Lung Disease in the United States. 2000 to 2011. *American journal of respiratory and critical care medicine* 2016: 193(10): 1161-1167.
40. Kitamura T, Uchida K, Tanaka N, Tsuchiya T, Watanabe J, Yamada Y, Hanaoka K, Seymour JF, Schoch OD, Doyle I, Inoue Y, Sakatani M, Kudoh S, Azuma A, Nukiwa T, Tomita T, Katagiri M, Fujita A, Kurashima A, Kanegasaki S, Nakata K. Serological diagnosis of idiopathic pulmonary alveolar proteinosis. *American journal of respiratory and critical care medicine* 2000: 162(2 Pt 1): 658-662.
41. Kitamura T, Tanaka N, Watanabe J, Uchida, Kanegasaki S, Yamada Y, Nakata K. Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. *J Exp Med* 1999: 190(6): 875-880.
42. Uchida K, Nakata K, Carey B, Chalk C, Suzuki T, Sakagami T, Koch DE, Stevens C, Inoue Y, Yamada Y, Trapnell BC. Standardized serum GM-CSF autoantibody testing for the routine clinical diagnosis of autoimmune pulmonary alveolar proteinosis. *Journal of immunological methods* 2014: 402(1-2): 57-70.
43. Bonella F, Bauer PC, Griese M, Ohshimo S, Guzman J, Costabel U. Pulmonary alveolar proteinosis: new insights from a single-center cohort of 70 patients. *Respiratory medicine* 2011: 105(12): 1908-1916.
44. McCarthy C, Carey B, Trapnell BC. Blood testing in the diagnosis of pulmonary alveolar proteinosis. *The Lancet Respiratory medicine* 2018: 6(11): e54.
45. Stanley E, Lieschke GJ, Grail D, Metcalf D, Hodgson G, Gall JA, Maher DW, Cebon J, Sinickas V, Dunn AR. Granulocyte/macrophage colony-stimulating factor-deficient mice show no major perturbation of hematopoiesis but develop a characteristic pulmonary pathology. *Proc Natl Acad Sci U S A* 1994: 91(12): 5592-5596.
46. Dranoff G, Crawford AD, Sadelain M, Ream B, Rashid A, Bronson RT, Dickersin GR, Bachurski CJ, Mark EL, Whitsett JA, et al. Involvement of granulocyte-macrophage colony-stimulating factor in pulmonary homeostasis. *Science* 1994: 264(5159): 713-716.
47. Tanaka N, Watanabe J, Kitamura T, Yamada Y, Kanegasaki S, Nakata K. Lungs of patients with idiopathic pulmonary alveolar proteinosis express a factor which neutralizes granulocyte-macrophage colony stimulating factor. *FEBS Lett* 1999: 442(2-3): 246-250.
48. Sakagami T, Uchida K, Suzuki T, Carey BC, Wood RE, Wert SE, Whitsett JA, Trapnell BC, Luisetti M. Human GM-CSF autoantibodies and reproduction of pulmonary alveolar proteinosis. *N Engl J Med* 2009: 361(27): 2679-2681.
49. Sakagami T, Beck D, Uchida K, Suzuki T, Carey BC, Nakata K, Keller G, Wood RE, Wert SE, Ikegami M, Whitsett JA, Luisetti M, Davies S, Krischer JP, Brody A, Ryckman F, Trapnell BC. Patient-derived granulocyte/macrophage colony-stimulating factor autoantibodies reproduce pulmonary alveolar proteinosis in nonhuman primates. *American journal of respiratory and critical care medicine* 2010: 182(1): 49-61.

50. Kusakabe Y, Uchida K, Hiruma T, Suzuki Y, Totsu T, Suzuki T, Carey BC, Yamada Y, Trapnell BC. A standardized blood test for the routine clinical diagnosis of impaired GM-CSF signaling using flow cytometry. *Journal of immunological methods* 2014: 413: 1-11.
51. Suzuki T, Sakagami T, Rubin BK, Nogee LM, Wood RE, Zimmerman SL, Smolarek T, Dishop MK, Wert SE, Whitsett JA, Grabowski G, Carey BC, Stevens C, van der Loo JC, Trapnell BC. Familial pulmonary alveolar proteinosis caused by mutations in CSF2RA. *J Exp Med* 2008: 205(12): 2703-2710.
52. Ramirez J, Kieffer RF, Jr., Ball WC, Jr. Bronchopulmonary lavage in man. *Annals of internal medicine* 1965: 63(5): 819-828.
53. 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, Group WLLIS. Whole lung lavage therapy for pulmonary alveolar proteinosis: a global survey of current practices and procedures. *Orphanet J Rare Dis* 2016: 11(1): 115.
54. Reiter K, Schoen C, Griese M, Nicolai T. Whole-lung lavage in infants and children with pulmonary alveolar proteinosis. *Paediatric anaesthesia* 2010: 20(12): 1118-1123.
55. Awab A, Khan MS, Youness HA. Whole lung lavage-technical details, challenges and management of complications. *Journal of thoracic disease* 2017: 9(6): 1697-1706.
56. Baumgartel M, Wurflein D, Neff U, Bohm J, Ficker JH, Swol J. Bridging Whole-Lung Lavage with Venovenous Extracorporeal Life Support for Pulmonary Alveolar Proteinosis. *Journal of cardiothoracic and vascular anesthesia* 2020: 34(4): 1115-1117.
57. Badiozaman R, Tahereh P, Shideh D, Mohammadreza B, Ahmadreza A, Seyyedahmad T. Whole lung lavage of nine children with pulmonary alveolar proteinosis: experience in a tertiary lung center. *Iranian journal of pediatrics* 2013: 23(1): 95-99.
58. Du Bois RM, McAllister WA, Branthwaite MA. Alveolar proteinosis: diagnosis and treatment over a 10-year period. *Thorax* 1983: 38(5): 360-363.
59. Marwah V, Katoch CDS, Singh S, Handa A, Vardhan V, Rajput AK, Barthwal MS, Bhattacharyya D, Rai SP. Management of primary pulmonary alveolar proteinosis: A multicentric experience. *Lung India : official organ of Indian Chest Society* 2020: 37(4): 304-309.
60. Mo Q, Wang B, Dong N, Bao L, Su X, Li Y, Chen C. The Clinical Clues of Pulmonary Alveolar Proteinosis: A Report of 11 Cases and Literature Review. *Canadian respiratory journal* 2016: 2016: 4021928.
61. Selecky PA, Wasserman K, Benfield JR, Lippmann M. The clinical and physiological effect of whole-lung lavage in pulmonary alveolar proteinosis: a ten-year experience. *The Annals of thoracic surgery* 1977: 24(5): 451-461.
62. Zhou X, Lu G, Yu Z, Gao F, Bian T. Long-term follow-up of whole lung lavage in patients with pulmonary alveolar proteinosis. *Experimental and therapeutic medicine* 2014: 8(3): 763-768.
63. 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. *Journal of cardiothoracic and vascular anesthesia* 2019: 33(9): 2453-2461.
64. Casanova S, Puglisi S, Gurioli C, Gurioli C, Maitan S, Martinello S, Sultani F, Ravaglia C, Poletti V. Whole lung lavage: our experience in pulmonary alveolar proteinosis and in type B Niemann Pick disease. *Rassegna di Patologia dell'Apparato Respiratorio* 2021: 36: 158-165.
65. Tian X, Yang Y, Chen L, Sui X, Xu W, Li X, Guo X, Liu L, Situ Y, Wang J, Zhao Y, Meng S, Song W, Xiao Y, Xu K-F. Inhaled granulocyte-macrophage colony stimulating factor for mild-to-moderate autoimmune pulmonary alveolar proteinosis - a six month phase II randomized study with 24 months of follow-up. *Orphanet Journal of Rare Diseases* 2020: 15(1): 174.
66. 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. *American journal of respiratory and critical care medicine* 2001: 163(2): 524-531.

67. Wylam ME, Ten R, Prakash UB, Nadrous HF, Clawson ML, Anderson PM. Aerosol granulocyte-macrophage colony-stimulating factor for pulmonary alveolar proteinosis. *The European respiratory journal* 2006: 27(3): 585-593.
68. Venkateshiah SB, Yan TD, Bonfield TL, Thomassen MJ, Meziane M, Czich C, Kavuru MS. An open-label trial of granulocyte macrophage colony stimulating factor therapy for moderate symptomatic pulmonary alveolar proteinosis. *Chest* 2006: 130(1): 227-237.
69. Papiris SA, Tsirigotis P, Kolilekas L, Papadaki G, Papaioannou AI, Triantafillidou C, Papaporfyriou A, Karakatsani A, Kagouridis K, Griese M, Manali ED. Long-term inhaled granulocyte macrophage-colony-stimulating factor in autoimmune pulmonary alveolar proteinosis: effectiveness, safety, and lowest effective dose. *Clin Drug Investig* 2014: 34(8): 553-564.
70. Zhang F, Weng D, Su Y, Yin C, Shen L, Zhang Y, Zhou Y, Li Q, Hu Y, Li H. Therapeutic effect of subcutaneous injection of low dose recombinant human granulocyte-macrophage colony-stimulating factor on pulmonary alveolar proteinosis. *Respiratory research* 2020: 21(1): 1.
71. Zhen G, Li D, Jiang J, Weng Y. Granulocyte-Macrophage Colony-Stimulating Factor Inhalation Therapy for Severe Pulmonary Alveolar Proteinosis. *American journal of therapeutics* 2020: 28(2): e171-e178.
72. Tazawa R, Inoue Y, Arai T, Takada T, Kasahara Y, Hojo M, Ohkouchi S, Tsuchihashi Y, Yokoba M, Eda R, Nakayama H, Ishii H, Nei T, Morimoto K, Nasuhara Y, Ebina M, Akira M, Ichiwata T, Tatsumi K, Yamaguchi E, Nakata K. Duration of benefit in patients with autoimmune pulmonary alveolar proteinosis after inhaled granulocyte-macrophage colony-stimulating factor therapy. *Chest* 2014: 145(4): 729-737.
73. Livingstone C, Corallo C, Siemienowicz M, Pilcher D, Stirling RG. Nebulised sargramostim in pulmonary alveolar proteinosis. *British journal of clinical pharmacology* 2022: 88(7): 3523-3528.
74. Ohkouchi S, Akasaka K, Ichiwata T, Hisata S, Iijima H, Takada T, Tsukada H, Nakayama H, Machiya JI, Irokawa T, Ogawa H, Shibata Y, Ichinose M, Ebina M, Nukiwa T, Kurosawa H, Nakata K, Tazawa R. Sequential Granulocyte-Macrophage Colony-Stimulating Factor Inhalation after Whole-Lung Lavage for Pulmonary Alveolar Proteinosis. A Report of Five Intractable Cases. *Annals of the American Thoracic Society* 2017: 14(8): 1298-1304.
75. Yamamoto H, Yamaguchi E, Agata H, Kandatsu N, Komatsu T, Kawai S, Baba K, Awaya T, Nishikomori R, Tsurusawa M, Nakata K. A combination therapy of whole lung lavage and GM-CSF inhalation in pulmonary alveolar proteinosis. *Pediatric pulmonology* 2008: 43(8): 828-830.
76. Price A, Manson D, Cutz E, Dell S. Pulmonary alveolar proteinosis associated with anti-GM-CSF antibodies in a child: successful treatment with inhaled GM-CSF. *Pediatric pulmonology* 2006: 41(4): 367-370.
77. Griese M, Panagiotou P, Manali ED, Stahl M, Schwerk N, Costa V, Douros K, Kallieri M, Urbantat RM, von Bernuth H, Kolilekas L, Morais L, Ramos A, Landwehr K, Knoflach K, Gothe F, Reiter K, Papaevangelou V, Kaditis AG, Kanaka-Gantenbein C, Papiris SA. Autoimmune pulmonary alveolar proteinosis in children. *ERJ open research* 2022: 8(1).
78. Gajewska ME, Sritharan SS, Santoni-Rugiu E, Bendstrup EM. Autoimmune pulmonary alveolar proteinosis in an adolescent successfully treated with inhaled rhGM-CSF (molgramostim). *Respiratory medicine case reports* 2018: 23: 167-169.
79. Kavuru MS, Malur A, Marshall I, Barna BP, Meziane M, Huizar I, Dalrymple H, Karnekar R, Thomassen MJ. An open-label trial of rituximab therapy in pulmonary alveolar proteinosis. *The European respiratory journal* 2011: 38(6): 1361-1367.
80. 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. *Respiratory research* 2018: 19(1): 74.
81. Amital A, Dux S, Shitrit D, Shpilberg O, Kramer MR. Therapeutic effectiveness of rituximab in a patient with unresponsive autoimmune pulmonary alveolar proteinosis. *Thorax* 2010: 65(11): 1025-1026.

82. Bird D, Evans J, Pahoff C. Rituximab rescue therapy for autoimmune pulmonary alveolar proteinosis. *Respiratory medicine case reports* 2022: 37: 101637.
83. Meybodi FA, Fard SK, Zarch MB, Babai M. Rituximab Therapy in Pulmonary Alveolar Proteinosis: A Rare Case Report. *Journal of Clinical & Diagnostic Research* 2018: 12(4).
84. Nagasawa J, Kurasawa K, Hanaoka R. Rituximab improved systemic lupus erythematosus-associated pulmonary alveolar proteinosis without decreasing anti-GM-CSF antibody levels. *Lupus* 2016: 25(7): 783-784.
85. Keske A, Destrampe EM, Barksdale B, Rose WN. Pulmonary Alveolar Proteinosis Refractory to Plasmapheresis and Rituximab despite GM-CSF Antibody Reduction. *Case reports in immunology* 2022: 2022: 2104270.
86. Garber B, Albores J, Wang T, Neville TH. A plasmapheresis protocol for refractory pulmonary alveolar proteinosis. *Lung* 2015: 193(2): 209-211.
87. Hunt S, Miller AL, Schissel S, Ross JJ. A crazy cause of dyspnea. *N Engl J Med* 2010: 363(25): e38.
88. Lopez-Olivo MA, Amezaga Urruela M, McGahan L, Pollono EN, Suarez-Almazor ME. Rituximab for rheumatoid arthritis. *The Cochrane database of systematic reviews* 2015: 1: Cd007356.
89. Liu S, Gui C, Lu Z, Li H, Fu Z, Deng Y. The Efficacy and Safety of Rituximab for Childhood Steroid-Dependent Nephrotic Syndrome: A Systematic Review and Meta-Analysis. *Front Pediatr* 2021: 9: 728010.
90. Bonfield TL, Kavuru MS, Thomassen MJ. Anti-GM-CSF titer predicts response to GM-CSF therapy in pulmonary alveolar proteinosis. *Clin Immunol* 2002: 105(3): 342-350.
91. Jézéquel A, Kerjouan M, Lederlin M, Lainé-Caroff C, Camus C, Delaval P, Jouneau S. Échec de plasmaphérèse dans une protéinose alvéolaire pulmonaire auto-immune. *Revue des Maladies Respiratoires* 2017: 34(3): 240-243.
92. Kavuru MS, Bonfield TL, Thomassen MJ. Plasmapheresis, GM-CSF, and alveolar proteinosis. *American journal of respiratory and critical care medicine* 2003: 167(7): 1036; author reply 1036-1037.
93. Luisetti M, Rodi G, Perotti C, Campo I, Mariani F, Pozzi E, Trapnell BC. Plasmapheresis for treatment of pulmonary alveolar proteinosis. *The European respiratory journal* 2009: 33(5): 1220-1222.
94. Yu H, Sun X, Wang Y, Xu Z, Huang H. Whole lung lavage combined with Granulocyte-macrophage colony stimulating factor inhalation for an adult case of refractory pulmonary alveolar proteinosis. *BMC pulmonary medicine* 2014: 14: 87.
95. Vis DC, Kelly MM, De Heuvel E, MacEachern PR. Reduction in Alveolar Macrophage Size in Refractory Autoimmune Pulmonary Alveolar Proteinosis After Treatment With Pioglitazone. *Journal of bronchology & interventional pulmonology* 2020: 27(3): 219-222.
96. Chevret S, Hughes RA, Annane D. Plasma exchange for Guillain-Barré syndrome. *The Cochrane database of systematic reviews* 2017: 2(2): Cd001798.
97. Mokrzycki MH, Kaplan AA. Therapeutic plasma exchange: complications and management. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 1994: 23(6): 817-827.
98. Eyre M, Hacohen Y, Barton C, Hemingway C, Lim M. Therapeutic plasma exchange in paediatric neurology: a critical review and proposed treatment algorithm. *Developmental medicine and child neurology* 2018: 60(8): 765-779.
99. Kobayashi K, Ohkouchi S, Sasahara Y, Ebina M, Nakata K, Saito R, Akiba M, Sado T, Oishi H, Watanabe T, Kurosawa H, Okada Y. Improvement of native pulmonary alveolar proteinosis after contralateral single living-donor lobar lung transplantation: A case report. *Pediatric transplantation* 2020: 24(2): e13659.
100. Lawi D, Dubruc E, Gonzalez M, Aubert JD, Soccal PM, Janssens JP. Secondary pulmonary alveolar proteinosis treated by lung transplant: A case report. *Respiratory medicine case reports* 2020: 30: 101108.
101. Liang J, Chen Y, Zheng M, Ye S, Liu F, Chen J, Ji Y. Single lung transplantation for idiopathic pulmonary alveolar proteinosis with intraoperative veno-venous extracorporeal membrane oxygenation support. *Transplant immunology* 2022: 74: 101627.

102. Ono M, Saito R, Tominaga J, Okada Y, Ohkouchi S, Takemura T. Pathological features of explant lungs with fibrosis in autoimmune pulmonary alveolar proteinosis. *Respirology case reports* 2017: 5(5): e00255.
103. Trukalj M, Perica M, Ferenčić Ž, Erceg D, Navratil M, Redžepi G, Nogalo B. Successful Treatment of Autoimmune Pulmonary Alveolar Proteinosis in a Pediatric Patient. *The American journal of case reports* 2016: 17: 641-645.
104. Wang YB, Li FK, Ding ZD, Zhao K, Fang ZM, Feng M, Chang SY, Jin F, Huang MJ, Zhao GF. [Lung transplantation for pulmonary alveolar proteinosis: a case report and literature review]. *Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases* 2022: 45(7): 667-670.
105. Beeckmans H, Ambrocio GPL, Bos S, Vermaut A, Geudens V, Vanstapel A, Vanaudenaerde BM, De Baets F, Malfait TLA, Emonds MP, Van Raemdonck DE, Schoemans HM, Vos R. Allogeneic Hematopoietic Stem Cell Transplantation After Prior Lung Transplantation for Hereditary Pulmonary Alveolar Proteinosis: A Case Report. *Frontiers in immunology* 2022: 13: 931153.
106. 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. *Respiratory medicine case reports* 2016: 19: 89-93.
107. Santamaria F, Brancaccio G, Parenti G, Francalanci P, Squitieri C, Sebastio G, Dionisi-Vici C, D'Argenio P, Andria G, Parisi F. Recurrent fatal pulmonary alveolar proteinosis after heart-lung transplantation in a child with lysinuric protein intolerance. *The Journal of pediatrics* 2004: 145(2): 268-272.
108. Murata H, Hara T, Matsumoto S, Inoue H, Yamashita H, Sumikawa K. Anesthetic management of a patient with a double inferior vena cava and pulmonary alveolar proteinosis who underwent bilateral living-donor lobar lung transplantation. *Journal of anesthesia* 2009: 23(4): 583-586.
109. Parker LA, Novotny DB. Recurrent alveolar proteinosis following double lung transplantation. *Chest* 1997: 111(5): 1457-1458.
110. Rahimi N, Matilla JR, Lang G, Schwarz S, Nachbaur E, Benazzo A, Klepetko W, Jaksch P, Hoetzenecker K. Simultaneous pectus excavatum correction and lung transplantation-A case series. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2021: 21(1): 410-414.
111. Tagawa T, Yamasaki N, Tsuchiya T, Miyazaki T, Matsuki K, Tsuchihashi Y, Morimoto K, Nagayasu T. Living-donor lobar lung transplantation for pulmonary alveolar proteinosis in an adult: report of a case. *Surgery today* 2011: 41(8): 1142-1144.
112. Huddleston CB, Bloch JB, Sweet SC, de la Morena M, Patterson GA, Mendeloff EN. Lung transplantation in children. *Annals of surgery* 2002: 236(3): 270-276.
113. Singer JP, Singer LG. Quality of life in lung transplantation. *Seminars in respiratory and critical care medicine* 2013: 34(3): 421-430.
114. Seiler A, Klaghofer R, Ture M, Komossa K, Martin-Soelch C, Jenewein J. A systematic review of health-related quality of life and psychological outcomes after lung transplantation. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2016: 35(2): 195-202.
115. Peel JK, Keshavjee S, Krahn M, Sander B. Economic evaluations and costing studies of lung transplantation: A scoping review. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2021: 40(12): 1625-1640.
116. Eguíluz-Gracia I, Schultz HH, Sikkeland LI, Danilova E, Holm AM, Pronk CJ, Agace WW, Iversen M, Andersen C, Jahnsen FL, Baekkevold ES. Long-term persistence of human donor alveolar macrophages in lung transplant recipients. *Thorax* 2016: 71(11): 1006-1011.
117. Oda M, Yamaura K, Ishii H, Kitamura N, Tazawa R, Abe M, Tatsumi K, Eda R, Kondoh S, Morimoto K, Tanaka T, Yamaguchi E, Takahashi A, Izumi S, Sugiyama H, Nakagawa A, Tomii K, Suzuki M, Konno S, Ohkouchi S, Tode N, Handa T, Hirai T, Inoue Y, Arai T, Asakawa K, Tanaka T, Takada T, Nonaka H, Nakata K.

Quantitative Evaluation of Changes in Three-Dimensional CT Density Distributions in Pulmonary Alveolar Proteinosis after GM-CSF Inhalation. *Respiration; international review of thoracic diseases* 2023: 102(2): 101-109.
118. Fujishima T, Honda Y, Shijubo N, Takahashi H, Abe S. Increased carcinoembryonic antigen concentrations in sera and bronchoalveolar lavage fluids of patients with pulmonary alveolar proteinosis. *Respiration; international review of thoracic diseases* 1995: 62(6): 317-321.
119. Arai T, Hamano E, Inoue Y, Ryushi T, Nukiwa T, Sakatani M, Nakata K. Serum neutralizing capacity of GM-CSF reflects disease severity in a patient with pulmonary alveolar proteinosis successfully treated with inhaled GM-CSF. *Respiratory medicine* 2004: 98(12): 1227-1230.
120. Fang SC, Lu KH, Wang CY, Zhang HT, Zhang YM. Elevated tumor markers in patients with pulmonary alveolar proteinosis. *Clin Chem Lab Med* 2013: 51(7): 1493-1498.
121. Takahashi T, Munakata M, Suzuki I, Kawakami Y. Serum and bronchoalveolar fluid KL-6 levels in patients with pulmonary alveolar proteinosis. *American journal of respiratory and critical care medicine* 1998: 158(4): 1294-1298.
122. Kuroki Y, Tsutahara S, Shijubo N, Takahashi H, Shiratori M, Hattori A, Honda Y, Abe S, Akino T. Elevated levels of lung surfactant protein A in sera from patients with idiopathic pulmonary fibrosis and pulmonary alveolar proteinosis. *Am Rev Respir Dis* 1993: 147(3): 723-729.
123. Iyonaga K, Suga M, Yamamoto T, Ichiyasu H, Miyakawa H, Ando M. Elevated bronchoalveolar concentrations of MCP-1 in patients with pulmonary alveolar proteinosis. *The European respiratory journal* 1999: 14(2): 383-389.
124. Bonella F, Long X, He X, Ohshimo S, Griese M, Guzman J, Costabel U. Serum YKL-40 is a reliable biomarker for pulmonary alveolar proteinosis. *Respirology* 2017: 22(7): 1371-1378.
125. Jehn LB, Bonella F. Pulmonary alveolar proteinosis - current and future therapeutical strategies. *Current opinion in pulmonary medicine* 2023: 29(5): 465-474.
126. Liu S, Cui X, Xia K, Duan Y, Xiong M, Li G. Efficacy and safety of whole-lung lavage for pulmonary alveolar proteinosis: a protocol for a systematic review and meta-analysis. *BMJ open* 2022: 12(4): e057671.
127. Zhang HT, Wang C, Wang CY, Fang SC, Xu B, Zhang YM. Efficacy of Whole-Lung Lavage in Treatment of Pulmonary Alveolar Proteinosis. *American journal of therapeutics* 2016: 23(6): e1671-e1679.
128. Campo I, Carey BC, Paracchini E, Kadija Z, De Silvestri A, Rodi G, De Amici M, Torre C, Zorzetto M, Griese M, Meloni F, Corsico AG, Trapnell BC, Mariani F. Inhaled GM-CSF reduces the need for whole lung lavage and improves gas exchange in autoimmune PAP patients. *The European respiratory journal* 2023.
129. Campo I, Luisetti M, Griese M, Trapnell BC, Bonella F, Grutters JC, Nakata K, Van Moorsel CHM, Costabel U, Cottin V, Ichiwata T, Inoue Y, Braschi A, Bonizzoni G, Iotti GA, Tinelli C, Rodi G, Arai T, Bazhanov AA, Ben-Dov I, Bonella F, Braschi A, Casey A, Costabel U, Cottin V, Dogru D, Gesierich W, Griese M, Grutters JC, Halme M, Henry M, Herth FJF, Hui-ying W, Ichiwata T, Ilkovich JM, Inoue Y, Iotti GA, Irani S, Kolek V, Morais A, Morgan C, Nicolai T, Novikova LN, Primhak R, Reiter K, Retsch-Bogart G, Rodi G, Russi E, Schmitz J, Schön C, Schumann C, Veltkamp M, Verwey C, Wood RE. A Global Survey on Whole Lung Lavage in Pulmonary Alveolar Proteinosis. *Chest* 2016: 150(1): 251-253.
130. Sargmalin for inhalation 250 µg Approved for Autoimmune Pulmonary Alveolar Proteinosis. 2024 [cited 16/04/2024]; Available from: https://www.nobelpharma.co.jp/_cms/wp-content/uploads/2024/03/614c680105bd78a974085a6534cd9ad6.pdf

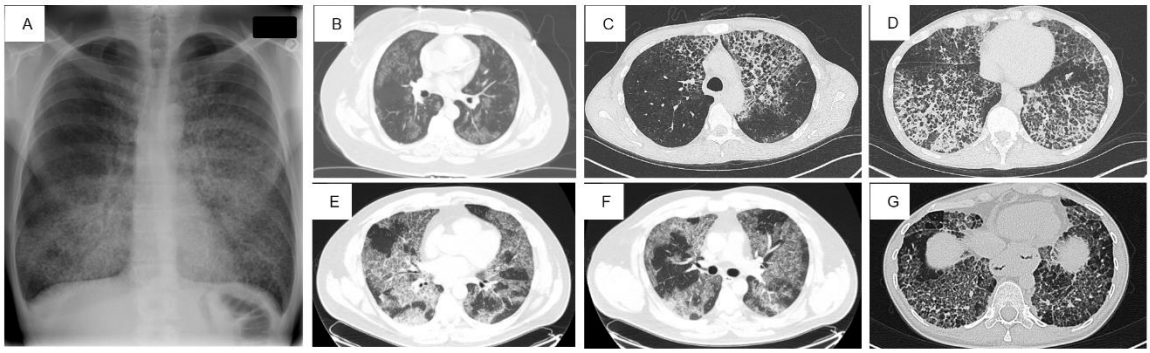


Figure 1

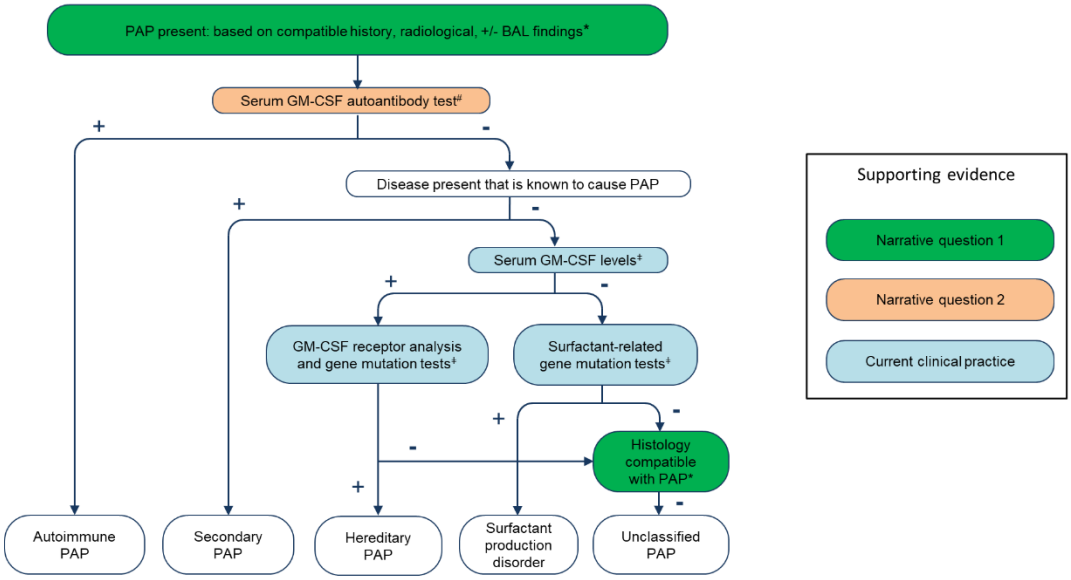

PAP present: based on compatible history, radiological, +/- BAL findings*
Serum GM-CSF autoantibody test#
+
-
Disease present that is known to cause PAP
+
-
Serum GM-CSF levels‡
+
-
GM-CSF receptor analysis and gene mutation tests‡
Surfactant-related gene mutation tests‡
+
-
-
Histology compatible with PAP*
+
-
Autoimmune PAP
Secondary PAP
Hereditary PAP
Surfactant production disorder
Unclassified PAP
Supporting evidence
Narrative question 1
Narrative question 2
Current clinical practice

Figure 2

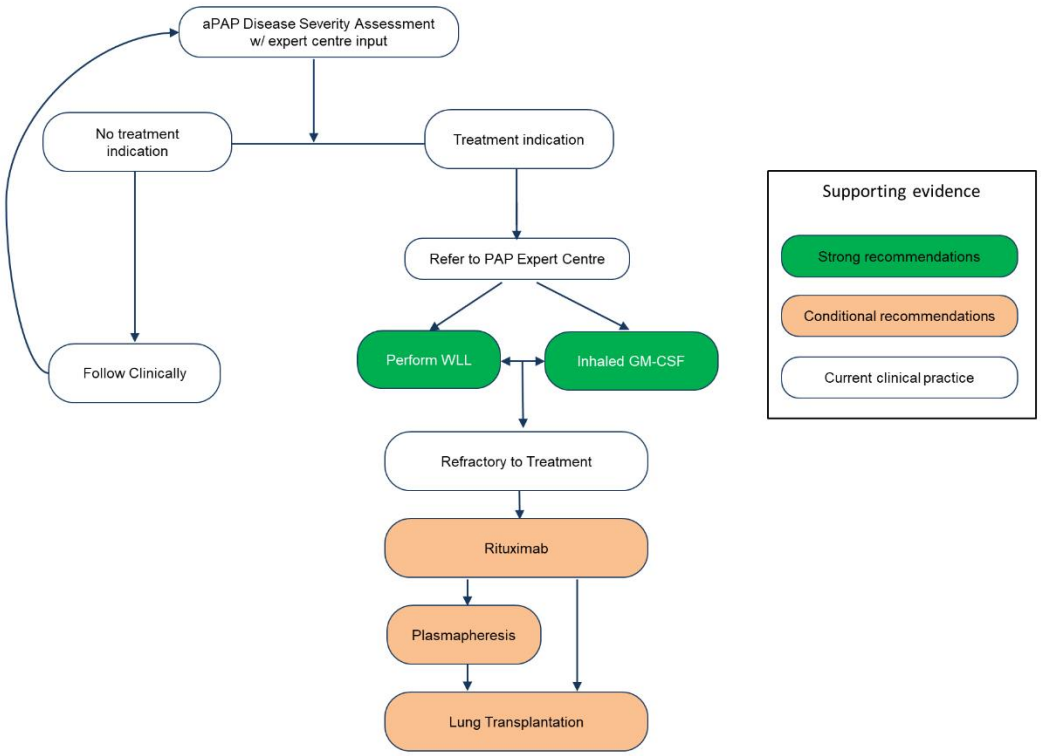

aPAP Disease Severity Assessment w/ expert centre input
No treatment indication
Treatment indication
Refer to PAP Expert Centre
Follow Clinically
Perform WLL
Inhaled GM-CSF
Refractory to Treatment
Rituximab
Plasmapheresis
Lung Transplantation
Supporting evidence
Strong recommendations
Conditional recommendations
Current clinical practice

Figure 3

Online appendix

European Respiratory Society guidelines for the Diagnosis and Management of Pulmonary Alveolar Proteinosis

Cormac McCarthy, Francesco Bonella, Marissa O'Callaghan, Clairelyne Dupin, Tiago Alfaro, Markus Fally, Raphael Borie, Ilaria Campo, Vincent Cottin, Aurelie Fabre, Matthias Griese, Alice Hadchouel-Duvergé, Stephane Jouneau, Maria Kokosi, Effrosyni Manali, Helmut Prosch, Bruce Trapnell, Marcel Veltkamp, Tisha Wang, Ingrid Toews, Alexander G. Mathioudakis, Elisabeth Bendstrup

Contents

Panel member expertise

Panel members	**Expertise**
Cormac McCarthy	Respiratory Medicine
Francesco Bonella	Respiratory Medicine
Elisabeth Bendstrup	Respiratory Medicine
Marissa O'Callaghan	Respiratory Medicine
Clairelyne Dupin	Respiratory Medicine
Tiago Alfaro	Respiratory Medicine
Markus Fally	Respiratory Medicine & Guidelines Methodology
Raphael Borie	Respiratory Medicine
Ilaria Campo	Respiratory Medicine
Vincent Cottin	Respiratory Medicine
Stephane Jouneau	Respiratory Medicine
Maria Kokosi	Respiratory Medicine
Effrosyni Manali	Respiratory Medicine
Bruce Trapnell	Respiratory Medicine
Marcel Veltkamp	Respiratory Medicine
Tisha Wang	Respiratory Medicine
Alexander G. Mathioudakis	Respiratory Medicine & Guidelines Methodology
Matthias Griese	Paediatric Respiratory Medicine
Alice Hadchouel-Duvergé	Paediatric Respiratory Medicine
Helmut Prosch	Radiology
Aurelie Fabre	Histopathology
Valeria Scotti	Librarian
Kristine M Bjelland	Patient representative
Sunita Dhir	Patient representative

Outcomes Table

Although we are not aware of any research evidence assessing how much people value the main outcomes, the task force patient representatives consider changes in AaDO2, PaO2, DLCO, VC/FVC and HRCT surrogate outcomes that are probably not important for patients. Patient representatives suggest adding patient reported outcome measures (PROMs) (e.g., symptoms, quality of life) in future clinical trials. Patient representatives specified a preference for non-invasive methods to treat their disease effectively with a strong appreciation for safety. A concern raised by patient representatives regarding inhaled GM-CSF is the time to treatment response and also concerns about reimbursement by insurance companies.

Question	Measure	Category	Level
Narrative question 1a. When should patients with clinical and radiological features consistent with a diagnosis of PAP undergo bronchoalveolar lavage (BAL)?	Sensitivity & Specificity		Critical
	Serious adverse events	Adverse events	Critical
Narrative question 1b. When should patients with clinical and radiological features consistent with a diagnosis of PAP undergo lung biopsy for histologic analysis?	Sensitivity & Specificity		Critical
	Safety	Adverse events	Critical
Narrative question 2. When should patients with clinical and radiological features consistent with PAP undergo GM-CSF antibody testing for diagnosing autoimmune PAP?	Sensitivity & Specificity		Critical
	Serious adverse events	Safety	Important
PICO 3. In patients with clinical symptoms and/or functional impairment due to PAP should whole lung lavage be used versus to no whole lung lavage?	Mortality	Safety	Critical
	Blood gas analysis	Lung function tests	Critical
	DLCO		Critical
	Serious adverse events	Safety	Critical
	HRCT	Scan	Critical
	Symptoms (dyspnoea)		Critical
	Exercise tolerance (6MWT)	Exercise capacity	Critical
PICO 4. In patients with confirmed autoimmune PAP should exogenous GM-CSF be used versus no exogenous GM-CSF?	Mortality	Safety	Critical
	Blood gas analysis	Lung function tests	Important
	DLCO		Critical
	Serious adverse events	Safety	Critical
	HRCT	Scan	Important
	Symptoms (dyspnoea)		Critical
	Exercise tolerance (6MWT)	Exercise capacity	Important
PICO 5. In patients with confirmed autoimmune PAP	Mortality	Safety	Critical
	Blood gas analysis		Important

should rituximab be used versus no immunosuppressive treatment?	DLCO	Lung function tests	Important
	Serious adverse events	Safety	Critical
	HRCT	Scan	Important
	Symptoms (dyspnoea)		Critical
	Exercise tolerance (6MWT)	Exercise capacity	Important
PICO 6. In patients with confirmed autoimmune PAP should plasmapheresis be used versus no plasmapheresis?	Mortality	Safety	Critical
	Blood gas analysis	Lung function tests	Important
	DLCO		Important
	Serious adverse events	Safety	Critical
	HRCT	Scan	Important
	Symptoms (dyspnoea)		Critical
	Exercise tolerance (6MWT)	Exercise capacity	Important
PICO 7. In patients with PAP progressing despite whole lung lavage or pharmacological treatment should lung transplantation be considered versus no lung transplantation?	Mortality		Critical
	Serious adverse events	Safety	Critical

NQ 1a: When should patients with clinical and radiological features consistent with a diagnosis of PAP undergo bronchoalveolar lavage?

Search Strategy

1. PubMed

("Pulmonary Alveolar Proteinosis"[Mesh] OR "Pulmonary alveolar proteinosis"[Title/Abstract] OR "Alveolar lipoproteinosis"[Title/Abstract] OR "Alveolar proteinosis"[Title/Abstract]) AND ("Bronchoalveolar lavage"[Title/Abstract] OR BAL[Title/Abstract] OR "Biopsy"[Mesh] OR "Bronchoscopy"[Mesh] OR "lung biopsy"[Title/Abstract] OR "Bronchoalveolar Lavage Fluid"[Mesh] OR "Bronchoalveolar Lavage Fluid"[Title/Abstract] OR Cryobiopsy[Title/Abstract] OR "Transbronchial biopsy"[Title/Abstract] OR "surgical lung biopsy"[Title/Abstract] OR "cytology"[Subheading] OR "cytological techniques"[MeSH Terms] OR "Differential cytology" OR "Histology"[Mesh] OR "pathology" [Subheading] OR histophatology[Title/Abstract]) NOT Case Reports[ptyp]

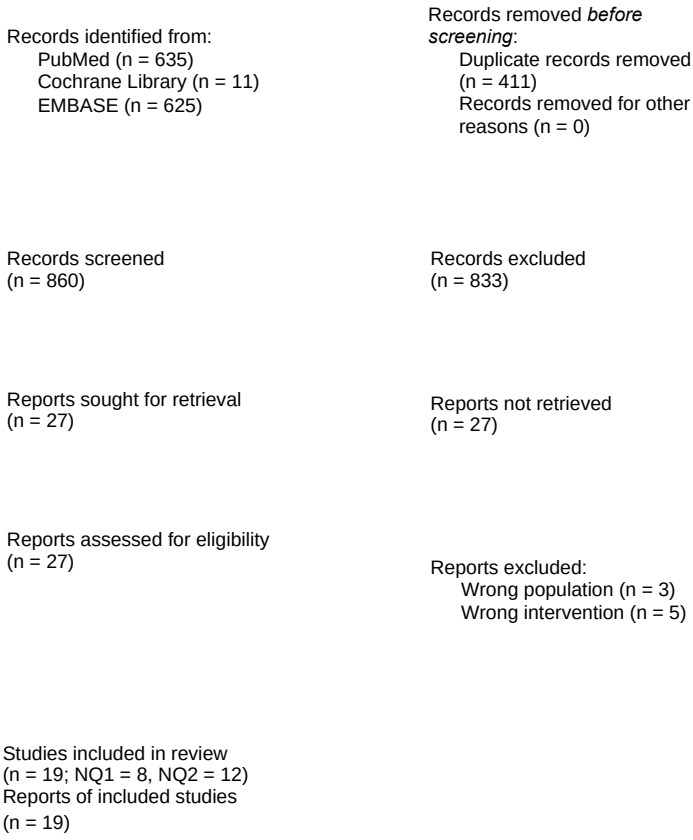
2. Cochrane Library

("Pulmonary alveolar proteinosis" OR "Alveolar lipoproteinosis" OR "Alveolar proteinosis") AND ("Bronchoalveolar Lavage" OR Biopsy OR "Bronchoscopy"R "lung biopsy" OR "Bronchoalveolar Lavage Fluid" OR Cryobiopsy OR "Transbronchial biopsy" OR "surgical lung biopsy") in Title Abstract Keyword

3. EMBASE

('lung alveolus proteinosis'/mj/exp OR 'lung alveolus proteinosis':ti,ab OR 'pulmonary alveolar proteinosis':ti,ab OR 'alveolar lipoproteinosis':ti,ab OR 'alveolar proteinosis':ti,ab) AND ('lung lavage'/exp OR 'lung lavage':ti,ab OR 'lavage fluid'/exp OR 'lavage fluid':ti,ab OR 'bronchoalveolar lavage'/exp OR 'bronchoalveolar lavage':ti,ab OR 'bronchoalveolar lavage fluid':ti,ab OR 'bronchoscopy'/exp OR 'bronchoscopy':ti,ab OR 'lung biopsy'/exp OR 'lung biopsy':ti,ab OR 'cryobiopsy'/exp OR 'cryobiopsy':ti,ab OR 'transbronchial biopsy'/exp OR 'transbronchial biopsy':ti,ab OR 'transbronchial lung biopsy'/exp OR 'transbronchial lung biopsy':ti,ab OR 'surgical lung biopsy'/exp OR 'surgical lung biopsy':ti,ab OR 'cytology'/exp OR 'cytology':ti,ab OR 'cytological techniques'/exp OR 'cytological techniques':ti,ab OR 'differential cytology':ti,ab OR 'histology'/exp OR 'histology':ti,ab OR 'pathology'/exp OR 'pathology':ti,ab OR 'histopathology'/exp OR 'histopathology':ti,ab) NOT 'case report'/exp AND ([english]/lim OR [french]/lim) AND ('article'/it OR 'article in press'/it OR 'review'/it)

PRISMA Flow diagram summarising the study selection process



Main studies considered by the panel.

1. Deleanu OC, Zaharie AM, Şerbescu A, NiŢu FM, MihălŢan FD, Arghir OC. Analysis of bronchoalveolar lavage fluid in a first Romanian pulmonary alveolar proteinosis cohort. Rom J Morphol Embryol. 2016;57(2 Suppl):737-743.
2. Ilkovich YM, Ariel BM, Novikova LN, Bazhanov AA, Dvorakovskaya IV, Ilkovich MM. Pulmonary alveolar proteinosis: a long way to correct diagnosis: problems of diagnostics and therapy in routine practice. Ann Clin Lab Sci. 2014 Fall;44(4):405-9.
3. Xu Z, Jing J, Wang H, Xu F, Wang J. Pulmonary alveolar proteinosis in China: a systematic review of 241 cases. Respirology. 2009 Jul;14(5):761-6. doi: 10.1111/j.1440-1843.2009.01539.x.
4. Bonella F, Bauer PC, Griese M, Ohshimo S, Guzman J, Costabel U. Pulmonary alveolar proteinosis: new insights from a single-center cohort of 70 patients. Respir Med. 2011 Dec;105(12):1908-16. doi: 10.1016/j.rmed.2011.08.018.
5. Enaud L, Hadchouel A, Coulomb A, Berteloot L, Lacaille F, Boccon-Gibod L, Boulay V, Darcel F, Griese M, Linard M, Louha M, Renouil M, Rivière JP, Toupance B, Verkarre V, Delacourt C, de Blic J. Pulmonary alveolar proteinosis in children on La Réunion Island: a new inherited disorder? Orphanet J Rare Dis. 2014 Jun 14;9:85. doi: 10.1186/1750-1172-9-85.
6. Maygarden SJ, Iacocca MV, Funkhouser WK, Novotny DB. Pulmonary alveolar proteinosis: a spectrum of cytologic, histochemical, and ultrastructural findings in bronchoalveolar lavage fluid. Diagn Cytopathol. 2001 Jun;24(6):389-95. doi: 10.1002/dc.1086.
7. Danel C, Israel-Biet D, Costabel U, Rossi GA, Wallaert B. The clinical role of BAL in alveolar proteinosis. Eur Respir J. 1990 Sep;3(8):950-1, 961-9.
8. Azuma K, Takimoto T, Kasai T, Hirose M, Hatsuda K, Sugimoto C, Arai T, Akira M, Inoue Y. Diagnostic yield and safety of bronchofiberscopy for pulmonary alveolar proteinosis. Respir Investig. 2021 Nov;59(6):757-765. doi: 10.1016/j.resinv.2021.03.012.

Evidence to decision framework

QUESTION

When should patients with clinical and radiological features consistent with a diagnosis of PAP undergo bronchoalveolar lavage (BAL)?	
POPULATION:	Pulmonary Alveolar Proteinosis
INTERVENTION:	Bronchoalveolar lavage (BAL)
COMPARISON:	MDT consensus diagnosis
MAIN OUTCOMES:	Sensitivity and specificity; safety

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	Pulmonary alveolar proteinosis (PAP) is a rare but burdensome disease, characterised by progressive respiratory symptoms, including breathlessness, that is characterised by significant morbidity and -if untreated- mortality. There are three distinct clinical forms of PAP; hereditary, primary (autoimmune) and secondary. For many years, BAL has been regarded as the gold standard to diagnose all forms of PAP. Since the advent of GM-CSF autoantibody testing and molecular/genomic testing for autoimmune PAP and hereditary & congenital PAP, the use of an invasive BAL in these cases can be questioned.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● **Large** ○ Varies ○ Don't know	**Available data:** Eight observational studies, mainly correlating and comparing clinical, radiology and tissue histology[1-8]. **Methodology** The technique and clinical utility of BAL for patients with ILD has been described in detail in the relevant ATS Clinical Practice Guidelines[9].	

	Desirable effects BAL is considered a gold standard test for diagnosing PAP. There are limited data around the diagnostic yield of BAL. Only two studies assessed the diagnostic yield of BAL for pulmonary alveolar proteinosis[1,4]. Azuma et al, in a prospective observational study involving 150 consecutive patients with PAP in Japan suggested a diagnostic yield of 90.7% (78/86 patients) for BAL[1]. Deleanu et al, in a retrospective analysis of 20 cases with PAP in Romania found a similar yield (90%, 18/20 patients)[4]. Anti-GM-CSF antibodies were not assessed in the BAL in either of these cohorts[1,4]. Several other studies and case reports (not referenced here) report on the widespread use of BAL for PAP diagnosis both in adults and children, without specifying the diagnostic yield[2,3,5-8].	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Trivial** ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Available data:** As above **Undesirable effects:** We did not find any studies reporting on the safety of BAL in patients with PAP or suspected PAP.	The safety of bronchoalveolar lavage has been assessed in a recent systematic review and meta-analysis of 17 studies, totalling 1,085 patients with acute respiratory failure[10]. This meta-analysis revealed an integrated frequency of death of 0.000% [0.000-0.045%] after BAL[10]. The overall risk of severe pulmonary complications was 1.32% [0.000%-4.410%], of severe cardiovascular complications 0.040% [0.000%-0.710%] and of major bleeding 0.000% [0.000%-0.270%][10]. These findings support the safety of BAL even among acutely unwell patients with acute respiratory failure. An expert review suggests that most adverse events of BAL are closely related to endoscopic technique, location, and extent of lavaged lung area, volume and temperature of instilled fluid[3].

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Very low** ○ Low Moderate ○ High ○ No included studies	Limited data on the diagnostic yield of PAP, that are based on two observational studies totalling 106 cases diagnosed using BAL. Risk of bias is high as the gold standard method for diagnosis is not described in detail. We did not find any studies directly assessing the undesirable effects of BAL among patients with PAP or suspected PAP.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● **No important uncertainty or variability**	No specific studies were identified to answer this question	The panel, including patient representatives, felt that the risks associated with BAL are trivial and acceptable for acquiring a confident diagnosis that will allow potentially life-saving, evidence-based treatment for patients with suspected PAP.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Favors the comparison** ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○Favors the intervention ○ Varies ○ Don't know	BAL has a high diagnostic yield and a low risk of complications.	The panel, including patient representatives feel that BAL is a well tolerated procedure.

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● **Negligible costs and savings** ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No specific studies were identified to answer this question.	Bronchoscopy and BAL can be performed as a day case, but required specialised equipment and personnel. While the procedure is associated with some costs, these are outweighed by the beneficial effects of gaining a confident diagnosis that will allow potentially life-saving, evidence-based treatment for patients with suspected PAP.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No specific studies were identified to answer this question.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● **Favors the intervention** ○ Varies ○ No included studies	No specific studies were identified to answer this question.	Bronchoscopy and BAL can be performed as a day case, but require specialised equipment and personnel. While the procedure is associated with some costs, these are outweighed by the beneficial effects of gaining a confident diagnosis that will allow potentially life-saving, evidence-based treatment for patients with suspected PAP.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No specific studies were identified to answer this question.	Acccess to bronchoscopy may be limited in developing countries, especially in sub-Saharan Africa. However, it is increasingly available in tertiary centres globally. The panel felt that BAL would not impact on equity

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No specific studies were identified to answer this question.	The panel, including patient representatives, conclude that BAL is a safe and well tolerated procedure that would be available to patients with suspected PAP, given the high likelihood of establishing an accurate diagnosis.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No specific studies were identified to answer this question.	While some centres may not have access to bronchoscopy and BAL, it is likely that tertiary centres with relevant expertise are available almost globally.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

Recommendation
We recommend BAL be performed as part of the diagnostic work up of patients with suspected pulmonary alveolar proteinosis syndrome (very low certainty, strong recommendation).

NQ 1b: When should patients with clinical and radiological features consistent with a diagnosis of PAP undergo a lung biopsy for histologic analysis?

Search Strategy

See NQ1a (combined search strategy)

PRISMA Flow diagram summarising the study selection process

See NQ1a (combined flow diagram)

Main studies and documents considered by the panel.

1. Korevaar DA, Colella S, Fally M, Camuset J, Colby TV, Hagmeyer L, Hetzel J, Maldonado F, Morais A, Ravaglia C, Spijker R, Tomassetti S, Troy LK, Verschakelen JA, Wells AU, Tonia T, Annema JT, Poletti V. European Respiratory Society guidelines on transbronchial lung cryobiopsy in the diagnosis of interstitial lung diseases. Eur Respir J. 2022 Nov 10;60(5):2200425. doi: 10.1183/13993003.00425-2022.
2. Sharp C, McCabe M, Adamali H, Medford AR. Use of transbronchial cryobiopsy in the diagnosis of interstitial lung disease-a systematic review and cost analysis. QJM. 2017 Apr 1;110(4):207-214. doi: 10.1093/qjmed/hcw142. PMID: 27521581.
3. Dhooria S, Sehgal IS, Aggarwal AN, Behera D, Agarwal R. Diagnostic Yield and Safety of Cryoprobe Transbronchial Lung Biopsy in Diffuse Parenchymal Lung Diseases: Systematic Review and Meta-Analysis. Respir Care. 2016 May;61(5):700-12. doi: 10.4187/respcare.04488.
4. Hewitt CJ, Hull D, Keeling JW. Open lung biopsy in children with diffuse lung disease. Arch Dis Child. 1974 Jan;49(1):27-35. doi: 10.1136/adc.49.1.27.
5. Prakash UB, Barham SS, Carpenter HA, Dines DE, Marsh HM. Pulmonary alveolar phospholipoproteinosis: experience with 34 cases and a review. Mayo Clin Proc. 1987 Jun;62(6):499-518. doi: 10.1016/s0025-6196(12)65477-9.
6. Chuang MT, Raskin J, Krellenstein DJ, Teirstein AS. Bronchoscopy in diffuse lung disease: evaluation by open lung biopsy in nondiagnostic transbronchial lung biopsy. Ann Otol Rhinol Laryngol. 1987 Nov-Dec;96(6):654-7. doi: 10.1177/000348948709600607.
7. Rubinstein I, Mullen JB, Hoffstein V. Morphologic diagnosis of idiopathic pulmonary alveolar lipoproteinosis-revisited. Arch Intern Med. 1988 Apr;148(4):813-6.

8. Fisher M, Roggli V, Merten D, Mulvihill D, Spock A. Coexisting endogenous lipoid pneumonia, cholesterol granulomas, and pulmonary alveolar proteinosis in a pediatric population: a clinical, radiographic, and pathologic correlation. Pediatr Pathol. 1992 May-Jun;12(3):365-83. doi: 10.3109/15513819209023316.

9. Han Q, Luo Q, Chen X, Xie J, Wu L, Chen R. The evaluation of clinical usefulness of transbrochoscopic lung biopsy in undefined interstitial lung diseases: a retrospective study. Clin Respir J. 2017 Mar;11(2):168-175. doi: 10.1111/crj.12318.

10. Azuma K, Takimoto T, Kasai T, Hirose M, Hatsuda K, Sugimoto C, Arai T, Akira M, Inoue Y. Diagnostic yield and safety of bronchofiberscopy for pulmonary alveolar proteinosis. Respir Investig. 2021 Nov;59(6):757-765. doi: 10.1016/j.resinv.2021.03.012.

11. McCarthy C, Carey B, Trapnell BC. Blood Testing for Differential Diagnosis of Pulmonary Alveolar Proteinosis Syndrome. Chest. 2019 Feb;155(2):450-452. doi: 10.1016/j.chest.2018.11.002.

12. Tomassetti S, Wells AU, Costabel U, Cavazza A, Colby TV, Rossi G, Sverzellati N, Carloni A, Carretta E, Buccioli M, Tantalocco P, Ravaglia C, Gurioli C, Dubini A, Piciucchi S, Ryu JH, Poletti V. Bronchoscopic Lung Cryobiopsy Increases Diagnostic Confidence in the Multidisciplinary Diagnosis of Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2016 Apr 1;193(7):745-52. doi: 10.1164/rccm.201504-0711OC.

Evidence to decision framework

QUESTION

When should patients with clinical and radiological features consistent with a diagnosis of PAP undergo lung biopsy for histologic analysis?	
POPULATION:	Pulmonary Alveolar Proteinosis
INTERVENTION:	Lung biopsy
COMPARISON:	MDT consensus diagnosis
MAIN OUTCOMES:	Sensitivity and specificity; safety

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	Pulmonary alveolar proteinosis (PAP) is a rare but burdensome disease, characterised by progressive respiratory symptoms, including breathlessness, that is characterised by significant morbidity and -if untreated- mortality. There are three distinct clinical forms of PAP; hereditary, primary (autoimmune) and secondary. For many years, lung tissue was needed to diagnose all forms of PAP and thus, an invasive procedure with its' associated risk. Since the advent of GM-CSF autoantibody testing and molecular testing for autoimmune PAP and hereditary & congenital PAP, which accounts for almost, the use of an invasive tissue biopsy in these cases is being challenged.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● **Moderate** ○ Large ○ Varies ○ Don't know	**Available data:** A recent ERS guideline on the use of transbronchial lung cryobiopsy in the diagnosis of ILDs[11], 2 meta-analyses assessing the diagnostic yield and safety of lung biopsy (transbronchial and/or surgical) in patients with ILD[12,13] and nine observational studies, mainly comparing clinical, radiology and tissue histology[1,14-20]. **Methodology**	

	Tissue can be obtained using endoscopic transbronchial biopsy (TBB), cryobiopsy (CTBLB) and surgical (video assisted or open) lung biopsy (SLB). **Desirable effects:** Five studies described the findings of biopsy in specifically in patients with PAP[1,15,18-20]. A limitation of both transbronchial and surgical lung biopsy is the limited sensitivity due to the patchy involvement of the lung parenchyma[18]. McCarty reported findings from the US National PAP registry suggesting a sensitivity of either transbronchial or surgical lung biopsy of around 72%[18]. Azuma et al, in a prospective observational study involving 150 consecutive patients with PAP in Japan suggests a diagnostic yield of 81.4% (70/86 patients) for transbronchial lung biopsy[1]. Rubinstein, based on a smaller cohort, reports a similar proportion 83% (5/6 patients)[20]. In older studies, surgical biopsy was considered the gold standard for diagnosing PAP and as a result no data were given around its sensitivity[9,15,19,20]. Similar findings were observed in cohorts of patients with various interstitial diseases, confirming the diagnostic limitations of biopsies, due to the patchy and/or non-specific nature of the findings[14,16,17]. A recent meta-analysis of 14 studies involving 1,183 patients, assessing the diagnostic yield of transbronchial biopsy in patients with diffuse parenchymal lung disease showed a diagnostic yield of 86.3%, 95% confidence intervals [80.2%-90.8%] for cryo-transbronchial lung biopsy and 56.5% [27.5%-83.2%] for flexible forceps biopsy[12]. Similarly, Sharp et al quantified the diagnostic yield of transbronchial cryobiospy (11 studies, 736 participants), forceps transbronchial biopsy (11 studies, n=1,539) and surgical biopsy (24 studies, n=2,773), as 84.4% [75.9%-91.4%], 64.3% [52.6%-75.1%], and 91.1% [84.9%-95.7%][13].	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● **Moderate** ○ Large ○ Varies ○ Don't know	**Available data:** As above As previously described (see desirable effects), an important undesirable effect is a non-diagnostic biopsy[1,12,18]. The safety and diagnostic yield of transbronchial lung biopsy in patients with diffuse parenchymal lung disease was appraised in a systematic review and meta-analysis of 14 studies[12]. Safety was reported in 13 studies totalling 764 transbronchial biopsies, suggesting an overall risk of major complications of 7.2%[12]. Pneumothorax occurred in 6.8% of the biopsies, major bleeding in 0.3%, while only one death was reported (0.1%)[12]. Sharp et al reported a 10% [5.4%-16.1%] risk of pneumothorax and 20.99% [5.6%-42.8%] risk of moderate bleeding, with a <0.01 risk of death for transbronchial cryobiopsy procedures[13]. Tomassetti et all revealed a higher risk of pneumothorax (33%, 19/58 participants), among patients undergoing bronchoscopic lung cryobiopsy for diffuse parenchymal lung disease[9]. Azuma et al, assessed the safety of bronchoscopy with transbronchial biopsy in 86 patients with PAP and did not report any serious adverse events[1]. Pneumothorax was observed in 3.5% of the participants,	

	but no drainage was required[1]. Minimal bleeding was noted in 7% of participants[1]. None of the patients experienced uncontrollable hypoxemia or fever during or after the bronchoscopy[1]. Sharp et al also assessed the safety of surgical biopsy for patients with ILD. Surgical mortality was 2.3% [1.3%-3.6%], while the surgical morbidity risk was estimated at 12.9% [9.3%-16.9%]. The mean hospitalisation time after a surgical lung biopsy has estimated to be 6 days after surgical lung biopsy (range: 3-17 days), in contrast to 3 days (range: 0-9 days), associated with transbronchial biopsy[9]. Hewitt et al quantified the safety of surgical lung biopsy among 24 children with ILD[17]. More specifically, one child (4.2%) died within 24 hours of the lung biopsy, and another one developed a serious complication, namely pneumothorax requiring drainage[17]. Less serious adverse events included small pleural effusions that resolved spontaneously (12.5%) and subcutaneous surgical emphysema (12.5%)[17].	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● **Moderate** ○ High ○ No included studies	While the certainty was not formally assessed, data on the safety and diagnostic yield of biopsy were based on good quality systematic reviews and large observational studies, suggesting moderate certainty.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● **Probably no important uncertainty or variability** ○ No important uncertainty or variability	No specific studies were identified to answer this question	The panel, including patient representatives, conclude that the risks associated with transbronchial or surgical lung biopsy outweigh potential benefits, especially due to limitations in the diagnostic yield that does not appear to clearly improve the diagnostic yield of the combination of bronchoalveolar lavage findings with multidisciplinary assessment.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● **Does not favor either the intervention or the comparison** ○ Probably favors the intervention ○Favors the intervention ○ Varies ○ Don't know	The diagnostic yield of both transbronchial and surgical lung biopsy is limited by the patchy involvement of the lung parenchyma, while both diagnostic procedures are associated with complications, including serious complications. Surgical biopsy is associated with more adverse events but still imperfect diagnostic yield. Overall, in view of the high diagnostic yield of the combination of BAL and multidisciplinary diagnostic approach, biopsy does not appear to add to the diagnostic process.	

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● **Moderate costs** ○ Negligible costs and savings Moderate savings ○ Large savings ○ Varies ○ Don't know	No specific studies to answer this question.	Some centers do not have access to tissue sampling, expert interventional pneumologists/endoscopists /thoracic surgeons and expert lung pathologist.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	No specific studies to answer this question.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● **Probably favors the comparison** ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No specific studies were identified to answer this question.	While a transbronchial biopsy is not very resource intensive, the limited evidence of benefit suggests this diagnostic test is not cost-effective.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● **Probably reduced** ○ Probably no impact ○Probably increased ○ Increased ○ Varies ○ Don't know	No specific studies were identified to answer this question.	Some centers will not have access to tissue sampling, expert interventional pneumologists/endoscopists /thoracic surgeons and expert lung pathologist

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	No specific studies were identified to answer this question.	The panel, including patient representatives, consider the intervention would be acceptable by the majority of patients in case of ongoing investigation for most diffuse parenchymal lung diseases. However, it would be important to explain the limited diagnostic yield and reason for the procedure.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ●**Probably yes** ○ Yes ○ Varies ○ Don't know	No specific studies were identified to answer this question.	Some centers might not have access to tissue sampling, expert interventional pneumologists/endoscopists /thoracic surgeons and expert lung pathologist

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	**High**			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

Recommendation
We suggest to not routinely perform lung biopsy as part of the diagnostic work up of patients with suspected PAP (moderate certainty, conditional recommendation).

NQ 2: When should patients with clinical and radiological features consistent with PAP undergo GM-CSF antibody testing for diagnosing autoimmune PAP?

Search Strategy

1. PubMed

("Pulmonary Alveolar Proteinosis"[Mesh] OR "Pulmonary alveolar proteinosis"[Title/Abstract] OR "Alveolar lipoproteinosis"[Title/Abstract] OR "Alveolar proteinosis"[Title/Abstract]) AND ("Granulocyte-Macrophage Colony-Stimulating Factor"[Mesh] OR "Granulocyte Macrophage Colony Stimulating Factor"[Title/Abstract] OR "Gm-csf"[Title/Abstract] OR "Rh-gmcsf" [Title/Abstract] OR "rgm-csf"[Title/Abstract] OR CSF-2[Title/Abstract] OR csf2rb [Title/Abstract] OR "Cytokine Receptor Common beta Subunit"[Mesh] OR 'colony stimulating factor 2' OR "Colony-Stimulating Factors"[Mesh] OR "Colony-Stimulating Factors" [Title/Abstract] OR "CSF2RA protein, human" [Supplementary Concept] OR "CSF2RB protein, human" [Supplementary Concept] OR Gm-ab[Title/Abstract] OR GMAb[Title/Abstract] OR "gm-antibody"[Title/Abstract] OR "Granulocyte Macrophage Colony Stimulating Factor Antibod*" [Title/Abstract] OR "anti-granulocyte-macrophage colony-stimulating factor antibod*" [Title/Abstract] OR "anti-granulocyte macrophage colony stimulating factor antibod*" [Title/Abstract] OR "anti-gm-csf antibod*" [Title/Abstract] OR "gm-csf antibod*" [Title/Abstract] OR "Autoantibodies"[Mesh] OR Autoantibodies[Title/Abstract] OR "Antibodies" [Mesh] OR Antibodies[Title/Abstract] OR "Auto-antibod*"[Title/Abstract] OR Antibod* [Title/Abstract] OR autoantibod*[Title/Abstract]) NOT Case Reports[ptyp]

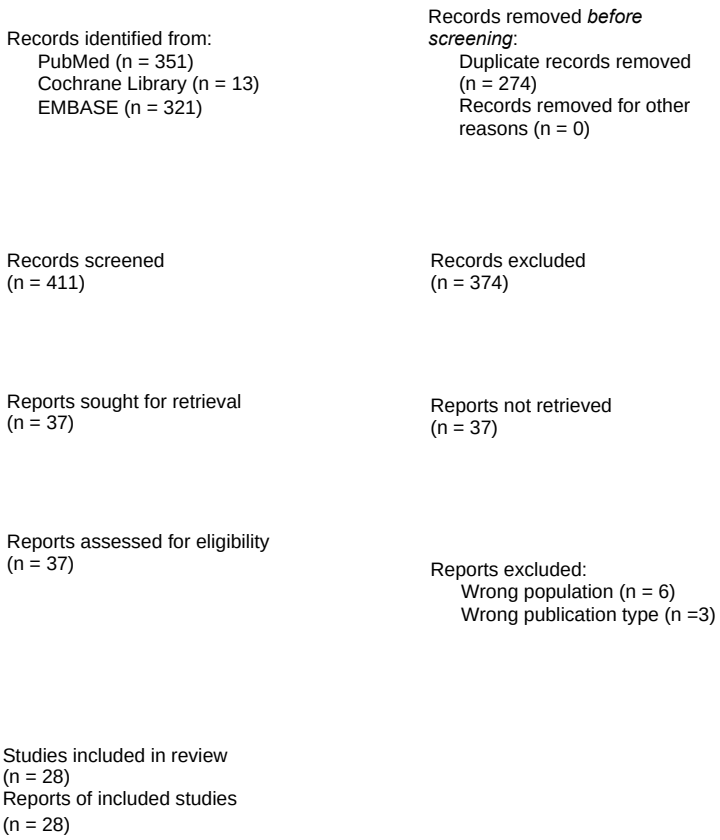
2. Cochrane Library

("Pulmonary Alveolar Proteinosis"[Mesh] OR "Pulmonary alveolar proteinosis" OR "Alveolar lipoproteinosis" OR "Alveolar proteinosis") AND ("Granulocyte-Macrophage Colony-Stimulating Factor"[Mesh] OR "Autoantibodies"[Mesh] OR "Antibodies"[Mesh] OR "Auto-antibody" OR Antibody OR autoantibody) in Title Abstract Keyword

3. EMBASE

('lung alveolus proteinosis'/mj/exp OR 'lung alveolus proteinosis':ti,ab OR 'pulmonary alveolar proteinosis':ti,ab OR 'alveolar lipoproteinosis':ti,ab OR 'alveolar proteinosis':ti,ab) AND ('granulocyte macrophage colony stimulating factor'/exp OR 'granulocyte macrophage colony stimulating factor':ti,ab OR 'gm-csf':ti,ab OR 'rh-gmcsf':ti,ab OR 'rgm-csf':ti,ab OR 'csf 2':ti,ab OR csf2rb:ti,ab OR 'colony stimulating factor 2'/exp OR 'colony stimulating factor 2':ti,ab OR 'gm-csf signaling'/exp OR 'gm-csf signaling':ti,ab OR 'cd131 antigen'/exp OR 'cd131 antigen':ti,ab OR 'csf2ra protein'/exp OR 'csf2ra protein':ti,ab OR 'csf2rb protein'/exp OR 'csf2rb protein':ti,ab OR 'gm ab':ti,ab OR gmab:ti,ab OR 'granulocyte macrophage colony stimulating factor antibody'/exp OR 'granulocyte macrophage colony stimulating factor antibod*':ti,ab OR 'anti-granulocyte-macrophage colony-stimulating factor antibod*':ti,ab OR 'anti-granulocyte macrophage colony stimulating factor antibod*':ti,ab OR 'anti-gm-csf antibod*':ti,ab OR 'gm-antibody':ti,ab OR 'gm-csf antibod*':ti,ab OR 'gm csf antibod*':ti,ab OR 'gmcsf antibod*':ti,ab OR 'autoantibody'/exp OR 'antibody'/exp OR autoantibod*:ti,ab OR antibod*:ti,ab OR 'auto antibody':ti,ab OR 'antibody, auto':ti,ab) NOT 'case report'/exp

PRISMA Flow diagram summarising the study selection process



Main studies considered by the panel.

1. Bonella F, Bauer PC, Griese M, Ohshimo S, Guzman J, Costabel U. Pulmonary alveolar proteinosis: new insights from a single-center cohort of 70 patients. Respir Med. 2011 Dec;105(12):1908-16. doi: 10.1016/j.rmed.2011.08.018.
2. Bonfield TL, John N, Barna BP, Kavuru MS, Thomassen MJ, Yen-Lieberman B. Multiplexed particle-based anti-granulocyte macrophage colony stimulating factor assay used as pulmonary diagnostic test. Clin Diagn Lab Immunol. 2005 Jul;12(7):821-4. doi: 10.1128/CDLI.12.7.821-824.2005.
3. Bonfield TL, Kavuru MS, Thomassen MJ. Anti-GM-CSF titer predicts response to GM-CSF therapy in pulmonary alveolar proteinosis. Clin Immunol. 2002 Dec;105(3):342-50. doi: 10.1006/clim.2002.5301.
4. Bonfield TL, Russell D, Burgess S, Malur A, Kavuru MS, Thomassen MJ. Autoantibodies against granulocyte macrophage colony-stimulating factor are diagnostic for pulmonary alveolar proteinosis. Am J Respir Cell Mol Biol. 2002 Oct;27(4):481-6. doi: 10.1165/rcmb.2002-0023OC.
5. Campo I, Meloni F, Gahlemann M, Sauter W, Ittrich C, Schoelch C, Trapnell BC, Gupta A. An exploratory study investigating biomarkers associated with autoimmune pulmonary alveolar proteinosis (aPAP). Sci Rep. 2022 May 24;12(1):8708. doi: 10.1038/s41598-022-11446-8.
6. Inoue Y, Trapnell BC, Tazawa R, Arai T, Takada T, Hizawa N, Kasahara Y, Tatsumi K, Hojo M, Ichiwata T, Tanaka N, Yamaguchi E, Eda R, Oishi K, Tsuchihashi Y, Kaneko C, Nukiwa T, Sakatani M, Krischer JP, Nakata K; Japanese Center of the Rare Lung Diseases Consortium. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. Am J Respir Crit Care Med. 2008 Apr 1;177(7):752-62. doi: 10.1164/rccm.200708-1271OC. Epub 2008 Jan 17.
7. Ishii H, Trapnell BC, Tazawa R, Inoue Y, Akira M, Kogure Y, Tomii K, Takada T, Hojo M, Ichiwata T, Goto H, Nakata K; Japanese Center of the Rare Lung Disease Consortium. Comparative study of high-resolution CT findings between autoimmune and secondary pulmonary alveolar proteinosis. Chest. 2009 Nov;136(5):1348-1355. doi: 10.1378/chest.09-0097.
8. McCarthy C, Carey BC, Trapnell BC. Autoimmune Pulmonary Alveolar Proteinosis. Am J Respir Crit Care Med. 2022 May 1;205(9):1016-1035. doi: 10.1164/rccm.202112-2742SO.
9. Han X, Uchida K, Jurickova I, Koch D, Willson T, Samson C, Bonkowski E, Trauernicht A, Kim MO, Tomer G, Dubinsky M, Plevy S, Kugathsan S, Trapnell BC, Denson LA. Granulocyte-macrophage colony-stimulating factor autoantibodies in murine ileitis and progressive ileal Crohn's disease. Gastroenterology. 2009 Apr;136(4):1261-71, e1-3. doi: 10.1053/j.gastro.2008.12.046.
10. Nishimura M, Yamaguchi E, Takahashi A, Asai N, Katsuda E, Ohta T, Ohtsuka Y, Kosaka K, Matsubara A, Tanaka H, Yokoe N, Kubo A, Konno S, Baba K. Clinical significance of serum anti-GM-

CSF autoantibody levels in autoimmune pulmonary alveolar proteinosis. Biomark Med. 2018 Feb;12(2):151-159. doi: 10.2217/bmm-2017-0362.
11. Kitamura N, Ohkouchi S, Tazawa R, Ishii H, Takada T, Sakagami T, Tanaka T, Nakata K. Incidence of autoimmune pulmonary alveolar proteinosis estimated using Poisson distribution. ERJ Open Res. 2019 Mar 18;5(1):00190-2018. doi: 10.1183/23120541.00190-2018.
12. Kitamura T, Tanaka N, Watanabe J, Uchida, Kanegasaki S, Yamada Y, Nakata K. Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. J Exp Med. 1999 Sep 20;190(6):875-80. doi: 10.1084/jem.190.6.875.
13. Kitamura T, Uchida K, Tanaka N, Tsuchiya T, Watanabe J, Yamada Y, Hanaoka K, Seymour JF, Schoch OD, Doyle I, Inoue Y, Sakatani M, Kudoh S, Azuma A, Nukiwa T, Tomita T, Katagiri M, Fujita A, Kurashima A, Kanegasaki S, Nakata K. Serological diagnosis of idiopathic pulmonary alveolar proteinosis. Am J Respir Crit Care Med. 2000 Aug;162(2 Pt 1):658-62. doi: 10.1164/ajrccm.162.2.9910032.
14. Latzin P, Tredano M, Wüst Y, de Blic J, Nicolai T, Bewig B, Stanzel F, Köhler D, Bahuau M, Griese M. Anti-GM-CSF antibodies in paediatric pulmonary alveolar proteinosis. Thorax. 2005 Jan;60(1):39-44. doi: 10.1136/thx.2004.021329.
15. Lee E, Miller C, Ataya A, Wang T. Opportunistic Infection Associated With Elevated GM-CSF Autoantibodies: A Case Series and Review of the Literature. Open Forum Infect Dis. 2022 Apr 9;9(5):ofac146. doi: 10.1093/ofid/ofac146.
16. Lin FC, Chang GD, Chern MS, Chen YC, Chang SC. Clinical significance of anti-GM-CSF antibodies in idiopathic pulmonary alveolar proteinosis. Thorax. 2006 Jun;61(6):528-34. doi: 10.1136/thx.2005.054171.
17. Manali ED, Papadaki G, Konstantonis D, Tsangaris I, Papaioannou AI, Kolilekas L, Schams A, Kagouridis K, Karakatsani A, Orfanos S, Griese M, Papiris SA. Cardiovascular risk in pulmonary alveolar proteinosis. Expert Rev Respir Med. 2016 Feb;10(2):235-40. doi: 10.1586/17476348.2016.1116389.
18. 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.
19. McCarthy C, Carey B, Trapnell BC. Blood Testing for Differential Diagnosis of Pulmonary Alveolar Proteinosis Syndrome. Chest. 2019 Feb;155(2):450-452. doi: 10.1016/j.chest.2018.11.002.
20. Nakata K, Sugi T, Kuroda K, Yoshizawa K, Takada T, Tazawa R, Ueda T, Aoki A, Abe M, Tatsumi K, Eda R, Kondoh S, Morimoto K, Tanaka T, Yamaguchi E, Takahashi A, Oda M, Ishii H, Izumi S, Sugiyama

H, Nakagawa A, Tomii K, Suzuki M, Konno S, Ohkouchi S, Hirano T, Handa T, Hirai T, Inoue Y, Arai T, Asakawa K, Sakagami T, Tanaka T, Mikami A, Kitamura N. Validation of a new serum granulocyte-macrophage colony-stimulating factor autoantibody testing kit. ERJ Open Res. 2020 Jan 27;6(1):00259-2019. doi: 10.1183/23120541.00259-2019.

21. Nei T, Urano S, Motoi N, Takizawa J, Kaneko C, Kanazawa H, Tazawa R, Nakagaki K, Akagawa KS, Akasaka K, Ichiwata T, Azuma A, Nakata K. IgM-type GM-CSF autoantibody is etiologically a bystander but associated with IgG-type autoantibody production in autoimmune pulmonary alveolar proteinosis. Am J Physiol Lung Cell Mol Physiol. 2012 May 1;302(9):L959-64. doi: 10.1152/ajplung.00378.2011.

22. Nishimura M, Yamaguchi E, Takahashi A, Asai N, Katsuda E, Ohta T, Ohtsuka Y, Kosaka K, Matsubara A, Tanaka H, Yokoe N, Kubo A, Konno S, Baba K. Clinical significance of serum anti-GM-CSF autoantibody levels in autoimmune pulmonary alveolar proteinosis. Biomark Med. 2018 Feb;12(2):151-159. doi: 10.2217/bmm-2017-0362.

23. Sakagami T, Uchida K, Suzuki T, Carey BC, Wood RE, Wert SE, Whitsett JA, Trapnell BC, Luisetti M. Human GM-CSF autoantibodies and reproduction of pulmonary alveolar proteinosis. N Engl J Med. 2009 Dec 31;361(27):2679-81. doi: 10.1056/NEJMc0904077.

24. Schulert GS, Yasin S, Carey B, Chalk C, Do T, Schapiro AH, Husami A, Watts A, Brunner HI, Huggins J, Mellins ED, Morgan EM, Ting T, Trapnell BC, Wikenheiser-Brokamp KA, Towe C, Grom AA. Systemic Juvenile Idiopathic Arthritis-Associated Lung Disease: Characterization and Risk Factors. Arthritis Rheumatol. 2019 Nov;71(11):1943-1954. doi: 10.1002/art.41073.

25. Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. N Engl J Med. 2003 Dec 25;349(26):2527-39. doi: 10.1056/NEJMra023226.

26. Uchida K, Nakata K, Carey B, Chalk C, Suzuki T, Sakagami T, Koch DE, Stevens C, Inoue Y, Yamada Y, Trapnell BC. Standardized serum GM-CSF autoantibody testing for the routine clinical diagnosis of autoimmune pulmonary alveolar proteinosis. J Immunol Methods. 2014 Jan 15;402(1-2):57-70. doi: 10.1016/j.jim.2013.11.011.

27. Uchida K, Nakata K, Trapnell BC, Terakawa T, Hamano E, Mikami A, Matsushita I, Seymour JF, Oh-Eda M, Ishige I, Eishi Y, Kitamura T, Yamada Y, Hanaoka K, Keicho N. High-affinity autoantibodies

specifically eliminate granulocyte-macrophage colony-stimulating factor activity in the lungs of patients with idiopathic pulmonary alveolar proteinosis. Blood. 2004 Feb 1;103(3):1089-98. doi: 10.1182/blood-2003-05-1565.

28. Xiao YL, Xu KF, Li Y, Li Y, Li H, Shi B, Zhou KF, Zhou ZY, Cai HR. Occupational inhalational exposure and serum GM-CSF autoantibody in pulmonary alveolar proteinosis. Occup Environ Med. 2015 Jul;72(7):504-12. doi: 10.1136/oemed-2014-102407.

Evidence to decision framework

QUESTION

When should patients with clinical and radiological features consistent with PAP undergo GM-CSF antibody testing for diagnosing autoimmune PAP?	
POPULATION:	Patients with clinical, radiological, and BAL features consistent with a diagnosis of PAP Syndrome
INTERVENTION:	GM-CSF antibody levels
COMPARISON:	Multidisciplinary team (MDT) consensus diagnosis (Gold standard: clinical-radiological findings/multidisciplinary discussion)
MAIN OUTCOMES:	Sensitivity and specificity; safety

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	Pulmonary alveolar proteinosis (PAP) is a syndrome characterized by progressive accumulation of surfactant in pulmonary alveoli. It results in breathlessness and other respiratory symptoms, restrictive lung impairment, and hypoxemia, and in some patients, it leads to immune deficiency, serious infections, pulmonary fibrosis, respiratory failure, and death. PAP syndrome occurs in a heterogeneous group of mechanistically and clinically distinct genetic and acquired disorders due to impaired functions and/or reduced numbers of pulmonary alveolar macrophages. Autoimmune PAP is the most common PAP-causing disease, accounts for approximately 90% of all PAP patients, and is caused by an increase in immunoglobulin G antibodies present in the lungs and blood. Other PAP-causing diseases accounting for the remaining 10% of cases include in-born errors caused by mutations in genes required for normal surfactant production and lung development, and acquired disorders caused by inhalation of toxic dusts, certain chronic infections, inflammatory diseases, or other disorders. While somewhat overlapping with respect to nomenclature, PAP associated with inborn errors are also still referred to as congenital PAP (or metabolic surfactant production disorders), while those associated with another underlying disease are referred to secondary PAP.	

	Differential diagnosis and identification of the specific PAP-causing disease in each patient with PAP syndrome is of fundamental importance in the context of emerging disease-specific therapies. While a multidisciplinary team-based approach based on historical, physical, radiological, histopathological, cytological, and biochemical data has traditionally been used in evaluating PAP patients, none of these measures are specific for any PAP-causing disease or permit disease-specific diagnosis. A lung biopsy is unable to identify autoimmune PAP (or any other specific PAP-causing disease) and is associated with high morbidity. In contrast, for autoimmune PAP, a blood-based enzyme-linked immunosorbent assay (ELISA) test is available and is reported to be highly sensitive and specific. Other routine blood or saliva-based tests are available for the accurate diagnosis of PAP- caused by inborn errors. The diagnosis of PAP caused by another underlying condition or disease (i.e, 'secondary PAP' caused by dust inhalation, hematologic diseases, etc.) still requires a multidisciplinary team-approach. Thus, while a lung biopsy or bronchoalveolar lavage cytology can identify the presence of PAP syndrome, neither is capable of specifically diagnosing autoimmune PAP (or any other PAP-causing disease). Furthermore, due to the patchy nature of PAP, a lung biopsy can be negative in a substantial portion of patients.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● **Large** ○ Varies ○ Don't know	**Available data:** (i) Multiple real-world observational studies (such as Bonella 2011, Trapnell 2003, McCarthy 2019, McCarthy 2022)[2,18,21,22], including a retrospective cohort study of 248 patients (Inoue 2008)[23]. (ii) Three leading methodology papers (Kitamura 1999, Kitamura 2000, Uchida 2014)[24-26]. **Desirable effects:** GM-CSF deficient mice were found to accumulate surfactant in the lungs and cause a PAP-like disease[21]. Next GM-CSF antibodies were found in the bronchoalveolar lavage (BAL) fluid from patients with what was known at the time as 'idiopathic' PAP[26]. The terminology of autoimmune PAP was coined when GM-CSF antibodies were consistently isolated from the serum of patients with idiopathic PAP[25]. Inoue 2008 described the use of GM-CSF antibody testing in 248 patients with a tissue biopsy confirmed diagnosis of PAP[23]. 223 or 89.9% of these patients had no underlying disease or cause explaining why they had developed PAP and subsequently all of these patients had elevated GM-CSF antibody levels. This was not the case for the patients with known secondary PAP (n=24), patients with other lung diseases (n=24) or health individuals (n=14). Similarly, Bonella 2011 described the results of GM-CSF antibody testing in 70 patients with PAP; 64 of whom had idiopathic PAP[2]. The GM-CSF antibody cut off for normal was <10 ug/ml and antibody levels were negative for all 6 patients with secondary PAP and mean level of 64 ug/ml was noted in the idiopathic or autoimmune PAP group. Furthermore, the serum levels were	

	significantly higher at diagnosis prior to treatment than at remission (n=10). The sensitivity and specificity of GM-SCF antibody testing for a diagnosis of autoimmune PAP is 100% (Kitamura 2000, Uchida 2014)[24,25]. McCarthy 2022 describe the availability of GM-CSF antibody testing which is provided by specific centres located in the United States, Europe, China, and Japan[27]. The reference ranges used for test result interpretation (normal, ⩽3.1 μg/ml; indeterminate, >3.1 to <10.2 μg/ml; and abnormal, ⩾10.2 μg/ml) were determined by the Clinical and Laboratory Standards Institute on the basis of results for 153 healthy individuals (median, 0.33 μg/ml; 90% confidence interval [CI], 0.3–0.4 μg/ml) and 339 patients with autoimmune PAP (median, 84 μg/ml; 90% CI, 10.2–499 μg/ml). Test results within the indeterminate range are typically confirmed by evaluation of GM-CSF signalling. Finally, while biopsy was once considered the gold standard for diagnosing PAP, McCarthy 2019 report the findings from a US National PAP Registry which reveal that histological examination failed to identify the presence of PAP syndrome in 28% of cases because of patchy involvement[18]. Furthermore, it described the significant procedure-related morbidity associated with transbronchial and surgical lung biopsies.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Trivial** ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Available data:** As above **Undesirable effects:** Mortality or severe adverse events were not observed in these uncontrolled studies. It was previously observed that 0.3-2% of blood serum from healthy controls contained GM-CSF antibodies at a low titre so it is therefore possible that serum from such subjects may show positive results by latex agglutination testing. Kitamura 2000 reported false positive GM-CSF antibody testing by latex agglutination in two cases but these results were not seen when tested via blot assay and antigen capture assay[25]. Neither of these two cases went on to develop clinical sequelae of PAP. Uchida 2014 report some small increases in serum GM-CSF antibody level observed in diseases not associated with development of PAP[24]. For example, in 272 paediatric and 88 adult patients with Crohn's disease who did not have PAP, the median serum GM-CSF antibody concentrations were 2.4 and 11.7 μg/ml, respectively[28]. Functional testing was helpful and indicated that GM-CSF signalling was reduced but not abolished in these patients. Since the clinical symptoms of autoimmune PAP do not occur in patients without significant radiographic findings, combining GM-CSF antibody level testing with routine chest computed tomography will likely resolve any discrepancy potentially arising from intermediate GM-CSF antibody values close to the cutoff. Further, in a typical clinical setting, GM-CSF antibody testing would likely be considered after radiographic evaluation had suggested a diagnosis of PAP.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● **Moderate** ○ High ○ No included studies	GM-CSF antibodies can be measured in an objective, reproducible manner and this has been demonstrated in large patient cohorts in real-world settings across multiple countries. It has continued to demonstrate consistently high sensitivity and specificity. This can be seen in the papers referenced above (Uchida 2014, Kitamura 2000, McCarthy 2019, McCarthy 2022, Bonella 2011, Inoue 2008)[2,18,22-25,27]. Not only do we know that GM-CSF antibody levels are detectable in autoimmune PAP, but we know that antibodies against the GM-CSF receptor are pathogenic. This was demonstrated in mice studies as described above where GM-CSF knockout mice accumulate surfactant in the alveoli and develop a PAP like disease (Trapnell 2004)[21]. It was also demonstrated in primates where GM-CSF antibodies reproduced the molecular, cellular, and histopathologic features of PAP in healthy primates, demonstrating that GMSCF antibodies directly cause PAP (Sakagami 2010)[29].	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● **Probably no important uncertainty or variability** ○ No important uncertainty or variability	No specific studies were identified to answer this question	Although we are not aware of any research evidence assessing how much people value the main outcomes, the clinical practice guideline development group, and the patient representatives consider that a non-invasive blood test to screen for the most common cause of PAP is beneficial. Especially given the high sensitivity and specificity of the test. Furthermore, this finding of the presence and role of GM-CSF antibodies in autoimmune PAP has been the basis upon which a number of treatments have been developed. Please refer to PICO 4-6 for more information.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● **Favors the intervention** ○ Varies ○ Don't know	GM-CSF antibody testing is a non-invasive test of proven clinical value and a treatment target. This test can safely inform the diagnosis that is otherwise based on multidisciplinary consensus based on inferior or more invasive tests (lung biopsy).	

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● **Moderate savings** ○ Large savings ○ Varies ○ Don't know	No specific studies to answer this question. However, this blood test can simplify diagnosis that is otherwise based on multidisciplinary consensus based on inferior or more invasive tests (such as lung biopsy).	The test for GM-CSF antibody levels is not universally available and thus there will be an extra cost incurred to centres where shipping of the sample will be needed.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	No specific studies to answer this question. Our judgement is based on the observation that GM-CSF antibody level testing may prevent the need for invasive surgical biopsies in patients being worked up for PAP. Both surgical lung biopsies and transbronchial biopsies are associated with considerable cost.	The test for GM-CSF antibody levels is not universally available and thus there will be an extra cost incurred to centres where shipping of the sample will be needed.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ No included studies	No specific studies were identified to answer this question	As above. The test for GM-CSF antibody levels is not universally available and thus there will be an extra cost incurred to centres where shipping of the sample will be needed. However, it is of proven clinical value and can inform and facilitate diagnosis, that is otherwise based on multidisciplinary consensus based on inferior or more invasive tests.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No specific studies were identified to answer this question. However, considering the cost and resource heavy implications of an invasive biopsy, a blood test is more accessible and cost effective for the patient/ centre/ country.	The test for GM-CSF antibody levels is not universally available and thus there will be an extra cost incurred to centres where shipping of the sample will be needed. This may limit access or delay access to testing for some centres/ countries.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No specific studies were identified to answer this question. Blood test likely more acceptable than a biopsy to patients given it is less invasive, more rapid result and safer for the patient	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes, this test is a simple blood test. It is feasible to conduct and implement into clinical practice.	The serum is processed and interpreted using ELISA. This is a simple and widely available lab technique, yet GM-CSF antibody testing is available in limited centres around the world. This test needs to be more broadly instituted across the world.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

Recommendation

We recommend GM-CSF antibody testing for diagnosing autoimmune PAP for all patients with suspected or confirmed PAP syndrome (moderate certainty, strong recommendation).

PICO3: In patients with clinical symptoms and/or functional impairment due to PAP should whole lung lavage be used versus to no whole lung lavage?

Search Strategy

1. PubMed

("Pulmonary Alveolar Proteinosis"[Mesh] OR "Pulmonary alveolar proteinosis" OR "Alveolar lipoproteinosis" OR "Alveolar proteinosis") AND (WLL[Title/Abstract] OR "Whole-lung lavage" [Title/Abstract] OR "whole lung lavage" [Title/Abstract] OR "Lung Lavage" [Title/Abstract] OR "Segmental lavage" [Title/Abstract] OR "lobar lavage" [Title/Abstract] OR "Double-lumen endotracheal tube" OR "Intubation, Intratracheal"[Mesh]) NOT Case Reports[ptyp]

2. Cochrane Library

("Pulmonary alveolar proteinosis" OR "Alveolar lipoproteinosis" OR "Alveolar proteinosis") AND ("Whole-lung lavage" OR "whole lung lavage" OR "Lung Lavage" OR "Segmental lavage" OR "lobar lavage" OR "Double-lumen endotracheal tube") in Title Abstract Keyword

3. EMBASE

("Pulmonary alveolar proteinosis" OR "Alveolar lipoproteinosis" OR "Alveolar proteinosis") AND ("Whole-lung lavage" OR "whole lung lavage" OR "Lung Lavage" OR "Segmental lavage" OR "lobar lavage" OR "Double-lumen endotracheal tube") in Title Abstract Keyword

PRISMA Flow diagram summarising the study selection process

Included studies

1. Alkady H, Hosam Fathy Ali, Ahmed Saber, Ashraf Fawzy Mahmoud, Mohamed Adel. Whole lung lavage in comparison with bronchoscopic lobar lavage using the rigid bronchoscope in patients with pulmonary alveolar proteinosis: Is it time to change strategy?, Journal of the Egyptian Society of Cardio-Thoracic Surgery, Volume 24, Issue 4, 2016, Pages 330-337, ISSN 1110-578X, https://doi.org/10.1016/j.jescts.2016.12.007.

2. Athayde RAB, Arimura FE, Kairalla RA, Carvalho CRR, Baldi BG. Characterization and outcomes of pulmonary alveolar proteinosis in Brazil: a case series. J Bras Pneumol. 2018 May-Jun;44(3):231-236. doi: 10.1590/S1806-37562017000000168.

3. Badiozaman R, Tahereh P, Shideh D, Mohammadreza B, Ahmadreza A, Seyyedahmad T. Whole lung lavage of nine children with pulmonary alveolar proteinosis: experience in a tertiary lung center. Iran J Pediatr. 2013 Feb;23(1):95-9.

4. 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.

5. Ben-Abraham R, Greenfeld A, Rozenman J, Ben-Dov I. Pulmonary alveolar proteinosis: step-by-step perioperative care of whole lung lavage procedure. Heart Lung. 2002 Jan-Feb;31(1):43-9. doi: 10.1067/mhl.2002.119831.

6. Byun MK, Kim DS, Kim YW, Chung MP, Shim JJ, Cha SI, Uh ST, Park CS, Jeong SH, Park YB, Lee HL, Park MS. Clinical features and outcomes of idiopathic pulmonary alveolar proteinosis in Korean population. J Korean Med Sci. 2010 Mar;25(3):393-8. doi: 10.3346/jkms.2010.25.3.393.

7. Casanova S, Puglisi S, Gurioli C, Gurioli C, Maitan S, Martinello S, Sultani F, Ravaglia C, Poletti V. Whole lung lavage: our experience in pulmonary alveolar proteinosis and in type B Niemann Pick disease. Rassegna di Patologia dell'Apparato Respiratorio. 2021; 36(3):158-165. DOI: 10.36166/2531-4920-528

8. Deleanu OC, Zaharie AM, Şerbescu A, NiŢu FM, MihălŢan FD, Arghir OC. Analysis of bronchoalveolar lavage fluid in a first Romanian pulmonary alveolar proteinosis cohort. Rom J Morphol Embryol. 2016;57(2 Suppl):737-743.

9. 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.

10. Du Bois RM, McAllister WA, Branthwaite MA. Alveolar proteinosis: diagnosis and treatment over a 10-year period. Thorax. 1983 May;38(5):360-3. doi: 10.1136/thx.38.5.360.

11. Gay P, Wallaert B, Nowak S, Yserbyt J, Anevlavis S, Hermant C, Lovis A, Menard O, Maitre B, Vandemoortele T, Dutau H, Briault A, Bourdin A, Vergnon JM, Froudarakis ME; Groupe d''Endoscopie Thoracique de Langue Française. Efficacy of Whole-Lung Lavage in Pulmonary Alveolar Proteinosis: A Multicenter International Study of GELF. Respiration. 2017;93(3):198-206. doi: 10.1159/000455179.

12. Goldstein LS, Kavuru MS, Curtis-McCarthy P, Christie HA, Farver C, Stoller JK. Pulmonary alveolar proteinosis: clinical features and outcomes. Chest. 1998 Nov;114(5):1357-62. doi: 10.1378/chest.114.5.1357.

13. Guan Y, Zeng Q, Yang H, Zheng J, Li S, Gao Y, Deng Y, Mei J, He J, Zhong N. Pulmonary alveolar proteinosis: quantitative CT and pulmonary functional correlations. Eur J Radiol. 2012 Sep;81(9):2430-5. doi: 10.1016/j.ejrad.2011.05.005.

14. Holbert JM, Costello P, Li W, Hoffman RM, Rogers RM. CT features of pulmonary alveolar proteinosis. AJR Am J Roentgenol. 2001 May;176(5):1287-94. doi: 10.2214/ajr.176.5.1761287.

15. Kaenmuang P, Navasakulpong A. Efficacy of whole lung lavage in pulmonary alveolar proteinosis: a 20-year experience at a reference center in Thailand. J Thorac Dis. 2021 Jun;13(6):3539-3548. doi: 10.21037/jtd-20-3308. Erratum in: J Thorac Dis. 2021 Sep;13(9):5575.

16. Kariman K, Kylstra JA, Spock A. Pulmonary alveolar proteinosis: prospective clinical experience in 23 patients for 15 years. Lung. 1984;162(4):223-31. doi: 10.1007/BF02715650.

17. Kiani A, Parsa T, Adimi Naghan P, Dutau H, Razavi F, Farzanegan B, Pourabdollah Tootkaboni M, Abedini A. An eleven-year retrospective cross-sectional study on pulmonary alveolar proteinosis. Adv Respir Med. 2018;86(1):7-12. doi: 10.5603/ARM.2018.0003.

18. Lan, L.; Cen, Y.; Chen, D.; Ouyang, B.; Does higher lavage height improve lavage effect for pulmonary alveolar proteinosis patients. International Journal of Clinical and Experimental Medicine - Volume 9, Issue 7, pp. 13802-13810 - published 2016-01-01.

19. Mariani F, Salvaterra E, Lettieri S, De Silvestri A, Corino A, Bosio M, Fraolini E, Piloni D, Rodi G, Corsico AG, Campo I. A mini-whole lung lavage to treat autoimmune pulmonary alveolar proteinosis (PAP). Respir Res. 2022 Mar 17;23(1):60. doi: 10.1186/s12931-022-01982-2.

20. Marwah V, Katoch CDS, Singh S, Handa A, Vardhan V, Rajput AK, Barthwal MS, Bhattacharyya D, Rai SP. Management of primary pulmonary alveolar proteinosis: A multicentric experience. Lung India. 2020 Jul-Aug;37(4):304-309. doi: 10.4103/lungindia.lungindia_401_19.

21. Mo Q, Wang B, Dong N, Bao L, Su X, Li Y, Chen C. The Clinical Clues of Pulmonary Alveolar Proteinosis: A Report of 11 Cases and Literature Review. Can Respir J. 2016;2016:4021928. doi: 10.1155/2016/4021928.

22. Perez A 4th, Rogers RM. Enhanced alveolar clearance with chest percussion therapy and positional changes during whole-lung lavage for alveolar proteinosis. Chest. 2004 Jun;125(6):2351-6. doi: 10.1378/chest.125.6.2351.

23. Selecky PA, Wasserman K, Benfield JR, Lippmann M. The clinical and physiological effect of whole-lung lavage in pulmonary alveolar proteinosis: a ten-year experience. Ann Thorac Surg. 1977 Nov;24(5):451-61. doi: 10.1016/s0003-4975(10)63440-6.

24. 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.

25. Zhao YY, Huang H, Liu YZ, Song XY, Li S, Xu ZJ. Whole Lung Lavage Treatment of Chinese Patients with Autoimmune Pulmonary Alveolar Proteinosis: A Retrospective Long-term Follow-up Study. Chin Med J (Engl). 2015 Oct 20;128(20):2714-9. doi: 10.4103/0366-6999.167295. PMID: 26481735; PMCID: PMC4736873.

26. Zhou X, Lu G, Yu Z, Gao F, Bian T. Long-term follow-up of whole lung lavage in patients with pulmonary alveolar proteinosis. Exp Ther Med. 2014 Sep;8(3):763-768. doi: 10.3892/etm.2014.1788.

Risk of bias assessment

Table 1. Risk of bias of the studies evaluating WLL for PAP

Study	Bias caused by confounding	Bias caused by selection of participants	Bias caused by classification of interventions	Bias caused by deviations from intended interventions	Attrition bias caused by missing data	Detection bias caused by measurement of outcomes	Reporting bias caused by selection of the reported results	Overall Risk of Bias
Alkady 2016	Serious	Serious	Low	Low	Low	Moderate	Low	Serious
Athayde 2018	Serious	Low	Low	Low	Serious	Moderate	Serious	Serious
Badiozaman 2013	Serious	Low	Low	Low	Serious	Moderate	Low	Serious
Beccaria 2004	Serious	Low	Low	Low	Serious	Moderate	Low	Serious
Ben-Abraham 2002	Serious	Serious	Low	Low	Low	Moderate	Serious	Serious
Byun 2010	Serious	Low	Low	Low	Serious	Moderate	Serious	Serious
Casanova 2021	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Deleanu 2016	Serious	Low	Low	Low	Low	Moderate	Serious	Serious
Diaz-Mendoza 2021	Serious	Low	Low	Low	Low	Moderate	Serious	Serious
Du Bois 1983	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Gay 2017	Serious	Low	Low	Low	Low	Moderate	Serious	Serious

Goldstein 1998	Serious	Low	Low	Low	Critical	Moderate	Serious	Serious
Guan 2012	Serious	Low	Low	Low	Serious	Moderate	Serious	Serious
Holbert 2001	Serious	Low	Low	Low	Low	Moderate	Serious	Serious
Kaenmuang 2021	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Kariman 1984	Serious	Low	Low	Low	Low	Moderate	Serious	Serious
Kiani 2018	Serious	Low	Low	Low	Low	Moderate	Serious	Serious
Lan 2016	Serious	Low	Low	Low	Low	Moderate	Serious	Serious
Mariani 2022	Serious	Low	Low	Low	Low	Moderate	Serious	Serious
Marwah 2020	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Mo 2016	Serious	Unpredictable	Low	Low	Low	Moderate	Low	Serious
Perez 2004	Serious	Low	Low	Low	Low	Moderate	Serious	Serious
Selecky 1977	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Smith 2019	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Zhao 2015	Serious	Low	Low	Low	Low	Moderate	Serious	Serious
Zhou 2014	Serious	Low	Low	Low	Low	Moderate	Low	Serious

Table 2. WLL indications and practices across the included studies.

Studies	Indications of WLL	Unilateral/ Bilateral	Lavage volume
Alkady 2016	Symptomatic, NYHA class III-IV.	Bilateral, 2-3 days interval.	3L per cycle, an average of 15-18L per lung, warmed.
Athayde 2018	Not reported.	Not reported.	Not reported.
Badiozaman 2013 (children)	Advanced PAP.	Some had bilateral, most unilateral. Unclear if single procedure	500-2,000 mls per per cycle, number of cycles not described, warmed.
Beccaria 2004	Progressive worsening of P(A-a)O2 and pulmonary symptoms with severe limitation of daily activities.	Bilateral, same day in all but one patient; 1h interval.	25-40L per lung, warmed.
Ben-Abraham 2002	Progressive effort intolerance or significant hypoxemia on room air while exercising.	Unilateral.	Up to 20L, warmed.
Byun 2010	Dyspnoea or hypoxaemia and deteriorated chest radiography.	Not reported.	Not reported.
Casanova 2021	Symptoms and/or deterioration in the pulmonary function tests and/or in the CT thorax.	Bilateral, ≥3 weeks interval.	7-8L, warmed.
Deleanu 2016	FVC <60% pred or TLC <60% pred or PaO2 <60mmHg or SatO2 <90% or TLCO<60% pred or significant desaturation at 6MWT (≥4%).	Not reported.	Not reported.
Diaz-Mendoza 2021	Worsening dyspnoea with worsening imaging findings.	Bilateral, single procedure if deemed safe.	1-2L per cycle, an average of 16L per lung, warmed.
Du Bois 1983	Dyspnoea at rest or mild exertion, with radiological and/or functional evidence of deterioration.	Bilateral, days to weeks interval.	0.5-1L per cycle, up to 40L per lung, warmed.
Gay 2017	72% of patients were hypoxic at rest, the remaining received WLL after GM-CSF failure.	48.5% bilateral, but only in 12% of all patients in a single procedure.	Ranged from 1-40L.
Goldstein 1998	Dyspnoea and/or hypoxemia. Radiographic deterioration alone was not an indication.	First WLL was bilateral in 76.9% cases – unclear whether single procedure.	Mean lavage volume of 11.8±3.68L.

Guan 2012	Not reported.	95% bilateral, single procedure	1-1.3L per cycle, warmed.
Holbert 2001	Not reported.	1/3 of patients underwent sequential WLL with 7 days interval. Rest of patients: Unclear.	Not reported.
Kaenmuang 2021	Any of: Dyspnoea, serial WLL, decline in baseline PaO2, or decline in DLCO.	Most had bilateral lavage. Unclear if single procedure	Up to 20L per lung, warmed. Median [IQR]: 9.45L [7.34-10].
Kariman 1984	Progressive dyspnoea as well as progressive deterioration of pulmonary function tests and arterial blood gases.	Bilateral lavage, in most patients in a single procedure, but in some with a 4 day interval (recruited earlier or more severe).	Not reported.
Kiani 2018	Not reported.	Not reported.	0.5-1L per cycle, up to 12 cycles. Warmed.
Lan 2016	ASA physical status II-III.	Bilateral, single procedure.	1L per cycle, until clear. Mean (SD) volume: ~20L (~6L).
Mariani 2022	Persistent or progressive respiratory failure; Absence of respiratory difficulty at rest, but drop by ≥5% in SatO2 on exercise tolerance test (modified Bruce); or, in young adults reporting significant limitation in daily or sports activities.	Bilateral, single procedure.	Standard WLL: 15-20L. Mini-WLL: 9L. Warmed.
Marwah 2020	Moderate to severe symptoms (DSS ≥3); or progressive symptoms; or [A-a] O2 gradient >40	Bilateral, sequential, 2-3 weeks interval.	0.75-1L per cycle. Total of 15-20L per lung.
Mo 2016	Severe dyspnoea, cough or chest pain with significant limitation in daily or sport activities; or presence of persistent or progressive respiratory failure; or exercise desaturation of >5%; or repeated pulmonary infection induced by PAP.	5/7 had bilateral WLL. Unclear if single procedure.	9-15L per lung.

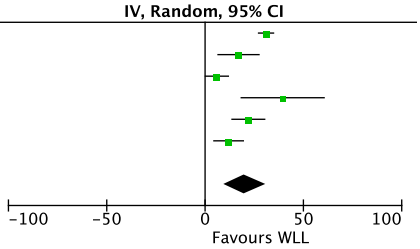
Perez 2004	Clinical and physiologic criteria, not further defined.	Bilateral. Unclear if single procedure.	45-60L per lung, warmed.
Selecky 1977	Progressive, severe exertional dyspnoea.	Bilateral. 2-3 day intervals	1-1.8L per cycle. Total of 15-18L per lung. Warmed
Smith 2019	ASA ≥ II.	90% bilateral, single procedure.	1L per cycle. Total volume per lung, mean (SD): 15 (6).
Zhao 2015	Resting PaO2 <65mmHg; or [A-a]O2 gradient >40mmHg; or shunt fraction >10%. Additional WLL in patients with worsening symptoms; or progressive respiratory failure (>10mmHg decrease in PaO2 or need for supplemental oxygen); or progressive radiology consistent with PAP.	Not reported.	Not reported.
Zhou 2014	Severe dyspnoea and/or hypoxemia (PaO2 <60mmHg).	Bilateral, 4-10 days interval.	500-600ml per cycle. Total volume of 6-26L, warmed.

Meta-analyses: Forest plots

PaO_2 within one month post-WLL compared to pre-procedure

Study or Subgroup	Post-WLL Mean	SD	Total	Pre-WLL Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Alkady 2016	85	1.2	7	54	5	7	19.0%	31.00 [27.19, 34.81]
Beccaria 2004	75	16	16	58	14	16	16.4%	17.00 [6.58, 27.42]
Gay 2017	65.1	14.2	33	59.1	9.5	33	18.4%	6.00 [0.17, 11.83]
Guan 2012	99.61	37.43	14	60.15	14.78	14	11.0%	39.46 [18.38, 60.54]
Kariman 1984	73	12	16	51	12	16	17.4%	22.00 [13.68, 30.32]
Zhou 2014	64.62	9.98	12	52.66	8.69	12	17.8%	11.96 [4.47, 19.45]
Total (95% CI)			**98**			**98**	**100.0%**	**20.07 [9.54, 30.60]**

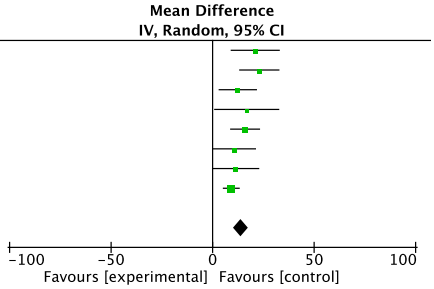
Heterogeneity: $Tau^2 = 147.78$; $Chi^2 = 60.78$, df = 5 ($P < 0.00001$); $I^2 = 92\%$
Test for overall effect: $Z = 3.74$ ($P = 0.0002$)



PaO_2 months to years post-WLL compared to pre-procedure

Study or Subgroup	Favours [experimental] Mean	SD	Total	Pre-WLL Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Athayde 2018	69	9	5	48	10	5	8.3%	21.00 [9.21, 32.79]
Beccaria 2004	78	11	11	55	12	11	11.2%	23.00 [13.38, 32.62]
Byun 2010	77.3	15.7	17	64.9	11.1	17	12.1%	12.40 [3.26, 21.54]
Kaenmuang 2021	66.1	27.5	19	49.3	21.6	19	5.1%	16.80 [1.08, 32.52]
Kariman 1984	67	8	16	51	12	16	16.7%	16.00 [8.93, 23.07]
Marwah 2020	67.86	7.88	8	57.13	12.67	8	10.1%	10.73 [0.39, 21.07]
Mo 2016	77.07	11.84	7	65.74	9.71	7	8.8%	11.33 [−0.01, 22.67]
Zhao 2015	68.2	12.9	80	59	12	80	27.7%	9.20 [5.34, 13.06]
Total (95% CI)			**163**			**163**	**100.0%**	**13.98 [10.15, 17.80]**

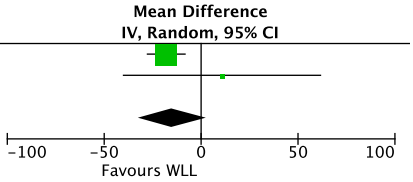
Heterogeneity: $Tau^2 = 9.84$; $Chi^2 = 10.76$, df = 7 ($P = 0.15$); $I^2 = 35\%$
Test for overall effect: $Z = 7.16$ ($P < 0.00001$)



A-a (DO_2) within one month post-WLL compared to pre-procedure

Study or Subgroup	Post-WLL Mean	SD	Total	Pre-WLL Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Beccaria 2004	31	14	16	49	14	16	89.1%	−18.00 [−27.70, −8.30]
Zhou 2014	62.06	84.87	12	51.28	29.44	12	10.9%	10.78 [−40.05, 61.61]
Total (95% CI)			**28**			**28**	**100.0%**	**−14.87 [−32.44, 2.70]**

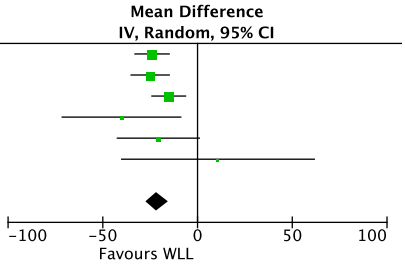
Heterogeneity: $Tau^2 = 65.66$; $Chi^2 = 1.19$, df = 1 ($P = 0.28$); $I^2 = 16\%$
Test for overall effect: $Z = 1.66$ ($P = 0.10$)



A-a (DO_2) months to years post-WLL compared to pre-procedure

Study or Subgroup	Post-WLL Mean	SD	Total	Pre-WLL Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Athayde 2018	23	5	5	47	9	5	31.1%	−24.00 [−33.02, −14.98]
Beccaria 2004	27	11	11	52	13	11	26.1%	−25.00 [−35.06, −14.94]
Byun 2010	20.1	13.2	16	35.3	12.4	16	31.9%	−15.20 [−24.07, −6.33]
Marwah 2020	48.86	12.49	8	89	43.38	8	3.2%	−40.14 [−71.42, −8.86]
Zhao 2015	52.6	43.5	80	73.3	88.6	80	6.6%	−20.70 [−42.33, 0.93]
Zhou 2014	62.06	84.87	12	51.28	29.54	12	1.2%	10.78 [−40.06, 61.62]
Total (95% CI)			**132**			**132**	**100.0%**	**−21.33 [−26.99, −15.66]**

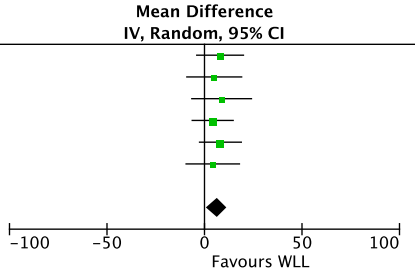
Heterogeneity: $Tau^2 = 5.69$; $Chi^2 = 5.60$, df = 5 ($P = 0.35$); $I^2 = 11\%$
Test for overall effect: $Z = 7.38$ ($P < 0.00001$)



DLCO within one month post-WLL compared to pre-procedure

Study or Subgroup	Experimental Mean	SD	Total	Pre-WLL Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Beccaria 2004	52	15	16	44	16	11	17.7%	8.00 [-3.98, 19.98]
Ben-Abraham 2002	48	17	10	43	15	10	12.8%	5.00 [-9.05, 19.05]
Guan 2012	54.64	19.09	14	45.85	22.09	14	10.8%	8.79 [-6.50, 24.08]
Lan 2016	49.1	16.9	18	44.9	15.2	18	23.0%	4.20 [-6.30, 14.70]
Mo 2016	46.77	10.4	7	38.6	10.04	7	22.1%	8.17 [-2.54, 18.88]
Zhou 2014	49.98	14.97	9	45.74	14.62	9	13.6%	4.24 [-9.43, 17.91]
Total (95% CI)			**74**			**69**	**100.0%**	**6.35 [1.32, 11.39]**

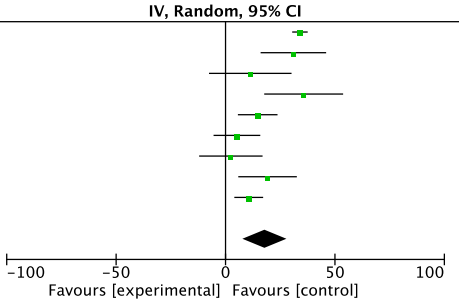
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 5 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.47 (P = 0.01)



DLCO months to years post-WLL compared to pre-procedure

Study or Subgroup	Experimental Mean	SD	Total	Pre-WLL Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Alkady 2016	82	1.8	7	48	4	7	13.2%	34.00 [30.75, 37.25]
Beccaria 2004	75	19	11	44	16	11	10.4%	31.00 [16.32, 45.68]
Byun 2010	65.2	17.6	9	53.9	22.3	9	9.1%	11.30 [-7.26, 29.86]
Du Bois 1983	81.3	21.4	10	45.6	19	10	9.4%	35.70 [17.96, 53.44]
Kaenmuang 2021	59.5	9.7	19	44.8	16.9	19	12.1%	14.70 [5.94, 23.46]
Lan 2016	50.1	14.6	14	44.9	15.2	18	11.7%	5.20 [-5.18, 15.58]
Marwah 2020	69.86	13.2	7	67.43	13.9	7	10.5%	2.43 [-11.77, 16.63]
Perez 2004	60.5	12.79	6	41.3	10.2	6	10.9%	19.20 [6.11, 32.29]
Zhao 2015	66.8	22.7	80	56.2	17.6	80	12.7%	10.60 [4.31, 16.89]
Total (95% CI)			**163**			**167**	**100.0%**	**18.17 [8.26, 28.08]**

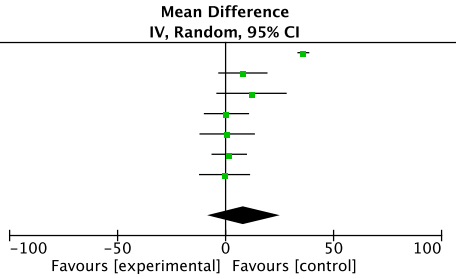
Heterogeneity: Tau² = 190.65; Chi² = 83.39, df = 8 (P < 0.00001); I² = 90%
Test for overall effect: Z = 3.59 (P = 0.0003)



FVC within one month post-WLL compared to pre-procedure

Study or Subgroup	Post-WLL Mean	SD	Total	Pre-WLL Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Alkady 2016	85	1.4	7	49	3	7	15.1%	36.00 [33.55, 38.45]
Beccaria 2004	72	15	16	64	17	16	14.2%	8.00 [-3.11, 19.11]
Ben-Abraham 2002	58	21	10	46	15	10	13.3%	12.00 [-4.00, 28.00]
Gay 2017	78.6	24	33	78.2	17.7	33	14.4%	0.40 [-9.77, 10.57]
Guan 2012	81.72	16.1	14	80.98	17.7	14	14.0%	0.74 [-11.79, 13.27]
Lan 2016	67	11.5	18	65.3	12.7	18	14.7%	1.70 [-6.21, 9.61]
Zhou 2014	73.17	13.24	11	73.65	14.34	11	14.2%	-0.48 [-12.01, 11.05]
Total (95% CI)			**109**			**109**	**100.0%**	**8.54 [-8.22, 25.29]**

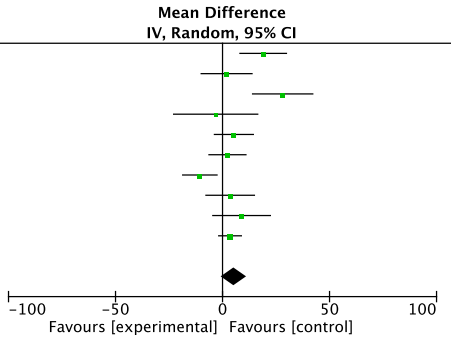
Heterogeneity: Tau² = 481.09; Chi² = 169.43, df = 6 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.00 (P = 0.32)



FVC months to years post-WLL compared to pre-procedure

Study or Subgroup	Post-WLL Mean	SD	Total	Pre-WLL Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Beccaria 2004	81	13	11	62	13	11	10.1%	19.00 [8.14, 29.86]
Byun 2010	68.2	11.9	12	66.3	17.3	12	9.5%	1.90 [-9.98, 13.78]
Du Bois 1983	91.8	14.8	10	63.7	17.2	10	8.3%	28.10 [14.04, 42.16]
Goldstein 1998	55.4	15.6	5	58.6	16.1	5	5.8%	-3.20 [-22.85, 16.45]
Kaenmuang 2021	74.5	14.6	19	69.2	14	19	11.2%	5.30 [-3.80, 14.40]
Lan 2016	67.7	12.1	14	65.4	12.7	18	11.4%	2.30 [-6.34, 10.94]
Mariani 2022	73.7	8	13	84.3	12.4	13	11.8%	-10.60 [-18.62, -2.58]
Marwah 2020	71.57	10.39	7	68	11.21	7	9.8%	3.57 [-7.75, 14.89]
Perez 2004	74.7	10.4	6	65.8	13.2	6	8.6%	8.90 [-4.55, 22.35]
Zhao 2015	81.3	15.3	80	77.8	18.7	80	13.4%	3.50 [-1.79, 8.79]
Total (95% CI)			**177**			**181**	**100.0%**	**5.43 [-0.67, 11.53]**

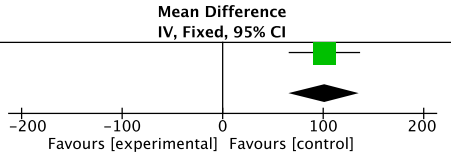
Heterogeneity: Tau² = 65.16; Chi² = 32.74, df = 9 (P = 0.0001); I² = 73%
Test for overall effect: Z = 1.75 (P = 0.08)



6MWT months to years post-WLL compared to pre-procedure

Study or Subgroup	Post-WLL Mean	SD	Total	Pre-WLL Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Zhao 2015	546.2	88.1	80	445	132.4	80	100.0%	101.20 [66.35, 136.05]
Total (95% CI)			**80**			**80**	**100.0%**	**101.20 [66.35, 136.05]**

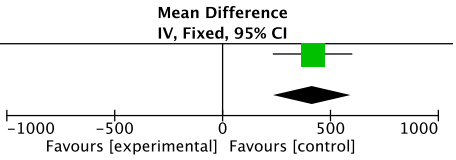
Heterogeneity: Not applicable
Test for overall effect: Z = 5.69 (P < 0.00001)



Exercise tolerance assessed using treadmill months to years post-WLL compared to pre-procedure

Study or Subgroup	Post-WLL Mean	SD	Total	Pre-WLL Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Beccaria 2004	626	264	11	209	156	11	100.0%	417.00 [235.79, 598.21]
Total (95% CI)			**11**			**11**	**100.0%**	**417.00 [235.79, 598.21]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.51 (P < 0.00001)



Evidence profile

Table 3. Evidence Profile. WLL compared to before WLL for PAP. It should be noted that no studies assessing head-to-head WLL versus control were identified.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Whole lung lavage	no whole lung lavage	Relative (95% CI)	Absolute (95% CI)		
A-a DO2 within one month post-WLL												
2	non-randomised studies	serious[a]	serious[b]	not serious	serious[c]	none	28	28	-	MD **14.87 mmHg lower** (32.44 lower to 2.7 higher)	⨁◯◯◯ Very low	CRITICAL
A-a DO2 months to years post-WLL												
6	non-randomised studies	serious[a]	not serious	not serious	not serious	none	132	132	-	MD **21.33 mmHg lower** (26.99 lower to 15.66 lower)	⨁⨁⨁◯ Moderate	CRITICAL
PaO2 within one month post-WLL												
6	non-randomised studies	serious[a]	not serious	not serious	not serious	none	98	98	-	MD **20.07 mmHg higher** (9.54 higher to 30.6 higher)	⨁⨁⨁◯ Moderate	CRITICAL
PaO2 months to years post-WLL												
8	non-randomised studies	serious[a]	not serious	not serious	not serious	none	163	163	-	MD **13.98 mmHg higher** (10.15 higher to 17.8 higher)	⨁◯◯◯ Very low	CRITICAL
DLCO (% predicted) within one month post-WLL												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Whole lung lavage	no whole lung lavage	Relative (95% CI)	Absolute (95% CI)		
6	non-randomised studies	serious[a]	not serious	not serious	serious[c]	none	74	69	-	MD **6.35 higher** (1.32 higher to 11.39 higher)	⨁⨁◯◯ Low	CRITICAL
DLCO (% predicted) months to years post-WLL												
9	non-randomised studies	serious[a]	not serious	not serious	not serious	none	163	167	-	MD **18.17 higher** (8.26 higher to 28.08 higher)	⨁⨁⨁◯ Moderate	CRITICAL
FVC (% predicted) within one month post-WLL												
6	non-randomised studies	serious[a]	not serious	not serious	serious[c]	none	74	69	-	MD **8.54 % higher** (8.22 lower to 25.29 higher)	⨁⨁◯◯ Low	CRITICAL
FVC (% predicted) months to years post-WLL												
10	non-randomised studies	serious[a]	not serious	not serious	not serious	none	177	181	-	MD **5.43 % higher** (0.67 lower to 11.53 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Exercise capacity (6MWT) months to years post-WLL												
1	non-randomised studies	serious[a]	not serious	not serious	serious[c]	none	80	80	-	MD **101.2 m more** (66.35 more to 136.05 more)	⨁⨁◯◯ Low	CRITICAL
Exercise capacity (treadmill) months to years post-WLL												
1	non-randomised studies	serious[a]	not serious	not serious	very serious[c]	none	11	11	-	MD **417 m more** (235.79 more to 598.21 more)	⨁◯◯◯ Very low	CRITICAL
Mortality (variable follow-up durations reported)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Whole lung lavage	no whole lung lavage	Relative (95% CI)	Absolute (95% CI)		
26	non-randomised studies	serious[a]	not serious	not serious	not serious	none	6/26 studies report limited number of mortalities (Badiozaman 2013: 1/9; Byun 2010: 1/26; Diaz-Mendoza 2011: 1/13; Gay 2017: 2/13; Kiani 2018: 1/45; Zhao 2015: 3/40				⨁⨁⨁◯ Moderate	CRITICAL
Serious adverse events												
0							Not consistently reported across the included studies				-	CRITICAL
Symptoms												
0							Not consistently reported across the included studies				-	CRITICAL
HRCT (radiologic) severity scores												
0							Not consistently reported across the included studies				-	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Risk of bias due to unaddressed confounding and concerns around selection of participants and reported outcomes; included studies were uncontrolled.
b. Significant inconsistency observed visually in the forest plot
c. Limited overall study population

Evidence to decision framework

QUESTION

In patients with clinical symptoms and/or functional impairment due to PAP should whole lung lavage be used versus to no whole lung lavage?	
POPULATION:	Auto-Immune Pulmonary Alveolar Proteinosis
INTERVENTION:	Whole Lung Lavage (WLL)
COMPARISON:	Before WLL
MAIN OUTCOMES:	A-a DO2; PaO2; DLCO (% predicted); FVC (% predicted); Exercise capacity (6MWT); Mortality; Serious adverse events; Symptoms; Exercise capacity (treadmill); HRCT (Radiologic) severity scores;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	Pulmonary alveolar proteinosis (PAP) is a rare but burdensome disease, characterised by progressive respiratory symptoms, including breathlessness, that is characterised by significant morbidity and -if untreated- mortality. Whole lung lavage (WLL) is the most common treatment for PAP. It is interventional requiring hospital admission and general anaesthesia and associated with significant complications, including hypoxia, pneumonia, prolonged intubation, pleural effusion, pneumothorax and a mortality risk. It is important to quantify the benefits and risks of WLL, to decide if and when it should be used.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● **Moderate** ○ Large ○ Varies	**Available data:** 26 retrospective case series with a total of 490 patients who underwent at least one, unilateral or bilateral WLL (median: 14 patients per study, interquartile range: 8, 21) WLL[4,30-54]. Twenty series included only adults, one assessed only children and five both children and adults. No clear differences were reported in the effects of children versus adults. These	

○ Don't know	case series described the clinical characteristics and laboratory results of patients pre- and post- WLL and compared laboratory values pre- and post-WLL. **Procedure:** WLL is done under general anaesthesia and intubation is performed using a double lumen endotracheal tube in order ventilate one lung while washing the other through a blocked catheter[55,56]. Volumes of fluid instilled into the washed lung varies between 500 and 1000ml per cycle[55,56]. Afterwards gravitational force is used to drain the fluid out into a lower positioned measuring cylinder[55,56]. This cycle of instillation and drainage is repeated several times until the returned fluid is clear, using an average of 15.4 litre per lung. Both lungs could be washed during the same session and same anaesthesia, however it is more common to wash the lungs a few days apart[55,56]. In the literature the main indications for WLL were decline in lung function and/or resting PaO2, and an increase in respiratory symptoms or parenchymal abnormalities on HRCT. The most common complications reported were fever (18%), pneumonia (5%), fluid leakage (4%) and pneumothorax (0.8%)[55,56]. The indications for WLL and procedures employed in the studies that informed this guideline are summarised in table 2. **Desirable effects:** There was low certainty evidence suggesting that WLL improves respiratory symptoms compared to pre-WLL measurements. While we were not able to pool data from all included studies due to reporting limitations the signal was clear: In six out of ten studies reporting on symptoms all participants experienced moderate or significant symptomatic improvement (Alkady 2016, Badiozaman 2013, Du Bois 1983, Marwah 2020, Mo 2016, Selecky 1977, Zhou 2014)[30,32,38,48,49,51,54], while the remaining studies reported symptomatic improvement in 68-90% of participants (Beccaria 2004, Casanova 2021, Kaenmuang 2021, Smith 2019)[33,36,43,52]. The duration of symptomatic improvement is not clearly described. Only one study evaluated change in 6-minutes walking test post-WLL and found statistically significant improvement (101.2m [95% CI 66.35, 136.05], low certainty]). Similarly, only one study assessed exercise tolerance using treadmill post-WLL and found statistically significant improvement compared to before the intervention (417m [95% CI 235, 598], very low certainty). Low certainty evidence suggests improved PaO2 within a month from WLL (20.07 mmHg [95% CI 9.54, 30.60], I^2=92%) and at longer follow-up, months to years from the WLL (13.98 mmHg [95% CI 10.15, 17.80], I^2= 35%). Moreover, a trend over improved A-a DO2 was observed post-WLL (-14.87 mmHg [-32.44, 2.70], I^2=16%, very low certainty), that was confirmed by a clear improvement at a longer follow-up, that was assessed in more studies, (-21.33 mmHg [-26.99, -15.66], I^2=11%, low certainty). No clear improvement was observed in FVC% predicted at short (8.54% [-8.22, 25.29], I^2 = 96%), or longer follow-up (5.43% [-0.67, 11.53]), low certainty.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● **Moderate** ○ Large ○ Varies ○ Don't know	**Available data:** As above **Undesirable effects:** Serious adverse events were not consistently reported across the included case series. Moreover, in the absence of a control group, it is not possible to confidently establish WLL as the causative factor. In general, the included case series reported infrequent serious adverse events. Occasionally reported adverse events included laryngeal trauma or oedema, infections, fever, mild pleural effusion, severe hypoxemia post-intervention or haemoptysis. General anaesthesia is also associate with well established risks. A small number of mortalities were reported in a number of studies: - Badiozaman 2013: One patient (out of 9) due to complications of general anaesthesia prior to WLL[32] - Byun 2010: One patient (out of 26) died "soon after the WLL", no further explanation given[35]. - Diaz-Mendoza 2021: One patient (out of 13) died within one year post-WLL, but no cause of death was given[37]. - Gay 2017: Two patients (out of 13) died within 4 weeks after WLL: A 70-year-old man with secondary PAP due to myelodysplastic syndrome and a 63-year-old female with severe respiratory insufficiency[39]. - Kiani 2018: One patient (out of 45) died five months after WLL because of respiratory insufficiency[45]. - Zhao 2015: Three patients (out of 40) died within one year following WLL[53]. The remaining studies did not report any deaths, at least in the period after WLL. However, interpretation remains poor in view of the lack of a control group.	Three studies commented on the average hospital stay for WLL. Alkady 2016 reported an average stay of 5±2 days for unilateral and 10±2 days for bilateral WLL[30]. Ben-Abraham 2002 reported a hospital stay of 2-3 days for unilateral WLL[34]. Finally, Diaz-Mendoza 2021 reported that only 36% of participants required admission overnight and among those the median duration of admission was 2.5 days (IQR:1)[37].

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Very low** ○ Low ○ Moderate ○ High ○ No included studies	All studies were deemed to be at high risk of bias, mainly due to the unaddressed confounding. Since PAP is characterised by variable course with episodes of progression, as well as spontaneous improvement, and interventional treatments such as WLL are often associated with placebo effect, studies assessing outcomes before versus after the intervention do hardly account for confounding sufficiently. In some studies, additional bias stemmed from the selection of participants, attrition, and selection of the reported results (as many studies did not report on patient important outcomes). Last, outcomes assessment was not blinded in any of the included studies, also potentially introducing bias. Overall, the certainty of evidence is very low. There are serious concerns around the methodological limitations of the included studies that were single arm and not controlled.	

	Moreover, there are serious concerns around imprecision, since the available studies were very underpowered. Most available data are from studies in adults or predominantly adults. While no clear differences were observed between the findings of the two groups, data on the safety and efficacy of WLL in children remain very limited.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● **Probably no important uncertainty or variability** ○ No important uncertainty or variability	No specific studies were identified to answer this question	Although we are not aware of any research evidence assessing how much people value the main outcomes, the clinical practice guideline development group, and the patient representatives consider that most patients would consider that the benefits of WLL as a rescue therapy in case of symptoms and hypoxia that are refractory to other treatments or as a bridging therapy to other treatments outweigh the potential risks outweigh the potential risks.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	Available data of low or very low certainty support that WLL when offered to severely symptomatic and/or hypoxic patients is associated with symptomatic benefit, improvement in the oxygenation and (A-a) DO_2. Very low certainty data suggest that WLL is associated with limited serious adverse events. The included studies did not describe any significant mortality signal in the short-term post-WLL.	

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Large costs** ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No specific studies were identified to answer this question	WLL is an expensive intervention requiring hospital admission, general anaesthesia and a specialised bronchoscopist with supporting staff to perform it. A single WLL is effective in some but not all patients and may need to be repeated. Overall, WLL requires considerable resources.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	No specific studies to answer this question. Our judgement is based on observation that WLL is a very expensive procedure, requiring hospital admission, general anaesthesia and a specialised bronchoscopist with supporting staff to perform this procedure.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ No included studies	No specific studies were identified to answer this question	WLL is an expensive intervention requiring hospital admission, general anaesthesia and a specialised bronchoscopist with supporting staff to perform it. A single WLL is effective in some but not all patients and may need to be repeated. Overall, WLL requires considerable resources. However, it is offered to patietns with clinical symptoms and/or functional impairment due to PAP, who suffers a significant disease burden and risk of progression. It can reduce disease burden and prevent adverse outcomes and it was therefore considered by the panel cost-effective.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Reduced** ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No specific studies were identified to answer this question	WLL lavage is an expensive procedure that can only be performed in very specialised centres. Access may be a cosniderable problem.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	No specific studies were identified to answer this question.	Data around the safety and clinical effectiveness of WLL in PAP are limited and of very low certainty. However, it is likely that patients would accept WLL in case of severe and refractory symptoms and hypoxia.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● **Varies** ○ Don't know	No specific studies were identified to answer this question.	WLL lavage is an expensive and complex procedure that can be performed in specialised centres. However, the panel felt there is available expertise in PAP and/or advanced bronchoscopic techniques covering most countries and the intervention would therefore be feasible in most countries.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies

	JUDGEMENT						
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

Recommendation

1. We recommend performing bilateral whole lung lavage in patients with autoimmune PAP with evidence of gas exchange impairment and either symptoms, or functional impairment. Strong recommendation, very low certainty of evidence.

2. No recommendation for or against whole lung lavage in other PAP types can be made due to lack of evidence. We suggest seeking advice from an expert centre on an individual case basis.

PICO 4: Should patients with confirmed autoimmune pulmonary alveolar proteinosis be treated with exogenous GM-CSF?

Search Strategy

1. PubMed

("Pulmonary Alveolar Proteinosis"[Mesh] OR "Pulmonary alveolar proteinosis"[Title/Abstract] OR "Alveolar lipoproteinosis"[Title/Abstract] OR "Alveolar proteinosis"[Title/Abstract]) AND ("Granulocyte-Macrophage Colony-Stimulating Factor"[Mesh] OR "Granulocyte Macrophage Colony Stimulating Factor"[Title/Abstract] OR "Gm-csf"[Title/Abstract] OR "Rh-gmcsf"[Title/Abstract] OR "rgm-csf"[Title/Abstract] OR "Recombinant Proteins"[Mesh] OR "sargramostim" [Supplementary Concept] OR "molgramostim" [Supplementary Concept] OR leukine) NOT Case Reports[ptyp]

2. Cochrane Library

"Pulmonary alveolar proteinosis" AND ("Granulocyte-Macrophage Colony-Stimulating Factor" OR "Gm-csf" OR "Rh-gmcsf" OR "rgm-csf") in Title Abstract Keyword

3. EMBASE

('lung alveolus proteinosis'/mj/exp OR 'lung alveolus proteinosis' OR 'lung alveolus proteinosis':ti,ab OR 'pulmonary alveolar proteinosis':ti,ab OR 'alveolar lipoproteinosis':ti,ab OR 'alveolar proteinosis':ti,ab) AND ('granulocyte macrophage colony stimulating factor'/exp OR 'granulocyte macrophage colony stimulating factor':ti,ab OR 'granulocyte-macrophage colony-stimulating factor':ti,ab OR 'gm-csf':ti,ab OR 'rh-gmcsf':ti,ab OR 'rgm-csf':ti,ab OR 'recombinant protein'/exp OR 'recombinant protein':ti,ab OR 'sargramostim'/exp OR 'sargramostim':ti,ab OR 'molgramostim'/exp OR 'molgramostim':ti,ab OR leukine:ti,ab) NOT 'case report'/exp AND ([english]/lim OR [french]/lim) AND ('article'/it OR 'article in press'/it OR 'review'/it)

PRISMA Flow diagram summarising the study selection process

Included studies

RCTs

1. Tazawa R, Ueda T, Abe M, Tatsumi K, Eda R, Kondoh S, Morimoto K, Tanaka T, Yamaguchi E, Takahashi A, Oda M, Ishii H, Izumi S, Sugiyama H, Nakagawa A, Tomii K, Suzuki M, Konno S, Ohkouchi S, Tode N, Handa T, Hirai T, Inoue Y, Arai T, Asakawa K, Sakagami T, Hashimoto A, Tanaka T, Takada T, Mikami A, Kitamura N, Nakata K. Inhaled GM-CSF for Pulmonary Alveolar Proteinosis. N Engl J Med. 2019 Sep 5;381(10):923-932. doi: 10.1056/NEJMoa1816216.

Trapnell BC, Inoue Y Bonella F, Morgan C, Jouneau S, Bendstrup E, Campo I, Waterer GW. Inhaled GM-CSF (molgramostim) therapy reduces the need for whole lung lavage in patients with autoimmune pulmonary alveolar proteinosis-long-term results from a randomized, double-blind trial (impala). Am J Respir Crit Care Med 2020;201:A2755. Doi: 10.1164/ajrccm-conference.2020.201.1_Meeting Abstracts.A2755

2. Trapnell BC, Inoue Y, Bonella F, Morgan C, Jouneau S, Bendstrup E, Campo I, Papiris SA, Yamaguchi E, Cetinkaya E, Ilkovich MM, Kramer MR, Veltkamp M, Kreuter M, Baba T, Ganslandt C, Tarnow I, Waterer G, Jouhikainen T; IMPALA Trial Investigators. Inhaled Molgramostim Therapy in Autoimmune Pulmonary Alveolar Proteinosis. N Engl J Med. 2020 Oct 22;383(17):1635-1644. doi: 10.1056/NEJMoa1913590.

3. Tian X, Yang Y, Chen L, Sui X, Xu W, Li X, Guo X, Liu L, Situ Y, Wang J, Zhao Y, Meng S, Song W, Xiao Y, Xu KF. Inhaled granulocyte-macrophage colony stimulating factor for mild-to-moderate autoimmune pulmonary alveolar proteinosis - a six month phase II randomized study with 24 months of follow-up. Orphanet J Rare Dis. 2020 Jul 2;15(1):174. doi: 10.1186/s13023-020-01450-4.

Tian X, Guo X, Chen L, Li X, Meng S, Zhao Y, Xiao Y, Xu K. The effect of inhaled granulocyte-macrophage colony stimulating factor (GM-CSF) for patients with mild-to-moderate autoimmune pulmonary alveolar proteinosis (APAP) in China. ATS 2018.

Observational studies including case-series (5+ cases)

1. Tazawa R, Trapnell BC, Inoue Y, Arai T, Takada T, Nasuhara Y, Hizawa N, Kasahara Y, Tatsumi K, Hojo M, Ishii H, Yokoba M, Tanaka N, Yamaguchi E, Eda R, Tsuchihashi Y, Morimoto K, Akira M, Terada M, Otsuka J, Ebina M, Kaneko C, Nukiwa T, Krischer JP, Akazawa K, Nakata K. Inhaled granulocyte/macrophage-colony stimulating factor as therapy for pulmonary alveolar proteinosis. Am J Respir Crit Care Med. 2010 Jun 15;181(12):1345-54. doi: 10.1164/rccm.200906-0978OC.

2. Tazawa R, Inoue Y, Arai T, Takada T, Kasahara Y, Hojo M, Ohkouchi S, Tsuchihashi Y, Yokoba M, Eda R, Nakayama H, Ishii H, Nei T, Morimoto K, Nasuhara Y, Ebina M, Akira M, Ichiwata T, Tatsumi K, Yamaguchi E, Nakata K. Duration of benefit in patients with autoimmune pulmonary alveolar proteinosis after inhaled granulocyte-macrophage colony-stimulating factor therapy. Chest. 2014 Apr;145(4):729-737. doi: 10.1378/chest.13-0603.
Note: long-term assessment of Tazawa 2010.

3. 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.
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.

4. Wylam ME, Ten R, Prakash UB, Nadrous HF, Clawson ML, Anderson PM. Aerosol granulocyte-macrophage colony-stimulating factor for pulmonary alveolar proteinosis. Eur Respir J. 2006 Mar;27(3):585-93. doi: 10.1183/09031936.06.00058305.

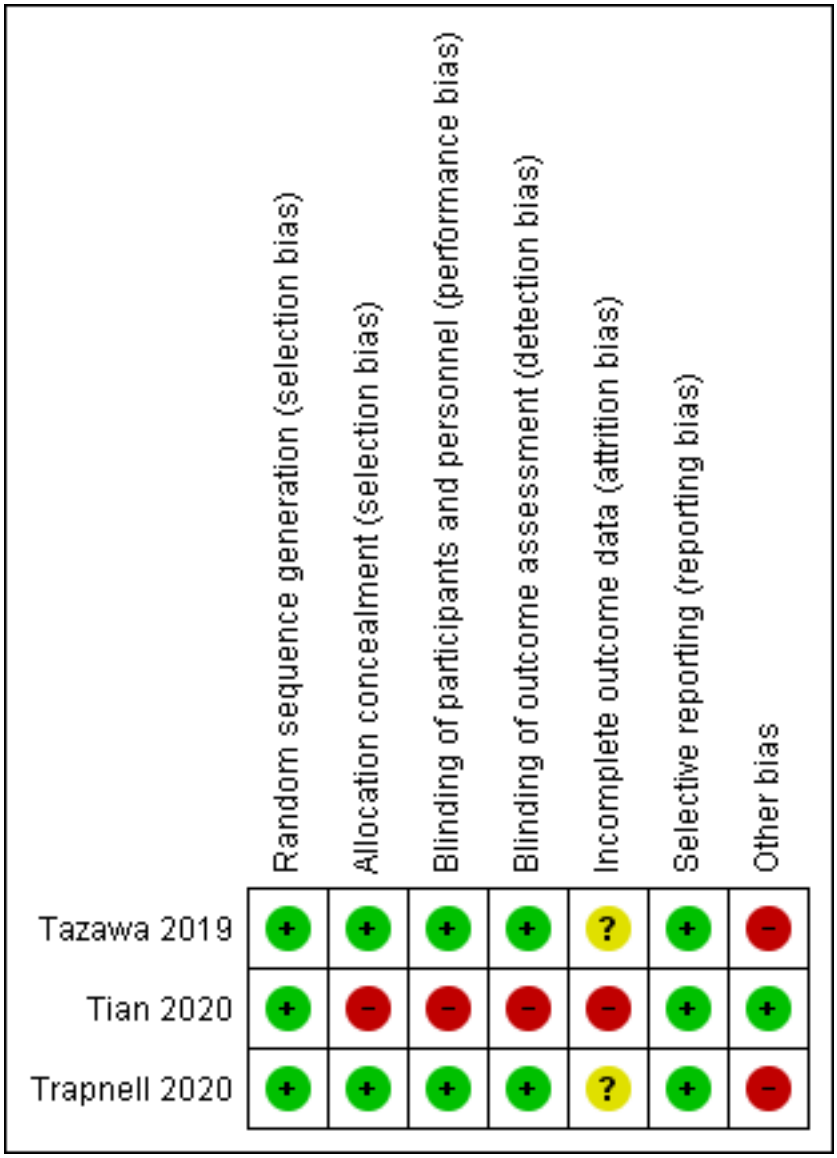
5. Zhang F, Weng D, Su Y, Yin C, Shen L, Zhang Y, Zhou Y, Li Q, Hu Y, Li H. Therapeutic effect of subcutaneous injection of low dose recombinant human granulocyte-macrophage colony-stimulating factor on pulmonary alveolar proteinosis. Respir Res. 2020 Jan 2;21(1):1. doi: 10.1186/s12931-019-1261-1.

6. Zhen G, Li D, Jiang J, Weng Y. Granulocyte-Macrophage Colony-Stimulating Factor Inhalation Therapy for Severe Pulmonary Alveolar Proteinosis. Am J Ther. 2020 Mar 25;28(2):e171-e178. doi: 10.1097/MJT.0000000000001053.

7. Venkateshiah SB, Yan TD, Bonfield TL, Thomassen MJ, Meziane M, Czich C, Kavuru MS. An open-label trial of granulocyte macrophage colony stimulating factor therapy for moderate symptomatic pulmonary alveolar proteinosis. Chest. 2006 Jul;130(1):227-37. doi: 10.1378/chest.130.1.227.
Note: data for non-responders and responders combined using Cochrane-formula.

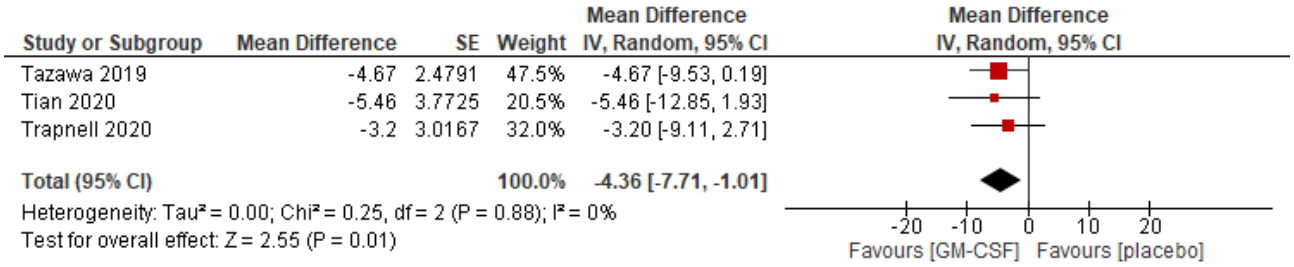
8. Papiris SA, Tsirigotis P, Kolilekas L, Papadaki G, Papaioannou AI, Triantafillidou C, Papaporfyriou A, Karakatsani A, Kagouridis K, Griese M, Manali ED. Long-term inhaled granulocyte macrophage-colony-stimulating factor in autoimmune pulmonary alveolar proteinosis: effectiveness, safety, and lowest effective dose. Clin Drug Investig. 2014 Aug;34(8):553-64. doi: 10.1007/s40261-014-0208-z. PMID: 24890235.

Risk of bias assessment

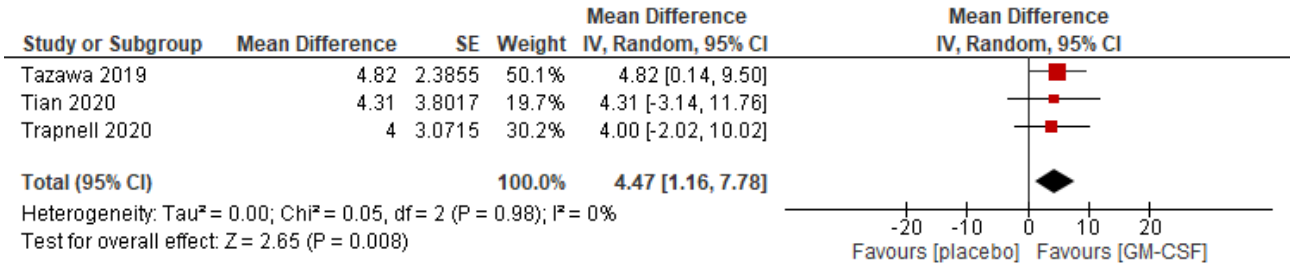


Meta-analyses: Forest plots

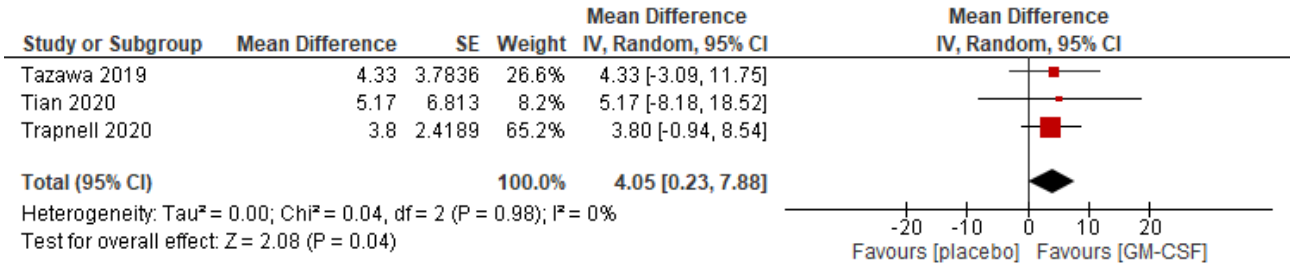
A-a DO2 mean changes from baseline at approx. 6 months, intermittent inhaled GM-CSF



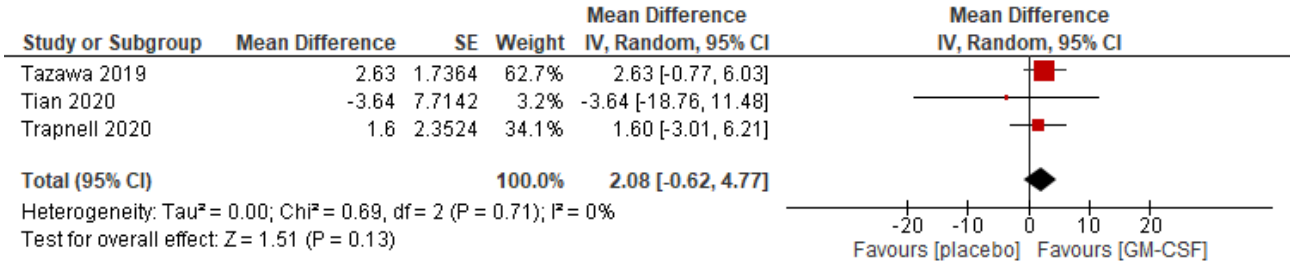
PaO2 mean changes from baseline at approx. 6 months, intermittent inhaled GM-CSF



DLCO mean changes from baseline at approx. 6 months, intermittent inhaled GM-CSF



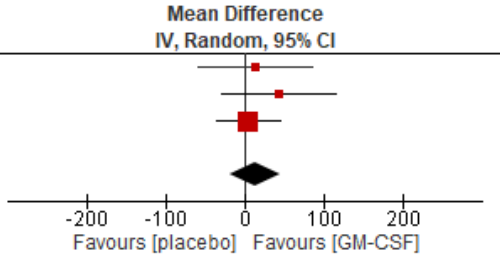
FVC/VC mean changes from baseline at approx. 6 months, intermittent inhaled GM-CSF



6MWT mean changes from baseline at approx. 6 months, intermittent inhaled GM-CSF

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
Tazawa 2019	13.56	36.7111	19.8%	13.56 [-58.39, 85.51]
Tian 2020	43.38	36.5956	19.9%	43.38 [-28.35, 115.11]
Trapnell 2020	5.3	21.0454	60.3%	5.30 [-35.95, 46.55]
Total (95% CI)			**100.0%**	**14.53 [-17.50, 46.55]**

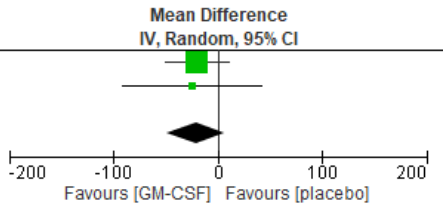
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.37)



Lung density mean changes from baseline at approx. 6 months

Study or Subgroup	GM-CSF Mean	GM-CSF SD	GM-CSF Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Tazawa 2019	-22.42	65.23	31	-2.47	55.9	29	82.5%	-19.95 [-50.63, 10.73]
Tian 2020	-45.9	82.563	17	-21	98.8261	13	17.5%	-24.90 [-91.43, 41.63]
Total (95% CI)			**48**			**42**	**100.0%**	**-20.82 [-48.68, 7.04]**

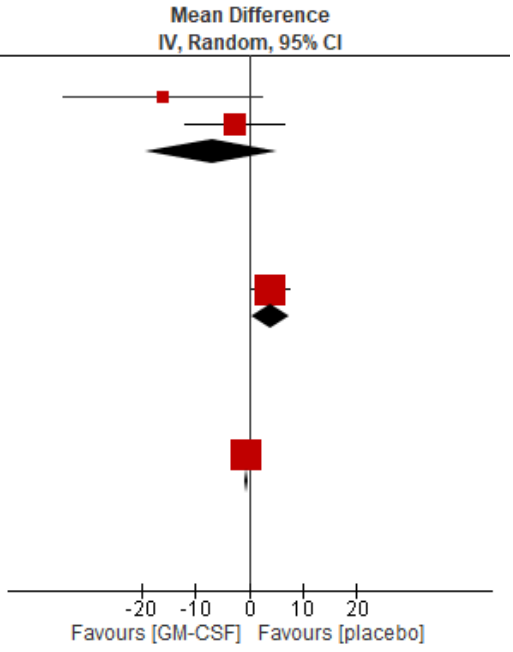
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.46 (P = 0.14)



Symptom changes from baseline at approx. 6 months, intermittent inhaled GM-CSF

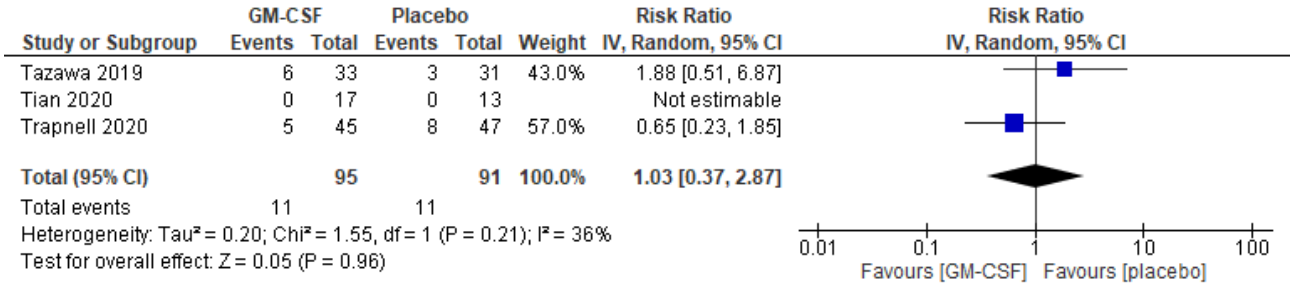
Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
1.6.1 SGRQ symptoms domain				
Tian 2020	-16.14	9.4247	31.6%	-16.14 [-34.61, 2.33]
Trapnell 2020	-2.7	4.7193	68.4%	-2.70 [-11.95, 6.55]
Subtotal (95% CI)			**100.0%**	**-6.94 [-19.19, 5.30]**
Heterogeneity: Tau² = 34.77; Chi² = 1.63, df = 1 (P = 0.20); I² = 38%				
Test for overall effect: Z = 1.11 (P = 0.27)				
1.6.2 CAT score				
Tazawa 2019	3.91	1.7706	100.0%	3.91 [0.44, 7.38]
Subtotal (95% CI)			**100.0%**	**3.91 [0.44, 7.38]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.21 (P = 0.03)				
1.6.3 mMRC				
Tazawa 2019	-0.42	0.1385	100.0%	-0.42 [-0.69, -0.15]
Subtotal (95% CI)			**100.0%**	**-0.42 [-0.69, -0.15]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 3.03 (P = 0.002)				

Test for subgroup differences: Chi² = 7.04, df = 2 (P = 0.03), I² = 71.6%



Additional evidence from observational trials and case series:

Serious adverse events at 24-42 wks.



Evidence profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GM-CSF	placebo	Relative (95% CI)	Absolute (95% CI)		
Alveolar-to-arterial O2 tension difference (follow-up: range 24 weeks to 26 weeks; assessed with: mmHg)												
3[57-59]	randomised trials	serious[a]	not serious	very serious[b,c]	serious[d]	none	92	84	-	MD **4.36 mmHg lower** (7.71 lower to 1.01 lower)	⨁◯◯◯ Very low	CRITICAL
Exercise: Treadmill - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Exercise: Six-minute walk test (follow-up: range 24 weeks to 26 weeks; assessed with: metres)												
3[57-59]	randomised trials	serious[a]	not serious	serious[c]	very serious[e]	none	91	83	-	MD **14.53 metres more** (17.5 fewer to 46.55 more)	⨁◯◯◯ Very low	CRITICAL
Mortality (follow-up: range 24 weeks to 26 weeks; assessed with: events during follow-up)												
3[57-59]	randomised trials	serious[a]	not serious	serious[c]	serious[f]	none	No deaths occurred in the studies.				⨁◯◯◯ Very low	CRITICAL
Partial pressure of oxygen (follow-up: range 24 weeks to 26 weeks; assessed with: mmHg)												
3[57-59]	randomised trials	serious[a]	not serious	very serious[b,c]	serious[d]	none	92	84	-	MD **4.47 mmHg higher** (1.16 higher to 7.78 higher)	⨁◯◯◯ Very low	CRITICAL
Symptoms: St. George's Respiratory Questionnaire symptoms domain (follow-up: range 24 weeks to 26 weeks; assessed with: points; Scale from: 0 to 100)												
2[58,59]	randomised trials	serious[a]	not serious	very serious[c,g]	very serious[e]	none	61	56	-	MD **6.94 points lower** (19.19 lower to 5.3 higher)	⨁◯◯◯ Very low	CRITICAL
Symptoms: COPD Assessment Test (follow-up: mean 25 weeks; assessed with: points; Scale from: 0 to 40)												
1[57]	randomised trials	serious[h]	not serious	very serious[c,g]	serious[d]	none	33	30	-	MD **3.91 points higher** (0.44 higher to 7.38 higher)	⨁◯◯◯ Very low	CRITICAL
Symptoms: Modified Medical Research Council dyspnoea scale (follow-up: mean 25 weeks; assessed with: points; Scale from: 0 to 4)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GM-CSF	placebo	Relative (95% CI)	Absolute (95% CI)		
1[57]	randomised trials	serious[h]	not serious	very serious[c,g]	serious[d]	none	33	30	-	MD **0.42 points lower** (0.69 lower to 0.15 lower)	⨁◯◯◯ Very low	CRITICAL
Diffusing capacity of the lungs for carbon monoxide (follow-up: range 24 weeks to 26 weeks; assessed with: % predicted)												
3[57-59]	randomised trials	serious[a]	not serious	very serious[b,c]	serious[d]	none	92	84	-	MD **4.05 % higher** (0.23 higher to 7.88 higher)	⨁◯◯◯ Very low	IMPORTANT
Vital Capacity/Forced Vital Capacity (follow-up: range 24 weeks to 26 weeks; assessed with: % predicted)												
3	randomised trials	serious[a]	not serious	very serious[b,c]	very serious[e]	none	92	86	-	MD **2.08 % higher** (0.62 lower to 4.77 higher)	⨁◯◯◯ Very low	IMPORTANT
HRCT: Lung density (follow-up: range 25 weeks to 26 weeks; assessed with: Hounsfield units)												
2[57,58]	randomised trials	serious[i]	not serious	very serious[b,c,j]	very serious[e]	none	48	42	-	MD **20.82 HU lower** (48.68 lower to 7.04 higher)	⨁◯◯◯ Very low	IMPORTANT
Safety: Serious adverse events (follow-up: range 24 weeks to 26 weeks; assessed with: events during follow-up)												
3[57-59]	randomised trials	serious[a]	not serious	serious[c]	very serious[e]	none	11/95 (11.6%)	11/91 (12.1%)	**RR 1.03** (0.37 to 2.87)	**4 more per 1.000** (from 76 fewer to 226 more)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Downgraded by 1 for methodological limitations because Tian 2020 was an open-label study, with high risk of bias regarding allocation and blinding. Trapnell 2020 was conducted by pharma. All studies had either unclear or high risk of bias regarding incomplete outcome data.
b. Downgraded by 1 for indirectness. The outcome is probably not important to patients (a surrogate outcome).
c. Downgraded by 1 for inidrectness because of different interventions (Tazawa 2019 125 ug BID every other week; Trapnell 2020 300 ug QD every other week; Tian 2020 150 ug BID every other week for 3 months, then 150 ug QD for 3 months).
d. Downgraded by 1 for imprecision due to small sample size and the resulting wide CI.
e. Downgraded by 2 for imprecision because (1) the effect size includes beneficial and non-beneficial values and (2) the small sample size.
f. Downgraded by 1 for imprecision because of small sample size and no events.
g. Downgraded by 1 for indirectness because the questionnaire is not disease-specific.
h. Downgraded by 1 for methodological limitations because of incomplete outcome data.
i. Downgraded by 1 for methodological limitations because Tian 2020 was an open-label study, with high risk of bias regarding allocation and blinding. Both studies had either unclear or high risk of bias regarding incomplete outcome data.

j. Downgraded by 1 for indirectness because the studies used different techniques to automatically calculate lung density.

Evidence to decision framework

QUESTION

In patients with confirmed autoimmune PAP should exogenous GM-CSF be used versus no exogenous GM-CSF?	
POPULATION:	Autoimmune Pulmonary Alveolar Proteinosis (PAP)
INTERVENTION:	Exogenous GM-CSF
COMPARISON:	Placebo
MAIN OUTCOMES:	Alveolar arterial oxygen difference, A-aDO2 (Critical) Exercise capacity: Treadmill (Critical) Exercise capacity: 6-minute walk test, 6MWT (Critical) Mortality (Critical) Partial concentration of oxygen measured on room air, PaO2 (Critical) Symptoms/breathlessness (Critical) Diffusing capacity of the lungs for carbon monoxide, DLCO (Important) Vital Capacity/Forced Vital Capacity, VC/FVC (Important) High-resolution Computed Tomography, HRCT (Important) Safety (Important)

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Pulmonary alveolar proteinosis (PAP) is a rare but burdensome disease, characterised by significant morbidity including respiratory symptoms and – if untreated – mortality. Whole lung lavage (WLL), the most common treatment for PAP requires hospital admission and general anaesthesia. It is associated with significant complications, including hypoxia, pneumonia, prolonged intubation, pleural effusion, pneumothorax, and an increased risk of mortality. The effect of WLL weans over time and patients often require repeated procedures. It is therefore a priority to identify less invasive and more cost-effective treatments for this burdensome disease.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Available data:** (i) An RCT that randomized 64 patients to either intermittent inhaled GM-CSF (125 ug BID every other week) or placebo with a treatment duration of 25 weeks (Tazawa 2019)[57]. (ii) An RCT that randomized 138 patients to either intermittent inhaled GM-CSF (300 ug QD every other week) or continuous GM-SCF (300 ug QD) or placebo with a treatment duration of 24 weeks (Trapnell 2020)[59]. (iii) An open-label RCT that randomized 36 patients to either intermittent inhaled GM-CSF (150 ug BID every other week for 3 months, then 150 ug QD for 3 months) or placebo with a treatment duration of 25 weeks (Tian 2020)[58] (iv) Seven non-comparative observational studies with a total of 156 included patients evaluating either inhaled (Tazawa 2010, Tazawa 2014, Papiris 2014)[60-62] or subcutaneous GM-CSF (Seymour 2001, Venkateshiah 2006, Zhang 2020)[63-65] (v) One observational study comparing WLL alone with a combination of WLL followed by GM-CSF in a total of 33 patients (Zhen 2020)[66] The three RCTs[57-59] were used as the main source of evidence and data were pooled for intermittent inhaled GM-CSF at approximately 6 months after treatment initiation. All three RCTs evaluated adults with autoimmune PAP, confirmed by the presence of high anti-GM-CSF titres. **Desirable effects:** Very low certainty evidence suggests that intermittent GM-CSF reduces A-a DO2 with a mean difference (MD) of 4.36 mmHg (95% confidence intervals [95% CI] 7.71; 1.01 mmHg). Very low certainty evidence suggests that it improves the PaO2 with a MD of 4.47 (1.16; 7.78) mmHg and the DLCO with a MD of 4.05 (0.23; 7.88) %. Very low certainty evidence suggests that intermittent GM-CSF either has beneficial or no beneficial effects on 6MWT (17.5 metres fewer to 46.55 metres more), VC/FVC (0.62% lower to 4.77% higher), lung density in HRCT (48.68 HU lower to 7.04 HU higher), and symptoms when measures by St. George's Respiratory Questionnaire (SGRQ) symptoms domain (from trial ii and iii, 19.19 points lower to 5.3 points higher). Trial i also assessed symptoms by measuring COPD Assessment Test (CAT) and Modified Medical Research Council (mMRC) dyspnoea scale. While the CAT was estimated to be higher in those treated with GM-CSF (MD 3.91 points higher, 95% CI 0.44;7.38), the mMRC was estimated to be lower (MD 0.42 points lower, 95% CI 0.69;0.15). The were no mortality events in the RCTs. No RCT evaluated the outcome “Exercise: Treadmill”.	Overall, the clinical magnitude of the effects is uncertain, as minimal important clinical differences (MICD) for the clinical outcomes are not established for PAP. Trapnell 2020 also evaluated continuous inhaled GM-CSF, which, when compared to placebo, seemed to result in more pronounced changes in A-aDO2, PaO2, DLCO, VC/FVC, lung density in HRCT and 6MWT than intermittent administration. However, these changes were not significant when compared directly (wide 95% CI crossing 0 and p-values >0.05). No differences were observed regarding SAE and symptoms measured by SGRQ. Tian 2020 evaluated clinical effects 6 months after a 6-month treatment period with intermittent inhaled GM-CSF, and benefits were maintained throughout the observation period. Tazawa 2014 was an observational study estimating long term effects of intermittent inhaled GM-CSF during a 30-month observation after another observational trial[61]. The results showed that inhaled GM-CSF sustained remission of PAP in more than one-half of cases. A case series of 6 patients with PAP also showed promising long-term results[62].

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Available data:** As above **Undesirable effects:** The were no mortality events in the RCTs. Very low certainty evidence suggests that intermittent GM-CSF either has beneficial or no beneficial effects on serious adverse events (76 fewer to 226 more).	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of evidence is very low for all outcomes. Tian 2020 was an open-label study, with high risk of bias regarding allocation and blinding[58]. All three RCTs had either unclear or high risk of bias regarding incomplete outcome data[57-59]. We downgraded the certainty of the evidence for A-a DO2, PaO2, symptoms: mMRC, and symptoms: CAT by 1 for imprecision due to small sample size and the resulting wide CI. We downgraded the certainty of the evidence for 6MWT, symptoms: SGRQ, VC/FVC, HRCT: lung density and safety: serious adverse events by 2 for imprecision because (1) the effect estimate, and 95% CI include considerable benefit and harm and (2) the small sample size. We downgraded the certainty of the evidence for mortality by 1 for imprecision because no events occurred in either arm in the studies and comparisons could not be performed.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important	No specific studies were identified to answer this question.	Overall, the clinical magnitude of the effects is uncertain, as minimal important clinical differences (MICD) for the outcomes are not established for PAP.

uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		Although we are not aware of any research evidence assessing how much people value the main outcomes, the clinical practice guideline development group, and the patient representatives consider changes in A-a DO2, PaO2, DLCO, VC/FVC and HRCT surrogate outcomes that probably are not important for patients.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	There were no safety concerns, and the intervention probably has a clear, beneficial effect on some outcomes. However, due to these outcomes being surrogate outcomes, we suggest that the results only probably favour the intervention.	

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	No specific studies were identified to answer this question.	While GM-CSF is an expensive intervention, its administration may prevent or delay the next WLL, a complex intervention that requires hospital admission and general anaesthesia and is therefore more expensive. Patients with PAP often require regular WLL, sometimes monthly. So, a potential reduction in the frequency of WLL would lead to cost savings. Tian 2020 evaluated clinical effects 6 months after a 6-month treatment period with intermittent inhaled GM-CSF, and benefits were maintained throughout the observation period[58]. Tazawa 2014 was an observational study estimating long term effects of intermittent inhaled GM-CSF during a 30-month observation after another observational trial[61]. The results demonstrated that inhaled GM-CSF sustained remission of PAP in more than one-half of cases. A

		case series of 6 patients with PAP also showed similar promising results[62] Altogether, inhaled GM-CSF might prevent the amount of WLL necessary, and the costs connected to this procedure.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No specific studies to answer this question. Our judgement is based on the very low certainty observation that GM-CSF may prevent or delay the frequency of WLL, which is a costly procedure.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies○ No included studies	No specific studies were identified to answer this question.	As above.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No specific studies were identified to answer this question.	WLL is only performed in tertiary specialist centres that may not be available in some countries. Hence, this procedure is connected with a significant amount of logistical expenses for patients. When found safe for the patients, treatment with inhaled GM-CSF can be administered at home or at local health institutions, which increases equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No specific studies were identified to answer this question.	Side effects including SAE were not more common in the GM-CSF arms as compared to the placebo arms in the included RCTs. As the treatment can, therefore, be considered safe, we believe that acceptability will be high. Administering nebulsied GM-CSF is easier than the prvision of WLL.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No specific studies were identified to answer this question.	The intervention is feasible to implement without major logistical issues.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies

	JUDGEMENT						
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

Recommendation

We recommend inhaled GM-CSF for symptomatic patients with confirmed autoimmune PAP. (Strong recommendation for the intervention; very low certainty of evidence).

PICO 5: In patients with confirmed autoimmune PAP should rituximab be used versus no immunosuppressive treatment?

Search strategy

1. PubMed

"Pulmonary Alveolar Proteinosis"[Mesh] OR "Pulmonary alveolar proteinosis"[Title/Abstract] OR "Alveolar lipoproteinosis"[Title/Abstract] OR "Alveolar proteinosis"[Title/Abstract]) AND ("Rituximab"[Mesh] OR Rituximab[Title/Abstract] OR rituxan[Title/Abstract] OR mabthera[Title/Abstract] OR "anti-CD20 antibody"[Title/Abstract] OR "anti-CD20 antibodies"[Title/Abstract] OR "CD20 Antibody"[Title/Abstract] OR "CD20 Antibodies"[Title/Abstract] OR "B-cell depletion"[Title/Abstract])

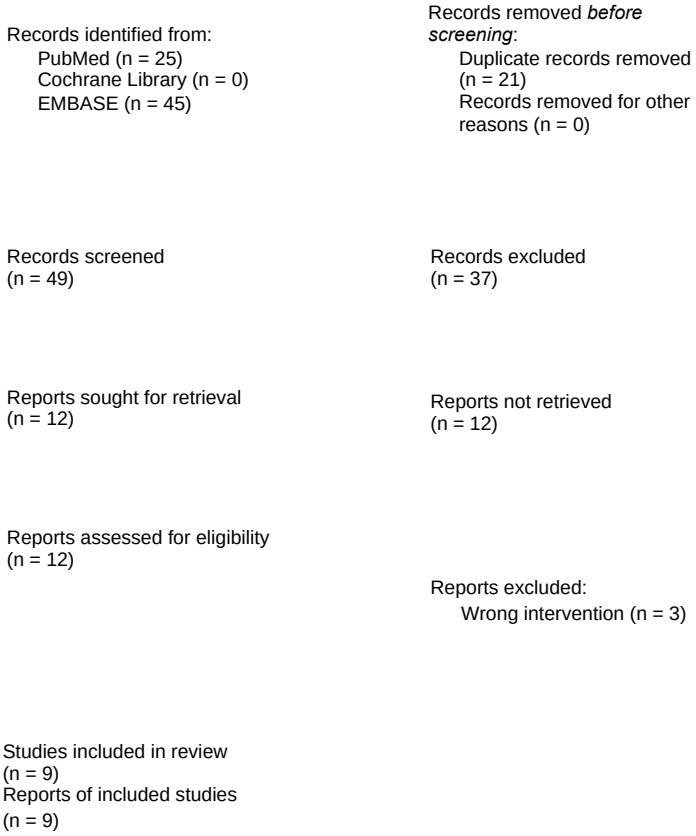
2. Cochrane Library

("Pulmonary Alveolar Proteinosis/drug therapy"[Mesh] OR "Pulmonary alveolar proteinosis" OR "Alveolar lipoproteinosis" OR "Alveolar proteinosis") AND ("Rituximab"[Mesh] OR Rituximab OR rituxan OR mabthera OR “CD20 Antibody” OR “B-cell depletion”)

3. EMBASE

('lung alveolus proteinosis'/mj/exp OR 'lung alveolus proteinosis':ti,ab OR 'pulmonary alveolar proteinosis':ti,ab OR 'alveolar lipoproteinosis':ti,ab OR 'alveolar proteinosis':ti,ab) AND ('rituximab'/exp OR 'rituximab':ti,ab OR rituxan:ti,ab OR mabthera:ti,ab OR 'cd20 antibody'/exp OR 'cd20 antibody':ti,ab OR 'cd20 antibodies':ti,ab OR 'anti cd20 antibody':ti,ab OR 'anti cd20 antibodies':ti,ab OR 'anticd20 antibody':ti,ab OR 'anticd20 antibodies':ti,ab OR 'b cell depletion therapy'/exp OR 'b cell depletion':ti,ab)

PRISMA Flow diagram summarising the study selection process



Included studies

Non-comparative interventional study

1. Kavuru MS, Malur A, Marshall I, Barna BP, Meziane M, Huizar I, Dalrymple H, Karnekar R, Thomassen MJ. An open-label trial of rituximab therapy in pulmonary alveolar proteinosis. Eur Respir J. 2011 Dec;38(6):1361-7. doi: 10.1183/09031936.00197710.

Non-comparative observational study

1. 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.

Case Reports

1. Amital A, Dux S, Shitrit D, Shpilberg O, Kramer MR. Therapeutic effectiveness of rituximab in a patient with unresponsive autoimmune pulmonary alveolar proteinosis. Thorax. 2010 Nov;65(11):1025-6. doi: 10.1136/thx.2010.140673.

2. Bird D, Evans J, Pahoff C. Rituximab rescue therapy for autoimmune pulmonary alveolar proteinosis. Respir Med Case Rep. 2022 Mar 21;37:101637. doi: 10.1016/j.rmcr.2022.101637.

3. 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.

4. Keske A, Destrampe EM, Barksdale B, Rose WN. Pulmonary Alveolar Proteinosis Refractory to Plasmapheresis and Rituximab despite GM-CSF Antibody Reduction. Case Reports Immunol. 2022 Jan 30;2022:2104270. doi: 10.1155/2022/2104270.

5. Meybodi FA, Fard SK, Zarch MB, Babai M. Rituximab therapy in pulmonary alveolar proteinosis: A rare case report. J Clin Diagn Res. 2018; 12(4):OD07-8. doi: 10.7860/JCDR/2018/32371.11419.

6. Hunt S, Miller AL, Schissel S, Ross JJ. A crazy cause of dyspnea. N Engl J Med. 2010 Dec 16;363(25):e38. doi: 10.1056/NEJMimc1008281.

7. Nagasawa J, Kurasawa K, Hanaoka R. Rituximab improved systemic lupus erythematosus-associated pulmonary alveolar proteinosis without decreasing anti-GM-CSF antibody levels. Lupus. 2016 Jun;25(7):783-4. doi: 10.1177/0961203315627204.

Risk of bias assessment

Table 4. Risk of bias assessment of the included studies.

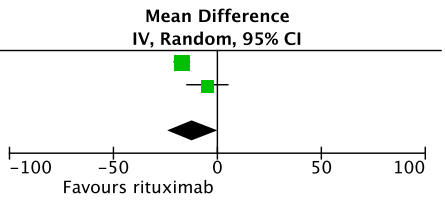
Bias domains	**Kavuru 2011[67]**	**Soyez 2018[68]**
Study design	Single arm interventional	Single arm observational
Bias caused by confounding	Serious	Serious
Bias caused by selection of participants	Low	Low
Bias caused by classification of interventions	Low	Low
Bias caused by deviations from intended interventions	Low	Low
Attrition bias caused by missing data	Moderate	Moderate
Detection bias caused by measurement of outcomes	Low	Low
Reporting bias caused by selection of the reported results	Low	Moderate
Overall risk of bias judgement	**Moderate**	**High**

Meta-analyses: Forest plots

A-a DO2 6-12 months post-rituximab, compared to baseline

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kavuru 2011	32.9	4.6	9	50	3.4	10	57.1%	-17.10 [-20.77, -13.43]
Soyez 2018	35.82	15.2	11	40.62	7.33	13	42.9%	-4.80 [-14.63, 5.03]
Total (95% CI)			**20**			**23**	**100.0%**	**-11.83 [-23.76, 0.10]**

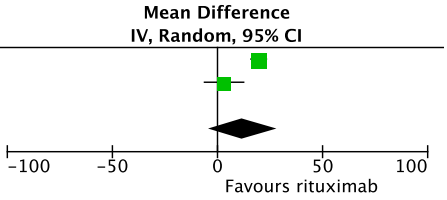
Heterogeneity: $Tau^2 = 61.32$; $Chi^2 = 5.28$, df = 1 (P = 0.02); $I^2 = 81\%$
Test for overall effect: Z = 1.94 (P = 0.05)



PaO_2 6-12 months post-rituximab, compared to baseline

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kavuru 2011	74.3	4.6	9	54.7	3.4	10	53.5%	19.60 [15.93, 23.27]
Soyez 2018	70.45	14.19	11	67.33	7.24	12	46.5%	3.12 [-6.21, 12.45]
Total (95% CI)			**20**			**22**	**100.0%**	**11.94 [-4.17, 28.05]**

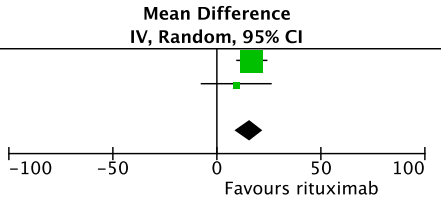
Heterogeneity: $Tau^2 = 122.71$; $Chi^2 = 10.37$, df = 1 (P = 0.001); $I^2 = 90\%$
Test for overall effect: Z = 1.45 (P = 0.15)



DLCO 6-12 months post-rituximab, compared to baseline

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kavuru 2011	56.4	9.7	9	39.6	5.3	10	84.6%	16.80 [9.66, 23.94]
Soyez 2018	63.3	20.07	10	54	18.86	11	15.4%	9.30 [-7.40, 26.00]
Total (95% CI)			**19**			**21**	**100.0%**	**15.64 [9.08, 22.21]**

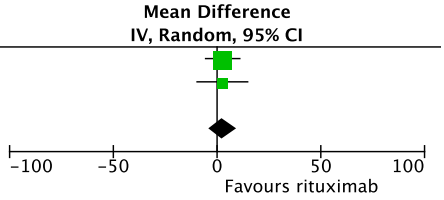
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.65$, df = 1 (P = 0.42); $I^2 = 0\%$
Test for overall effect: Z = 4.67 (P < 0.00001)



FVC 6-12 months post-rituximab, compared to baseline

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kavuru 2011	63.7	10.2	9	61	7.8	10	68.7%	2.70 [-5.53, 10.93]
Soyez 2018	81.55	11.74	11	79	18.44	13	31.3%	2.55 [-9.64, 14.74]
Total (95% CI)			**20**			**23**	**100.0%**	**2.65 [-4.17, 9.48]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 0.98); $I^2 = 0\%$
Test for overall effect: Z = 0.76 (P = 0.45)



Evidence profile

Table 5. Evidence Profile. Rituximab compared to before rituximab for primary autoimmune PAP. It should be noted that no studies assessing head-to-head rituximab versus control were identified.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	Before Rituximab	Relative (95% CI)	Absolute (95% CI)		
A-a DO2 (follow-up: range 6 months to 12 months)												
2[67,68]	observational studies	serious[a]	serious[b]	not serious	very serious[c]	none	20	23	-	MD **11.83 mmHg lower** (23.76 lower to 0.10 higher)	⨁◯◯◯ Very low	CRITICAL
PaO2 (follow-up: 6 months)												
2[67,68]	observational studies	serious[a]	not serious	not serious	very serious[c]	none	20	22	-	MD **11.94 mmHg higher** (4.19 lower to 20.81 higher)	⨁◯◯◯ Very low	CRITICAL
DLCO (% predicted) (follow-up: 6 months)												
2[67,68]	observational studies	serious[a]	not serious	not serious	very serious[c]	none	19	21	-	MD 15.64**% higher** (9.08 higher to 22.21 higher)	⨁◯◯◯ Very low	CRITICAL
FVC (% predicted) (follow-up: 6 months)												
2[67,68]	observational studies	serious[a]	not serious	not serious	very serious[c]	none	20	23	-	MD **2.65 % higher** (4.17 lower to 9.48 higher)	⨁◯◯◯ Very low	IMPORTANT
Exercise capacity (6MWT) (follow-up: 6 months)												
1[67]	observational studies	serious[a]	not serious	not serious	very serious[c]	none	9	10	-	MD **19 m higher** (93.47 lower to 131.47 higher)	⨁◯◯◯ Very low	CRITICAL
Mortality (follow-up: range 6 months to 12 months)												
2[67,68]	observational studies	serious[a]	not serious	not serious	very serious[c]	none	0/20 (0.0%)	0/23 (0.0%)	not estimable		⨁◯◯◯ Very low	CRITICAL
Serious adverse events (follow-up: range 6 months to 12 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	Before Rituximab	Relative (95% CI)	Absolute (95% CI)		
2[67,68]	observational studies	serious[a]	not serious	not serious	very serious[c]	none	0/20 (0.0%)	0/23 (0.0%)	not estimable		⨁◯◯◯ Very low	CRITICAL
Symptoms - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Exercise capacity (treadmill) - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Exercise capacity (treadmill) - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Rated down by 1 for methodological limitations. Included study/studies were at high risk for confounding and attrition bias.
b. Rated down by 1 for inconsistency. I2 = 81%.
c. Rated down by 2 for imprecision. The s sample size was very small.

Case reports

Table 6. Risk of bias of case reports and case series evaluating the use of rituximab for primary autoimmune PAP.

	Amital 2010[69]	Bird 2022[70]	Garber 2015[71]	Keske 2022[72]	Meyobi 2018[73]	Hunt 2010[74]	Nagasawa 2016[75]
Were patient's demographic characteristics clearly described?	Y	Y	Y	Y	Y	Y	Y
Was the patient's history clearly described and presented as a timeline?	Y	Y	Y	Y	N	Y	Y
Was the current clinical condition of the patient on presentation clearly described?	Y	Y	Y	N	N	Y	Y
Were diagnostic tests or assessment methods and the results clearly described?	Y	Y	Y	Y	N	Y	Y
Was the intervention(s) or treatment procedure(s) clearly described?	Y	Y	Y	Y	Y	N	Y
Was the post-intervention clinical condition clearly described?	Y	Y	Y	N	N	N	Y
Were adverse events (harms) or unanticipated events identified and described?	Y	N	N	N	N	N	N
Does the case report provide takeaway lessons?	Y	Y	Y	Y	Y	Y	Y

Table 7. Case reports and case series up to 5 cases reporting on the use of rituximab for primary autoimmune PAP.

BAL: Broncho-alveolar lavage. CT: Computed tomography. DLCO: Diffusing capacity for carbon monoxide. GM-CSF: Granulocyte macrophage colony-stimulating factor. LDH: Lactate dehydrogenase. mMRC: modified Medical Research Council Scale. NR: Not reported. NYHA: New York Heart Association. PaO2: Partial pressure of oxygen. PFTs: Pulmonary function tests. QoL: Quality of life. SatO2: Oxygen saturation. WLL: Whole lung lavage.

Study ID	Age, Gender, Smoking	History	Condition upon presentation	Intervention	Post-intervention condition	Adverse events / harms
Amital 2010[69]	40, Female, Non smoker	Progressive dyspnoea and hypoxia. Diagnosed with BAL and transbronchial biopsies. Within 2.5 years from diagnosis she required 7x WLL, while she also received GM-CSF replacement therapy. She was breathless at rest with supplemental oxygen requirements between 0.5L and 6L.	After the last WLL patient remained hypoxemic, with high oxygen requirements. Anti-GM-CSF antibody titre >1:12 800 (normal <1:400)	Rituximab 375mg/m^2 IV weekly for four weeks.	✓ SatO2 >94% on room air after 1st dose, >98% on room air after 2nd dose. ✓ Oxygen therapy stopped. ✓ 6MWT: 420m (previously: 198m). ✓ Ongoing dyspnoea on exertion only. ✓ Improved DLCO. ✓ LDH 589 from 1062 U/l.	No adverse events
Bird 2022[70]	41, Male, Smoker (tobacco and cannabis)	Progressive exertional dyspnoea, recurrent chest infections, pleuritic chest pains. Diagnosed by consistent BAL, PFTs and radiological findings and positive GM-CSF antibodies. Received sequential, bilateral WLL	Hydropneumothorax after the sixth WLL. Further WLL contra-indicated. Significant deterioration in exercise tolerance within two months. Became oxygen	Rituximab 1g IV. Two doses 2 weeks apart. Maintenance treatment planned every 6 months	Six months post treatment: ✓ Oxygen therapy stopped. ✓ 6MWT: 562m (previously 33om). ✓ Improved FEV_1, FVC, DLCO. ✓ Reduced anti-GM-CSF titres. ✓ Significant radiological improvement. ✓ QoL improved.	Not reported

		every 6 months with a partial clinical response.	dependent with PaO2 of 47mmHg. House bound.			
Garber 2015[71]	40, Male, NR	Breathlessness. Diagnosis based on imaging, open lung biopsy and raised anti-GM-CSF titer (44.89 mcg/mL; normal <5). 14 WLL in a 20-month period, with short-lived benefits. GM-CSF replacement trial was ineffective	See history. Prior treatments were unsuccessful	Rituximab 1g IV. Two doses 2 weeks apart.	✓ Decreased WLL frequency (3 WLL in 8 months). ✓ Symptoms recurred. ✓ 6MWT 205 from 384. ✓ Required rescue treatment (plasmapheresis)	Not reported.
Keske 2022[72]	28, Male, Smoker	Progressive dyspnoea, fevers, and sweats. Diagnosed based on BAL, radiological findings and positive anti-GM-CSF titers (103mcg/ml, normal <5).	See history. Persistent symptoms despite, repeated WLLs every 3-4 weeks, inhaled GM-CSF, plasmapheresis and one dose of rituximab after the last plasmapheresis procedure.	Rituximab 1000mg IV, single dose	✓ No clinical improvement reported after these treatments. ✓ No further information reported.	Not reported.
Meyobi 2018[73]	49, Female, Non smoker	Four years history of exertional dyspnoea, cough and sputum. Diagnosis was previously known and not described in this case report.		Rituximab 800mg IV. 0,1,7,12 months.	✓ At one year: Improved FEV_1 (69% from 56% predicted), FVC (72% from 63%) and FEV_1/FVC (102% from 94%). ✓ Stable SatO2 (95% from 93%).	Not reported

Hunt 2010[74]	18, Female Non smoker	Progressive dyspnoea on exertion and cough. Diagnosis based on consistent CT and spirometry findings and a positive GM-CSF antibody (1:12800)	Multiple WLL (4 times a year) with some symptomatic benefit. Trials of rituximab and mycophenolate without benefit.	Rituximab, no additional information reported	✓ No effect.	Not reported
Nagasawa 2016[75]	26, Female, NR	Background SLE. Presented with cough and dyspnoea on exertion. Diagnosed based on consistent CT and BAL, and a positive serum anti-GM-CSF antibody.	Progressive symptoms despite repeated WLLs. Required supplemental oxygen. Two years later, she started rituximab	Rituximab 365 mg/m^2 IV. Four doses	✓ Radiologic improvement. ✓ Oxygen therapy stopped. ✓ Returned to her work and activities of daily living.	Not reported

Evidence to decision framework

QUESTION

In patients with confirmed autoimmune PAP should rituximab be used versus no immunosuppressive treatment?	
POPULATION:	Auto-Immune Pulmonary Alveolar Proteinosis
INTERVENTION:	Rituximab
COMPARISON:	No rituximab
MAIN OUTCOMES:	A-a DO2; PaO2; DLCO (% predicted); FVC (% predicted); Exercise capacity (6MWT); Mortality; Serious adverse events; Symptoms; Exercise capacity (treadmill); HRCT (Radiologic) severity scores.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	Pulmonary alveolar proteinosis (PAP) is a rare but burdensome disease, characterised by progressive respiratory symptoms, including breathlessness, that is characterised by significant morbidity and -if untreated- mortality. Whole lung lavage (WLL), the most common treatment for PAP is interventional requiring hospital admission and general anaesthesia. It is associated with significant complications, including hypoxia, pneumonia, prolonged intubation, pleural effusion, pneumothorax and a mortality risk. The effect of WLL weans over time and patients often require repeated procedures. It is therefore a priority to identify safer and more cost effective treatments for this burdensome disease.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● **Moderate** ○ Large ○ Varies ○ Don't know	**Available data:** (i) A single arm interventional study of 10 patients (Kavuru 2011)[67], (ii) A retrospective case series of 11 patients (Soyez 2018)[68], and (iii) Seven case reports[69-75]. All studies evaluated adults with auto-immune PAP, confirmed by the presence of high anti-GM-CSF titers. Most patients had undergone WLL and / or GM-CSF treatment prior to recruitment. Both Kavuru 2011 and Soyez 2018 compared the clinical status of patients 6-12 months after rituximab treatment, compared to the	

	baseline, before receiving rituximab, so, data were pooled together[67,68]. Participants in both studies received two doses of rituximab 1,000 mg, administered 15 days apart[67,68]. One patient in the Soyez 2018 study only received a single dose, while three received an additional, maintenance dose[68]. **Desirable effects:** There was very low certainty evidence suggesting that rituximab may reduce the alveolar arterial oxygen difference (A-a) DO2, Mean difference (MD) -11.83 mmHg, 95% confidence intervals: [-23.76, 0.10 mmHg, I^2 = 81% and improve the partial concentration of oxygen measured on room air (MD 11.94 [-4.17, 28.05] mmHg, I^2 =90%). In addition, very low certainty evidence suggests trivial or no impact of rituximab on the diffusing capacity of the lungs for carbon monoxide (DLCO, MD: 15.64% [9.08%, 22.21%] predicted, I^2 =0%), the forced vital capacity (FVC, MD: 2.65% [-4.17%, 9.48%] predicted) or on exercise capacity evaluated using 6-minute walking test (6-MWT, MD: 19 [-93.47, 131.47] meters). Kavuru 2011 reports that four out of seven patients that were observed for a mean of 32 (± 6) months did not require WLL[67]. The remaining three patients required one WLL each during follow-up. Interestingly, one of these patients required monthly WLL prior to the intervention. This suggests a reduced symptoms burden and lack of hypoxia. Soyez 2018 reports 4/11 patients exerted significant improvement at 12 months, compared to baseline[68]. Improvement was defined as a decrease in the A-a DO2 by at least 10mmHg. One patient was lost of follow-up and 1 received lung transplant and were not evaluated at 12 months. Kavuru 2011[67] also reported a significant improvement in the HRCT scores (p = 0.027), which was however not observed in Soyez 2018 (NS)[68]. Six out of seven case reports documented a clinically significant improvement at various time points after rituximab initiation (3-12 months)[69-73,75]. Benefits included better oxygenation that led to discontinuation of domiciliary oxygen, improved oxygen saturation on room air, improved exercise capacity, reduction in the frequency of WLL, and/or improvement in the pulmonary function parameters. one out of seven cases (14.2%) did not gain any benefits from rituximab.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Trivial** ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Available data:** As above **Undesirable effects:** Mortality or severe adverse events were not observed in these uncontrolled studies. Only two of the case reports addressed safety. No serious adverse events were reported either.	The safety profile of rituximab at a similar dose (two doses of 1,000 mg) in adults has been evaluated in more detail in a Cochrane review evaluating rituximab for patients with rheumatoid arthritis[76]. The addition of rituximab was not associated with increased risk of serious adverse events (at 24 weeks follow-up: relative risk = 1 [0.69, 1.5], at 48-56 weeks follow-up RR 0.94 [0.57, 1.5], at 104 weeks follow-up RR 0.78 [0.51, 1.2]). Rituximab was associated with a trend over increased discontinuation due to adverse events during the first six months (RR 2.1 [0.88, 4.9]), this trend disappeared at 1 year follow-up (RR 1.0 [0.44, 2.30]) and was reverted at longer follow-up (72 months: RR 0.33 [0.04, 3.10]; 104 months: RR 0.56 [0.25, 1.30]) The safety of rituximab in children at a dose of 1-4 infusions of 375mg/m^2 has been assessed in more detail in a meta-analysis evaluating rituximab for childhood steroid-dependent nephrotic syndrome[77]. This meta-analysis did not reveal any increase in the risk of infections (Odds ratio – OR: 1.58 [0.25, 10.07]), or cardiovascular disease events (OR 1.30 [0.31, 5.44]), but found a trend over increased risk of infusion reactions (OR: 3.22 [0.90, 11.46]). The latter can be alleviated by slowing down the rate of infusion or applying antihistamins. The authors reported that the rate of severe allergic reactions in children is very low[78]. The European Medicines Agency reports that the most common side effects to rituximab are related to infusion (fever, chills and shivering), while most common serious side effects are infusion reactions, infections and heart-related problems. It recommends against the use of rituximab for people who are allergic to rituximab, mouse proteins or any of its other ingredients, for those with a severe infection or severe immunosuppression, or severe heart problems.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Very low** ○ Low ○ Moderate ○ High ○ No included studies	The certainty of evidence is very low. There are serious concerns around the methodological limitations of the included studies, that were single-arm and not controlled. Spontaneous remission is observed in approximately one in four patients with PAP and therefore, a treatment effect cannot confidently be established based on the available, uncontrolled studies and case reports. Moreover, there are very serious concerns around imprecision, since the available studies were very underpowered. Finally, data around D A-a O2 were inconsistent across the included studies. The direct evidence around the safety of rituximab in patients with PAP is very limited for the same reasons. However, high certainty evidence data from a Cochrane systematic review evaluating rituximab for rheumatoid arthritis supported the safety of the intervention. All available data are from adult studies. We did not found any data around the safety and efficacy of rituximab in children and adolescents.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● **Probably no important** uncertainty or variability ○ No important uncertainty or variability	No specific studies were identified to answer this question	Although we are not aware of any research evidence assessing how much people value the main outcomes, the clinical practice guideline development group, and the patient representatives consider that prevention of WLL and improvement in the hypoxia would be considered important by most patients, especially given the reassuringly safe profile of rituximab.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	Available data of very low certainty support the safety of rituximab, which may improve (A-a) DO2 and PaO2, and prevent or delay the next WLL.	

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● **Moderate savings** ○ Large savings ○ Varies ○ Don't know	No specific studies were identified to answer this question	While rituximab is an expensive intervention, it's administration may prevent or delay the next WLL, a complex intervention that requires hospital admission and general anaesthesia and is therefore more expensive. Patients with PAP often require regular WLL, sometimes monthly. So, a potential reduction in the frequency of WLL would lead to cost savings, although this remain to be confirmed in more rigorous studies.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	No specific studies to answer this question. Our judgement is based on the very low certainty observation that rituximab may prevent or delay the frequency of WLL, which is a costly procedure.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies○ No included studies	No specific studies were identified to answer this question	As above. Rituximab may improve symptoms and hypoxia and prevent or delay the frequency of WLL, which is a costly procedure.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● **Probably increased** ○ Increased ○ Varies ○ Don't know	No specific studies were identified to answer this question	The patent of rituximab expired in 2016 and there are available biosimilars at a significantly reduced price. In addition, WLL is only performed in multi-disciplinary centres of expertise in PAP, that may not be available globally. On the contrary, rituximab could possibly be administered at a secondary/ tertiary care setting.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	No specific studies were identified to answer this question.	While data around the safety and clinical effectiveness of rituximab in PAP are limited, there are ample indirect data from other diseases (such as rheumatoid arthritis) supporting the safety of this medicine. In parallel, while they are based on very low certainty data, the potential benefits of rituximab are important to patients (improvement in symptoms and oxygenation, prevention or delay of WLL).

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know		

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Recommendation

We suggest the use of rituximab for patients with confirmed primary autoimmune pulmonary alveolar proteinosis who remain significantly symptomatic, requiring supplemental oxygen, despite whole lung lavage therapy or exogenous GM-CSF treatment (very low certainty, conditional recommendation).

PICO 6: In patients with confirmed autoimmune PAP should plasmapheresis be used versus no plasmapheresis?

Search Strategy

1. PubMed

("Pulmonary Alveolar Proteinosis"[Mesh] OR "Pulmonary alveolar proteinosis"[Title/Abstract] OR "Alveolar lipoproteinosis"[Title/Abstract] OR "Alveolar proteinosis"[Title/Abstract]) AND ("Plasmapheresis"[Mesh] OR Plasmapheresis[Title/Abstract] OR Plasmaphereses [Title/Abstract] OR "Plasma Exchange"[Mesh] OR "Plasma Exchange"[Title/Abstract] OR "Blood Component Removal"[Mesh] OR apheresis[Title/Abstract])

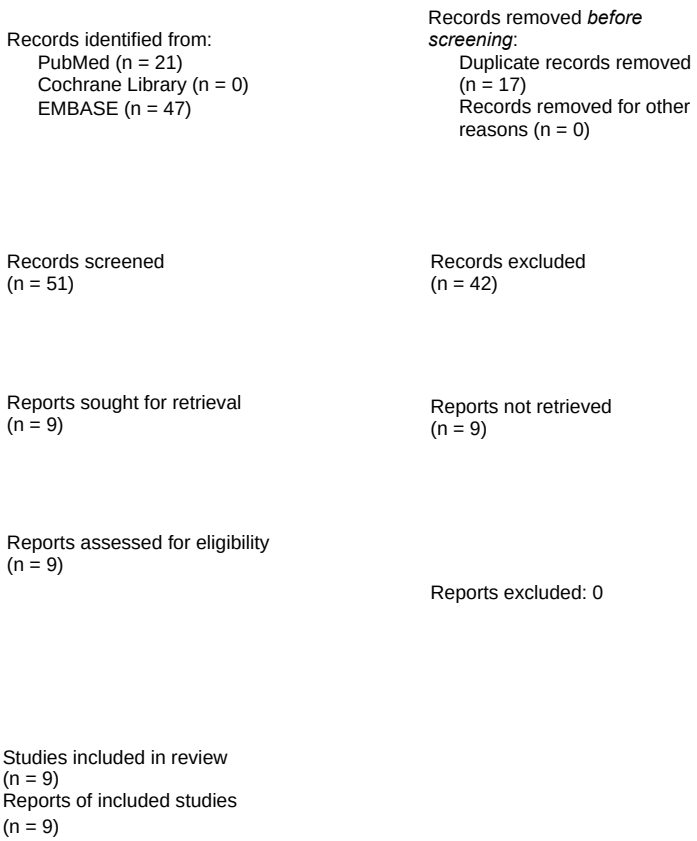
2. Cochrane Library

("Pulmonary Alveolar Proteinosis"[Mesh] OR "Pulmonary alveolar proteinosis" OR "Alveolar lipoproteinosis" OR "Alveolar proteinosis") AND ("Plasmapheresis"[Mesh] OR Plasmaphereses OR "Plasma Exchange"[Mesh] OR "Plasma Exchanges" OR "Blood Component Removal"[Mesh] OR apheresis) in Title Abstract Keyword

3. EMBASE

('lung alveolus proteinosis'/mj/exp OR 'lung alveolus proteinosis' OR 'lung alveolus proteinosis':ti,ab OR 'pulmonary alveolar proteinosis':ti,ab OR 'alveolar lipoproteinosis':ti,ab OR 'alveolar proteinosis':ti,ab) AND ('plasmapheresis'/exp OR 'plasmapheresis':ti,ab OR 'plasmaphoresis'/exp OR plasmaphoresis:ti,ab OR 'plasma pheresis'/exp OR 'plasma pheresis':ti,ab OR 'plasma apheresis'/exp OR 'plasma apheresis':ti,ab OR 'plasma exchange'/exp OR 'plasma exchange':ti,ab OR 'apheresis'/exp OR 'apheresis':ti,ab OR 'blood component removal'/exp OR 'blood component removal':ti,ab) AND ([english]/lim OR [french]/lim) AND ('article'/it OR 'article in press'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it)

PRISMA Flow diagram summarising the study selection process



Included studies

Case reports

1. Bonfield TL, Kavuru MS, Thomassen MJ. Anti-GM-CSF titer predicts response to GM-CSF therapy in pulmonary alveolar proteinosis. Clin Immunol. 2002 Dec;105(3):342-50. doi: 10.1006/clim.2002.5301.
2. 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.
3. Griese M, Panagiotou P, Manali ED, Stahl M, Schwerk N, Costa V, Douros K, Kallieri M, Urbantat RM, von Bernuth H, Kolilekas L, Morais L, Ramos A, Landwehr K, Knoflach K, Gothe F, Reiter K, Papaevangelou V, Kaditis AG, Kanaka-Gantenbein C, Papiris SA. Autoimmune pulmonary alveolar proteinosis in children. ERJ Open Res. 2022 Mar 21;8(1):00701-2021. doi: .
4. Jézéquel A, Kerjouan M, Lederlin M, Lainé-Caroff C, Camus C, Delaval P, Jouneau S. Échec de plasmaphérèse dans une protéinose alvéolaire pulmonaire auto-immune [Plasmapheresis failure in the treatment of auto-immune pulmonary alveolar proteinosis]. Rev Mal Respir. 2017 Mar;34(3):240-243. French. doi: 10.1016/j.rmr.2016.06.002.
5. Kavuru MS, Bonfield TL, Thomassen MJ. Plasmapheresis, GM-CSF, and alveolar proteinosis. Am J Respir Crit Care Med. 2003 Apr 1;167(7):1036; author reply 1036-7. doi: 10.1164/ajrccm.167.7.950.
6. Keske A, Destrampe EM, Barksdale B, Rose WN. Pulmonary Alveolar Proteinosis Refractory to Plasmapheresis and Rituximab despite GM-CSF Antibody Reduction. Case Reports Immunol. 2022 Jan 30;2022:2104270. doi: 10.1155/2022/2104270.
7. Luisetti M, Rodi G, Perotti C, Campo I, Mariani F, Pozzi E, Trapnell BC. Plasmapheresis for treatment of pulmonary alveolar proteinosis. Eur Respir J. 2009 May;33(5):1220-2. doi: 10.1183/09031936.00097508.
8. Vis DC, Kelly MM, De Heuvel E, MacEachern PR. Reduction in Alveolar Macrophage Size in Refractory Autoimmune Pulmonary Alveolar Proteinosis After Treatment With Pioglitazone. J Bronchology Interv Pulmonol. 2020 Jul;27(3):219-222. doi: 10.1097/LBR.0000000000000686.
9. Yu Hy, Sun Xf, Wang Yx, Xu Zj, Huang H. Whole lung lavage combined with Granulocyte-macrophage colony stimulating factor inhalation for an adult case of refractory pulmonary alveolar proteinosis. BMC Pulm Med. 2014 May 19;14:87. doi: 10.1186/1471-2466-14-87.

Case reports

Table 9. Risk of bias of case reports and case series evaluating the use of plasmapheresis for primary autoimmune PAP.

	Bonfield 2002[79]	Garber 2015[71]	Griese 2022[80]	Jezequel 2017[81]	Kavuru 2003[82]	Keske 2022[72]	Luisietti 2009[83]	Vis 2020[84]	Yu 2014[85]
Were patient's demographic characteristics clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the patient's history clearly described and presented as a timeline?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the current clinical condition of the patient on presentation clearly described?	Y	Y	Y	Y	Y	N	Y	Y	Y
Were diagnostic tests or assessment methods and the results clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the intervention(s) or treatment procedure(s) clearly described?	Y	Y	Y	Y	Y	Y	Y	N	Y
Was the post-intervention clinical condition clearly described?	Y	Y	Y	Y	Y	N	N	N	N
Were adverse events (harms) or unanticipated events identified and described?	N	N	N	N	Y	N	N	N	N
Does the case report provide takeaway lessons?	Y	Y	Y	Y	Y	Y	Y	Y	Y

Case reports and case series up to 5 cases reporting on the use of plasmapheresis for auto-immune PAP.
BAL: Broncho-alveolar lavage. CT: Computed tomography. DLCO: Diffusing capacity for carbon monoxide. ECMO: Extracorporeal membrane oxygenation. GM-CSF: Granulocyte macrophage colony-stimulating factor. LDH: Lactate dehydrogenase. mMRC: modified Medical Research Council Scale. NR: Not reported. NYHA: New York Heart Association. PaO2: Partial pressure of oxygen. PFTs: Pulmonary function tests. QoL: Quality of life. SatO2: Oxygen saturation. WLL: Whole lung lavage.

Study ID	Age, Gender, Smoking	History	Condition upon presentation	Intervention	Post-intervention condition	Adverse events / harms
Bonfield 2002[79]	43, Female, Non smoker	Autoimmune PAP based on lung biopsy and anti-GM-CSF titres. Three years after diagnosis she was offered GM-CSF, but did not respond, as she required 3 WLL within the first 6 months of threatment	See history. Has failed GM-CSF and required frequent WLL. Dependent on supplemental oxygen 3-6L/min at rest. Considered for transplantation.	Sequential Plasmapheresis 10 sessions of 1.5L plasma volume exchange over 2 months	✓ Reduced anti-GM-CSF titre from 1:6400 to 1:400. ✓ Radiologic improvement. ✓ Improved oxygenation (room air PaO2 of 70 mmHg from 50 mmHg). ✓ Suppression of anti-GM-CSF titre maintained for at least 4 months post-plasmapheresis	Not reported.
Garber 2015[71]	40, Male, NR	Breathlessness. Diagnosis based on imaging, open lung biopsy and raised anti-GM-CSF titer (44.89 mcg/mL; normal <5). 14 WLL in a 20-month period, with short-lived benefits.	See history. GM-CSF replacement and rituximab trials were ineffective.	Following WLL, patient received five daily consecutive sessions of plasmapheresis and one dose of rituximab after the last plasmapheresis.	✓ Reduced anti-GM-CSF titre from 24.8 to 2.7 mcg/mL. ✓ Subjective improvement in dyspnoea at three months ✓ Increased DLCO (42% from 28% predicted) at three months ✓ Symptoms recurrence 5 months post procedure that led to WLL followed by repeat plasmapheresis protocol	Not reported.

					✓ Reduced need for WLL	
Griese 2022[80]	15, Male, NR	Malnourishment (BMI <14 kg/m^2, <3rd percentile), dry cough and breathlessness. Consistent BAL, CT imaging and strongly positive anti-GM-CSF antibody levels.	Developed respiratory failure within 4 months from symptoms onset, requiring FiO2 of 60-75%. Had six WLLs, the first under ECMO, without significant clinical improvement.	Ten sessions of plasmapheresis followed by 2 doses of rituximab 375 mg/m^2 per dose.	✓ Improved breathlessness. ✓ Reduced need for supplemental oxygen. (FiO2 of 30% during sleep, 8 months post-intervention). ✓ Reduced need for WLL. Only one WLL was necessary within 8 months of follow-up. ✓ BMI improved (16kg/m^2). ✓ CT and lung function improved but not normalised.	Not reported.
Jezequel 2017[81]	41, Smoker 15 PY	PAP diagnosed on bilateral pneumonia + PAS+ material in BAL. Anti-GMCSF antibody were positive (900µg/mL).	Developed respiratory failure within 4 months from symptoms onset, requiring supplemental oxygen up to 8L/min. Had 3 WLL in 8 months with significant clinical improvement but too close relapse. GM-CSF was administered after 3rd WLL, but another relapse led to 4th WLL 6 months	10 sessions over 6 weeks (five sessions of plasmapheresis over 10 days, followed by 1 session a week for 5 weeks) Mean 1.3 [1.0-1.5] plasma volume exchange via centrifugal apheresis with 4% albumin volume replacement	x Plasmapheresis was not effective ✓ NYHA 4 dyspnea ✓ Increased O2 uptake ✓ Persisting diffuse ILD on chest Xray	Not reported Metastatic lung cancer was diagnosed concomitely to the plasmapheresis procedure, but considered an independent event

			later with very low improvement.			
Kavuru 2003[82]	41, Female Non-smoker	5-years history of non-resolving pulmonary infiltrates. Open lung biopsy confirmed PAP (air spaces filled with eosinophilic proteinaceous material without significant inflammation or tissue destruction). Positive anti-GM-CSF 1:6,400 on multiple occasions.	Had three WLL with modest benefit. Had GM-CSF replacement at 18mcg/kg/day for 6 months without objective improvement. She continued to require 3-6L/min oxygen at rest.	Ten sessions of plasmapheresis of 1.5 plasma volume exchange over a 2-month period	✓ Reduce anti-GM-CSF antibody titer to 1:400. ✓ Improvement in symptoms ✓ Improvement in oxygenation. Remained off Oxygen with a room air PaO2 of 75mmHg. ✓ Improvement in radiograph.	One session of plasmapheresis was complicated by gram -ve sepsis and respiratory failure. Made full recovery
Keske 2022[72]	28, Male, Smoker	Progressive dyspnoea, fevers, and sweats. Diagnosed based on BAL, radiological findings and positive anti-GM-CSF titers (103mcg/ml, normal <5).	See history. Persistent symptoms despite, repeated WLLs every 3-4 weeks, and inhaled GM-CSF replacement.	Five plasmapheresis procedures in 6 days. Each procedure consisted of 1-plasma volume exchange via centrifugal apheresis with 5% albumin volume replacement	✓ Reduced GM-CSF antibody titers (17.6 mcg/ml after the 3rd session from 103 mcg/ml). x The patient reported no significant clinical improvement.	Not reported.
Luisetti 2009[83]	40, Male	Progressive respiratory failure. Diagnosed with PAP based on consistent results of a lung biopsy, high-resolution	Persistent, progressive symptoms, requiring repeated	**Low intensity plasma exchange:**	✓ Modest reduction GM-CSF antibody titers (153 mcg/ml from 250 mcg/ml).	Not reported

		CT scan of the chest and raised GM-CSF neutralising antibody titer.	WLL every few months (x4)	Ten 1.5L sessions over 2 months.	✓ Reduced frequency of WLL (3x in the 24 months after completion of plasmapheresis) x No significant clinical improvement.	
Vis 2020[84]	52, Male	Presented with hypoxic respiratory failure. Pap diagnosed based on consistent results of high-resolution CT scan of the chest, BAL, and a raised GM-CSF neutralising antibody-titer.	During the next decade, he developed refractory symptoms and hypoxemia requiring repeated WLL (x42 unilateral WLL in total).	8-week course (24 sessions) of plasmapheresis	x No significant clinical benefit	Not reported
Yu 2014[85]	47, Female	Presented with breathlessness and cough productive of clear sputum. Diagnosed with PAP based on consistent high-resolution CT scan of the chest and BAL. **GM-CSF neutralising antibody titers not reported.** Type 1 respiratory failure requiring 2L supplemental oxygen.	Within two years she had 4x B/L WLL with short term benefit.	5 sessions of plasmapheresis over 2 weeks. Exchange volume: 2.5L	✓ Improved clinical symptoms for 5 months ✓ Improved radiological findings for 5 months. x PAP symptoms relapsed again 5 months later, at the time requiring 8-9L/min supplemental oxygen.	Not reported

Evidence profile

Table 10. Evidence Profile. Plasmapheresis compared to before plasmapheresis.

Certainty assessment							№ of patients	Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Plasmapheresis			
Mortality										
9	Case reports	serious[a]	not serious	not serious	very serious[b]	none	9	No deaths reported	⊕◯◯◯ Very low	CRITICAL
PaO2										
6	Case reports	serious[a]	not serious	not serious	very serious[b]	none	6	6 case reports noted improved oxygenation or reduced requirement for supplemental oxygenation. The remaining 3 reported lack of significant clinical improvement but did not specifically comment on PaO2	⊕◯◯◯ Very low	IMPORTANT
DLCO										
1	Case reports	serious[a]	not serious	not serious	very serious[b]	none	1	A single case reported improved DLCO post plasmapheresis, while the remaining did not comment on DLCO	⊕◯◯◯ Very low	IMPORTANT
Serious adverse events										
1	Case reports	serious[a]	not serious	not serious	very serious[b]	none	1	A single case reported gram -ve sepsis and respiratory failure post-plasmapheresis, the remaining cases did not clearly report on safety.	⊕◯◯◯ Very low	CRITICAL
HRCT (radiologic) severity										
5	Case reports	serious[a]	not serious	not serious	very serious[b]	none	5	Five case reports described radiologic findings post-intervention. Four reported radiological improvement and one lack thereof	⊕◯◯◯ Very low	IMPORTANT
Symptoms (Dyspnoea)										
8	Case reports	serious[a]	not serious	not serious	very serious[b]	none	8	Of 8 case reports commenting on symptom, only half (4/8) reported symptomatic improvement	⊕◯◯◯ Very low	CRITICAL
Exercise tolerance (6MWT)										

Certainty assessment							№ of patients	Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Plasmapheresis			
0							Not reported in the identified case reports		-	IMPORTANT

CI: confidence interval; **MD:** mean difference

Explanations

a. All included case reports were deemed at high risk of bias, see table 9
b. Based on limited number of case reports only

Evidence to decision framework

QUESTION

In patients with confirmed autoimmune PAP should plasmapheresis be used versus no plasmapheresis?	
POPULATION:	Auto-Immune Pulmonary Alveolar Proteinosis
INTERVENTION:	Plasmapheresis
COMPARISON:	Before plasmapheresis
MAIN OUTCOMES:	A-a DO2; PaO2; DLCO (% predicted); FVC (% predicted); Exercise capacity (6MWT); Mortality; Serious adverse events; Symptoms; Exercise capacity (treadmill); HRCT (Radiologic) severity scores;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	Pulmonary alveolar proteinosis (PAP) is a rare but burdensome disease, characterised by progressive respiratory symptoms, including breathlessness, that is characterised by significant morbidity and -if untreated- mortality. Whole lung lavage (WLL), the most common treatment for PAP is interventional requiring hospital admission and general anaesthesia. It is associated with significant complications, including hypoxia, pneumonia, prolonged intubation, pleural effusion, pneumothorax and a mortality risk. The effect of WLL weans over time and patients often require repeated procedures. It is therefore a priority to identify safer and more cost effective treatments for this burdensome disease.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● **Moderate** ○ Large ○ Varies ○ Don't know	**Available data:** 9 case reports [71,72,79-85] **Desirable effects:** No significant clinical benefits were observed in three of the reported cases (Jezequel 2016, Keske 2002, Vis 2020)[72,81,84].	

	Two other cases reported a modest response[83,85]. More specifically, Yu et al reported improved clinical symptoms and radiological findings, that were however short-lived, since a significant PAP relapse was observed five months later[85]. However, while the diagnosis of this patient was confirmed by HRCT and BAL, the GM-CSF antibody titres were not reported. Therefore, it was not clear whether he had auto-immune PAP. Luisetti et al reported a reduced frequency of WLL after plasmapheresis, but no clear improvement in the symptoms after plasmapheresis[83]. Finally, four cases reported significant improvement in the symptoms (3/4), oxygenation (3/4), radiological findings (3/4) and/or pulmonary function (only reported in one study)[71,79,80,82]. A significant reduction in the GM-CSF antibody titres was reported in 5/9 cases. Rituximab was also administered after completion of plasmapheresis in two case reports, that only reported outcomes after both treatments were administered. Rituximab treatment has previously failed in one of these cases (Keske 2009)[72]. WLL also preceded plasmapheresis in one of these cases (Garber 2015)[71]. The plasmapheresis regimen is not standardised but it appears that higher intensity regimens that successfully suppress anti-GM-CSF antibodies offer clinical benefits.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● **Small** ○ Moderate ○ Large ○ Varies ○ Don't know	**Available data:** As above **Undesirable effects:** Only one case reported that one session of plasmapheresis was complicated by gram -ve sepsis and respiratory failure that were successfully treated and the patient recovered fully [71]. However, it is not clear whether the remaining cases did not have any plasmapheresis complications or whether these were just not recorded.	The safety of plasmapheresis was evaluated in detail in a Cochrane meta-analysis of the safety and efficacy of plasmapheresis for Guillain-Barre disease[86]. Based on data from three trials totalling 556 participants, plasmapheresis did not increase the risk of infection (RR 0.91 [0.73, 1.13]), of blood pressures instability (RR 0.88 [0.64, 1.22]), cardiac arrhythmias (RR 0.75 [0.56, 1.00]), or pulmonary embolus (RR 1.01 [0.26, 4.00]). However, it should be noted that the included studies employed 2-6 sessions of plasmapheresis, a lower number compared to those proposed for auto-immune PAP. The incidence of death associated with plasmapheresis has been estimated to be 0.05%, based on a systematic review meta-analysis of >15,500 patients (mainly adults)[87]. The complications of >4,500 sessions of plasmapheresis in 593 children with neurological disease have been summarised in a narrative review, that concluded that the intervention is well-tolerated and associated with adverse events that can be anticipated and avoided[88]. Complications were reported in 15%

		of plasmapheresis sessions and 70% of children. However, life-threatening complications were observed in 0.4% of treatment sessions and 2.4% of children.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Very low** ○ Low ○ Moderate ○ High ○ No included studies	The certainty of evidence is very low. Our only evidence comes from case reports. Spontaneous remission is observed in approximately one in four patients with PAP and therefore, a treatment effect cannot confidently be established based on the available case reports. In addition, the reported benefits were mostly subjective and not based on a validated measurement instrument. Only one case report described the use of plasmapheresis in an adolescent with PAP, while all other cases were adults.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● **Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No specific studies were identified to answer this question	Although we are not aware of any research evidence assessing how much people value the main outcomes, the clinical practice guideline development group, and the patient representatives consider that potential prevention of WLL and improvement in the hypoxia may be considered important by patients with PAP that is refractory to treatment and associated with a significant disease burden.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	Available data of very low certainty support a potential benefit of plasmapheresis in some patients with auto-immune PAP.	Indirect evidence support the safety of plasmapheresis.

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● **Negligible costs and savings** ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No specific studies were identified to answer this question	The costs of plasmapheresis varies significantly across the world[89]. In the UK, the cost has been estimated at 1,000€ per session. In PAP, available case reports describe 5-10 sessions of plasmapheresis, at an estimated total cost of 5,000-10,000€. On the other hand, WLL is also a complex intervention that requires hospital admission and general anaesthesia. The cost varies and is challenging to estimate. A 2004 report from Brompton suggested a cost between 4,600-5,700€ per WLL[90]. Patients with PAP often require regular WLL, sometimes monthly. So, a potential reduction in the frequency of WLL would balance the costs of plasmapheresis, or even lead to cost savings, although this remain to be confirmed in more rigorous studies.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	No specific studies to answer this question. Our judgement is based on the very low certainty observation that plasmapheresis may prevent or delay the frequency of WLL, which is a costly procedure.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies○ No included studies	No specific studies were identified to answer this question	As above. Plasmapheresis may improve symptoms and hypoxia in selected patients who are refractory to other treatments and experience a significant disease burden. It may also prevent or delay the frequency of WLL, which is a costly procedure.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● **Probably reduced** ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No specific studies were identified to answer this question	Both plasma exchange and WLL are expensive procedures which can only be performed in multi-disciplinary centres of expertise in PAP, that may not be available globally. In some areas where plasma exchange but not WLL may be available, plasma exchange may improve equity, however, in other areas, it is likely to reduce it.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	No specific studies were identified to answer this question.	While data around the safety and clinical effectiveness of plasmapheresis in PAP are limited, there are ample indirect data from other diseases (such as Guillain-Barre disease) supporting the safety of this medicine. In parallel, while they are based on very low certainty data, the potential benefits of rituximab are important to patients with refractory disease and significant disease burden (potential for improvement in symptoms and oxygenation, prevention or delay of WLL).

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	No specific studies were identified to answer this question.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Recommendation

We suggest the use of plasmapheresis for patients with confirmed autoimmune PAP who remain significantly symptomatic, requiring high flow of supplemental oxygen (≥4L /min) or two or more WLL over a period of a year, despite receiving exogenous GM-CSF and rituximab, or having previously failed these treatments (conditional recommendation, very low certainty,).

PICO 7: In patients with PAP progressing despite whole lung lavage or pharmacological treatment should lung transplantation be considered versus no lung transplantation?

Search Strategy

1. PubMed

("Pulmonary Alveolar Proteinosis"[Mesh] OR "Pulmonary alveolar proteinosis"[Title/Abstract] OR "Alveolar lipoproteinosis"[Title/Abstract] OR "Alveolar proteinosis"[Title/Abstract]) AND("Lung Transplantation"[Mesh] OR "lung transplant"[Title/Abstract]OR "Lung Grafting" [Title/Abstract] OR "Lung Transplantation"[Title/Abstract] OR "Double-lung"[Title/Abstract] OR "Double lung"[Title/Abstract] OR "single-lung"[Title/Abstract] OR "single lung" [Title/Abstract]) NOT ((children[Mesh]) NOT (adults[Mesh]))

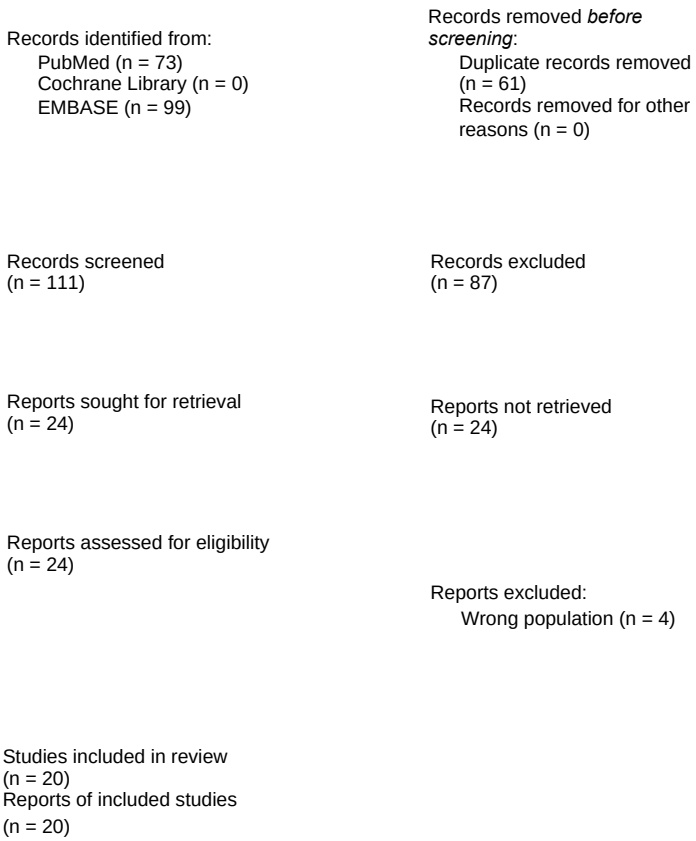
2. Cochrane Library

("Pulmonary Alveolar Proteinosis"[Mesh] OR "Pulmonary alveolar proteinosis" OR "Alveolar lipoproteinosis" OR "Alveolar proteinosis") AND ("Lung Transplantation"[Majr] OR "lung transplant" OR "Lung Grafting" OR "Lung Transplantations" OR "Double-lung" OR "Double lung" OR "single-lung" OR "single lung")

3. EMBASE

('lung alveolus proteinosis'/mj/exp OR 'lung alveolus proteinosis' OR 'lung alveolus proteinosis':ti,ab OR 'pulmonary alveolar proteinosis':ti,ab OR 'alveolar lipoproteinosis':ti,ab OR 'alveolar proteinosis':ti,ab) AND ('lung transplantation'/exp OR 'lung transplantation':ti,ab OR 'lung transplant':ti,ab OR 'lung transplantations':ti,ab OR 'double lung transplantation'/exp OR 'double-lung':ti,ab OR 'double lung':ti,ab OR 'single lung transplantation'/exp OR 'single-lung transplantation':ti,ab) NOT (('child'/exp) NOT 'adult'/exp)) AND ('article'/it OR 'article in press'/it OR 'review'/it)

PRISMA Flow diagram summarising the study selection process



Included studies

Case reports and case series

1. Lawi D, Dubruc E, Gonzalez M, Aubert JD, Soccal PM, Janssens JP. Secondary pulmonary alveolar proteinosis treated by lung transplant: A case report. Respir Med Case Rep. 2020 May 30;30:101108. doi: 10.1016/j.rmcr.2020.101108.

2. Liang J, Chen Y, Zheng M, Ye S, Liu F, Chen J, Ji Y. Single lung transplantation for idiopathic pulmonary alveolar proteinosis with intraoperative veno-venous extracorporeal membrane oxygenation support. Transpl Immunol. 2022 Oct;74:101627. doi: 10.1016/j.trim.2022.101627.

3. 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.

4. Beeckmans H, Ambrocio GPL, Bos S, Vermaut A, Geudens V, Vanstapel A, Vanaudenaerde BM, De Baets F, Malfait TLA, Emonds MP, Van Raemdonck DE, Schoemans HM, Vos R. Allogeneic Hematopoietic Stem Cell Transplantation After Prior Lung Transplantation for Hereditary Pulmonary Alveolar Proteinosis: A Case Report. Front Immunol. 2022 Jul 14;13:931153. doi: 10.3389/fimmu.2022.931153.

5. Kobayashi K, Ohkouchi S, Sasahara Y, Ebina M, Nakata K, Saito R, Akiba M, Sado T, Oishi H, Watanabe T, Kurosawa H, Okada Y. Improvement of native pulmonary alveolar proteinosis after contralateral single living-donor lobar lung transplantation: A case report. Pediatr Transplant. 2020 Mar;24(2):e13659. doi: 10.1111/petr.13659.

6. Santamaria F, Brancaccio G, Parenti G, Francalanci P, Squitieri C, Sebastio G, Dionisi-Vici C, D'argenio P, Andria G, Parisi F. Recurrent fatal pulmonary alveolar proteinosis after heart-lung transplantation in a child with lysinuric protein intolerance. J Pediatr. 2004 Aug;145(2):268-72. doi: 10.1016/j.jpeds.2004.04.047.

7. Tagawa T, Yamasaki N, Tsuchiya T, Miyazaki T, Matsuki K, Tsuchihashi Y, Morimoto K, Nagayasu T. Living-donor lobar lung transplantation for pulmonary alveolar proteinosis in an adult: report of a case. Surg Today. 2011 Aug;41(8):1142-4. doi: 10.1007/s00595-010-4411-0.

8. Murata H, Hara T, Matsumoto S, Inoue H, Yamashita H, Sumikawa K. Anesthetic management of a patient with a double inferior vena cava and pulmonary alveolar proteinosis who underwent bilateral living-donor lobar lung transplantation. J Anesth. 2009;23(4):583-6. doi: 10.1007/s00540-009-0803-y.

9. Parker LA, Novotny DB. Recurrent alveolar proteinosis following double lung transplantation. Chest. 1997 May;111(5):1457-8. doi: 10.1378/chest.111.5.1457.

10. Ono M, Saito R, Tominaga J, Okada Y, Ohkouchi S, Takemura T. Pathological features of explant lungs with fibrosis in autoimmune pulmonary alveolar proteinosis. Respirol Case Rep. 2017 Jul 21;5(5):e00255. doi: 10.1002/rcr2.255.

11. Rahimi N, Matilla JR, Lang G, Schwarz S, Nachbaur E, Benazzo A, Klepetko W, Jaksch P, Hoetzenecker K. Simultaneous pectus excavatum correction and lung transplantation-A case series. Am J Transplant. 2021 Jan;21(1):410-414. doi: 10.1111/ajt.16180.

12. Miyazaki T, Tagawa T, Yamasaki N, Tsuchiya T, Matsumoto K, Tomoshige K, Tsuchihashi Y, Morimoto K, Nagayasu T. Immune function in a patient with aspergillosis after lung transplantation: Case report. Acta Medica Nagasakiensia. 2012; 57(1): 25-28. Fulltext available here: https://www.jstage.jst.go.jp/article/amn/57/1/57_25/_pdf

13. Trukalj M, Perica M, Ferenčić Ž, Erceg D, Navratil M, Redžepi G, Nogalo B. Successful Treatment of Autoimmune Pulmonary Alveolar Proteinosis in a Pediatric Patient. Am J Case Rep. 2016 Sep 5;17:641-5. doi: 10.12659/ajcr.897868.

Other references deemed relevant by the panel.

1. Huddleston CB, Bloch JB, Sweet SC, de la Morena M, Patterson GA, Mendeloff EN. Lung transplantation in children. Ann Surg. 2002 Sep;236(3):270-6. doi: 10.1097/00000658-200209000-00003.

2. Peel JK, Keshavjee S, Krahn M, Sander B. Economic evaluations and costing studies of lung transplantation: A scoping review. J Heart Lung Transplant. 2021 Dec;40(12):1625-1640. doi: 10.1016/j.healun.2021.08.007.

3. Seiler A, Klaghofer R, Ture M, Komossa K, Martin-Soelch C, Jenewein J. A systematic review of health-related quality of life and psychological outcomes after lung transplantation. J Heart Lung Transplant. 2016 Feb;35(2):195-202. doi: 10.1016/j.healun.2015.07.003.

4. Singer JP, Singer LG. Quality of life in lung transplantation. Semin Respir Crit Care Med. 2013 Jun;34(3):421-30. doi: 10.1055/s-0033-1348470.

5. ISHLT registry 2021 registry data slides available at: https://ishlt.org/research-data/registries/ttx-registry/ttx-registry-slides

6. Nayak DK, Zhou F, Xu M, Huang J, Tsuji M, Hachem R, Mohanakumar T. Long-Term Persistence of Donor Alveolar Macrophages in Human Lung Transplant Recipients That Influences Donor-Specific Immune Responses. Am J Transplant. 2016 Aug;16(8):2300-11. doi: 10.1111/ajt.13819.

7. Eguíluz-Gracia I, Schultz HH, Sikkeland LI, Danilova E, Holm AM, Pronk CJ, Agace WW, Iversen M, Andersen C, Jahnsen FL, Baekkevold ES. Long-term persistence of human donor alveolar macrophages in lung transplant recipients. Thorax. 2016 Nov;71(11):1006-1011. doi: 10.1136/thoraxjnl-2016-208292.

Case reports and case series

Table 11. Risk of bias of case reports and case series evaluating lung transplantation for progressive PAP.

	Lawi 2020[91]	Liang 2022[92]	Takaki 2016[93]	Beeckmans 2022[94]	Kobayashi 2020[95]	Santamaria 2004[96]	Tagawa 2011[97]	Murata 2009[98]	Parker 1997[99]	Ono 2017[100]	Rahimi 2021[101]	Huddleston 2022[102]
Were patient's demographic characteristics clearly described?	N	N	Y	Y	Y	Y	N	N	N	Y	Y	N
Was the patient's history clearly described and presented as a timeline?	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	N
Was the current clinical condition of the patient on presentation clearly described?	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N
Were diagnostic tests or assessment methods and the results clearly described?	Y	N	Y	Y	Y	Y	N	N	N	Y	N	N
Was the intervention(s) or treatment procedure(s) clearly described?	N	Y	Y	Y	Y	N	Y	Y	N	N	Y	Y
Was the post-intervention clinical condition clearly described?	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y
Were adverse events (harms) or unanticipated events identified and described?	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	Y
Does the case report provide takeaway lessons?	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y

Table 12. Case reports and case series reporting on lung transplantation in progressive PAP.

Study ID	Age (years), Gender, Smoking	Adult/ Pediatric	Cause of PAP	History	Condition upon presentation	Intervention	Post-intervention condition	Adverse events / harms
Lawi 2020[91]	30 Female Smoking status unknown	A	HSCT	Allogenic hematopoietic stem cell transplantation (HSCT) for treatment of an acute myeloid leukaemia. At +6 months post HSCT, development of progressive dyspnea, dry cough and severe asthenia; PFT: mixed ventilatory defect. Chest CT: crazy paving; BAL and TBB normal. Secondary PAP and OB related to GVHD.	Despite intensive immunosuppressive treatment for GVHD, rapid worsening of the respiratory insufficiency requiring continuous oxygen therapy and subsequently nocturnal non-invasive ventilation. Recurrent LRT infections	Bilateral lung transplantation 48 months after HSCT	Follow-up at 2 years post BMT: good clinical condition, normalization of PFT, lung parenchyma normal on HRCT.	None described
Liang 2022[92]	Female Age and smoking status unknown	A	Auto-immune	Auto-immune PAP, 8 WLL and nebulized inhalation of GM-CSF	Worsening despite treatment 10 years after the diagnosis of PAP: home oxygen therapy, bedridden state, secondary pulmonary hypertension and chronic pulmonary heart disease	Left lung transplantation	Follow-up at 5 years post LT. Good general condition, no oxygen, normal activity tolerance, persistent restrictive defect on PFT: FVC 1.09 L (45.5%) FEV1 0.88 L (43.7%), six-	2 hospitalizations for pulmonary infections

							minute walking test 440 m. Left lung parenchyma satisfactory on chest CT with only a few bands of atelectasis	
Takaki 2016[93]	36 Female Smoking status unknown	A	CSF2RB	Hereditary PAP by mutation of the *CSF2RB* gene. Diagnosis made AFTER LT	6 years after the onset of PAP, decision to perform LT because of the worsening of the respiratory insufficiency	Bilateral lung transplantation from 2 living donors (husband and brother)	Death 4 years after LT	Recurrence of PAP at 9 nine months post BLT, fungal infection of the lungs with several species of aspergillus, OB post LT, death 4 years after LT
Beeckmans 2022[94]	19 Male Non smoker	P	CSF2RA	Tachypnea from 6 months of age, then recurrent coughing and fever. Diagnosis of hereditary PAP related to a complete homozygous *CSF2RA* deletion	Received 32 WLL from the age of 3 to 17. Gradual worsening of pulmonary status since the age of 13 with progressive restrictive lung disease and fibrosis, cachexia, finally necessitating oxygen treatment and non-invasive ventilation at	BLT at the age of 19 and allo-HSCT 11 months later	Good condition 4.5 years after lung transplantation: excellent quality of life, actively performing sports, working as Data Analyst. FVC 1.5 L prior to LT then 2 L at last follow-up, improvement of DLCO but no value	Probable invasive pulmonary aspergillosis at 6 months post-LT CMV reactivation 1 month after HSCT, intermittent EBV reactivation during the

					night as the age of 20. Referred for LT at age 18. Decision to perform LT and then HSCT one year later to prevent recurrence of the disease on the lung graft		given. Chest CT: no recurrence of PAP, no sign of BO.	following years without evolution to lymphoproliferative disease
Kobayashi 2020[95]	Female 14 Non smoker	P	HSCT	HSCT from her mother for Diamand-Blackfan anaemia at age 8.3 months after HSCT, development of respiratory symptoms leading to the diagnosis of BO related to GVHD. Diagnosis of BO + PAP was made on the pathological analysis of the excised right lung	Progression to respiratory insufficiency from age 8 years with need for home oxygen therapy from age 10 despite immunosuppressive treatments for GVHD. Severe mixed restrictive and obstructive impairments on PFT. Registered for LT at age 12	Right single LDLLT from her mother at age 14. Same donor for HSCT and LT	Follow-up at 7 years post LT. Quite good quality of life but remained on home oxygen therapy and PFT parameters only slightly improved or remained stable: FVC from 36.9% to 35.2%, DLCO not given. Minimal immunosuppression (2 mg of prednisolone and 250 mg of MMF) because the BMT and LT donors were the same person. Improvement of	Non described

							the GGO of the left native lung on chest CT	
Santamaria 2004[96]	Male 3 Non smoker	P	LPI	Lysinuric protein intolerance diagnosed at age 1. PAP diagnosed at age 1.7 with tachypnea and subcostal and suprasternal retractions. Rapid decline with recurrent lower respiratory tract infections and progressive hypoxemia requiring. O_2 supplementation	Chronic respiratory insufficiency requiring home oxygen therapy despite 2 WLL and GM-CSF therapy. Referred for LT	Heart-lung transplantation at age 3	Death 26 months after LT from recurrence of PAP on the graft, despite WLL and GMCSF therapy	EBV pneumonia 18 months after LT, recurrence of PAP on the graft
Tagawa 2011[97]	Female 42 Smoker status unknown	A	UK	PAP diagnosed at age 35, no cause provided in the case report. Development of chronic respiratory insufficiency and lung fibrosis by age 42, reason for which she was referred for LT at this age.	Severe restrictive lung defect, low DLCO, SpO_2 77% after 2 min walk. Honey combing on chest CT	Bilateral lung transplantation from 2 living donors (husband and brother)	Follow-up at 1 year post LT. Good condition, no oxygen, normal FVC and FEV_1, DLCO 58% (vs 17.6% prior to LT)	Invasive pulmonary aspergillosis 6 months after LT, cured by amphotericin B, micafungin and voriconazole
Murata 2009[98]	Female 43	A	UK	Referred for LT at age 43 for pulmonary fibrosis secondary to PAP after 8	Chronic respiratory insufficiency requiring home oxygen therapy	Bilateral living-donor lobar lung transplantation	Discharged home without requiring oxygen therapy on	Not detailed

	Smoker status unknown			years of progressive dyspnea. No cause of PAP provided in the case report	despite several WLL and GMCSF therapy		post-operative day 76	
Parker 1997[99]	Female 41 Smoker status unknown	A	UK	PAP diagnosed at age 27. Cause not provided. 12 WLL.	Progression to chronic respiratory insufficiency and referred for LT at age 41. FVC at 30% and hypoxemia in room air prior to LT.	Double LT at age 41	Not described	Periodic episodes of bronchitis and development of mild obliterative bronchiolitis. Recurrence of PAP on lung graft 3 years after LT
Ono 2017[100]	Female 51 Smoker status unknown	A	Auto-immune	Auto-immune PAP diagnosed at age 46	Worsening of respiratory status and progression to fibrosis despite WLL and GMCSF therapy. Chronic hypoxemia. Bilateral pneumothorax. Referred for LT	Bilateral lung transplantation	Not described	Not described
Rahimi 2021[101] Case 1	Male 14 Smoker status unknown	P	UK	PAP diagnosed at age 4. Cause not described	Worsening of respiratory insufficiency, evolution to fibrosis and pulmonary hypertension. Listed	Bilobar lung transplantation	Good condition 5 years after LT. No sign of recurrence of PAP	Post-operative Klebsiella pneumonia. EBV induced lymphoproliferative disease at 4

					for lung transplantation.			weeks post-transplant
Rahimi 2021[101] Case 2	Female 10 Non smoker	P	UK	PAP, no cause described. Referred for LT at age 9	Chronic respiratory insufficiency requiring home oxygen therapy and enteral feeding	Bilateral lung transplantation	Follow-up at 12 months post LT. good condition, back to school, no recurrence of PAP.	Prolonged stay in ICU post-transplant necessitating a tracheotomy. 4 Acinetobacter baumannii pneumonia
Huddleston 2022[102]	190 children with LT Aged 1 to 18 years at diagnosis	P	UK	12 children diagnosed with PAP not further differentiated	Respiratory failure	Bilateral LT in all but 9 pts	Survival 1/3/5 y: 77 / 63 / 54%. Children with PAP, as a group together with other rare cases (Pulmonary fibrosis, BO, other) had better survival than average and in particular children transplanted for cystic fibrosis and pulmonary vascular disease	Bronchiolitis obliterans 62%, Infection 22%, malignancies 14%; no relapses of original diseases described

Table 13. Evidence Profile. Lung for PAP.

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lung transplantation	Relative (95% CI)	Absolute (95% CI)		
Mortality (various follow-up reported)											
14	Case reports	very serious[a]	n/a	not serious	very serious[a]	Very serious[a]	14	-	2 deaths reported	⨁◯◯◯ Very low	CRITICAL
Serious adverse events (various follow-up reported)											
2	Case reports	very serious[a]	not serious	not serious	very serious[c]	none	14	-	2 cases of BOS reported	⨁◯◯◯ Very low	CRITICAL

[a] Only available data from a very limited number of case reports that are uncontrolled, at high risk of bias and at a significant risk of publication bias

Evidence to decision framework

QUESTION

In patients with PAP progressing despite whole lung lavage or pharmacological treatment should lung transplantation be considered versus no lung transplantation?	
POPULATION:	Pulmonary Alveolar Proteinosis whatever the age and the cause of PAP
INTERVENTION:	Lung transplantation
COMPARISON:	Before transplantation
MAIN OUTCOMES:	Mortality, safety (including infectious complications, BOS and recurrence of PAP on lung graft), DLCO (% predicted); FVC (% predicted), need for oxygen, quality of life

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Pulmonary alveolar proteinosis (PAP)** is a rare but burdensome disease, characterised by progressive respiratory symptoms, including breathlessness, that is characterised by significant morbidity and -if untreated- mortality. **Sometimes whole lung lavage (WLL) and other treatments cannot prevent the progression** of the disease. Patients may develop chronic respiratory insufficiency, fibrosis and end-stage lung disease that render them eligible for lung transplantation. One **important** issue before deciding if a patient should undergo lung transplantation is definitely evaluating the **aetiology of PAP**, as this maybe linked to the estimated risk of recurrence of the original lung disease in the graft. **Lung transplantation** is an established procedure to treat chronic end-stage respiratory failure with no options to cure by other treatments, both in children[103] and adults (ISHLT registry 2021 registry data). Major complications include infections due to life-long immune-suppressive treatment, chronic rejection and bronchiolitis obliterans, and (rarely) pulmonary alveolar proteinosis itself[104-107].	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	**Desirable effects:** The desirable effect of lung transplantation is to cure the underlying lung disease by replacing one or the two lungs when the disease is responsible for terminal chronic respiratory failure not accessible to a curative treatment. In the setting of PAP, the desirable effect of lung transplantation is to restore lung function and hopefully avoid the recurrence of PAP on the lung graft. As the intervention aims at replacing the lungs, the desirable effects are anticipated to be large. **Available data:** *Data are available from 14 distinct case reports, among which 8 adults and 6 children[91-102]. Cause of PAP included GVHD (2 cases), auto-immune PAP (4 cases), hereditary PAP (2 cases: 1 CSF2RA and 1 CSF2RB mutations), and 1 case with lysinuric protein intolerance. Cause was not reported and assumed to be unknown in 5 cases. *12 additional paediatric PAP cases were cumulatively reported in a report on the outcome of 190 children after lung transplantation; no causes of PAP and individual patient data were given[102]. *Additional data were obtained from Thoracic Organ Transplant Registry (ISHLT) after special request based on the question above. ISHLT provided data from between Jan 1, 1990 and June 30, 2018.on successfully lung transplanted patients due to the underlying conditions of alveolar proteinosis (adults 33, peds 6), and the paediatric surfactant dysfunction disorders often manifesting initially with PAP, i.e. surfactant protein B deficiency (adults 0, peds 30), surfactant protein C deficiency (adults 1, peds 13) and.ABCA3 deficiency (adults 2, peds 16). Effects : - Lung function improvement post-LT among alive patients at last follow-up: yes 6/12 (40%), stable 1/10 (10%), worse 0/12 (0%), not available 5/10 (50%) - Durable wean of oxygen post-LT among alive patients: 9/12 (70%), not available 2/10 (20%), still on home oxygen therapy 1/10 (10%) - Good quality of life post-LT among alive patients: 10/12 (80%); not available 2/12 (20%) - Based on the post-transplant report including the 12 paediatric PAP patients (Huddleston 2002), overall outcome of their group of conditions (excluding Cystic fibrosis, vascular diseases) was better than average. It is important to note that those PAP cases were likely due to surfactant dysfunction disorders. - Of 101 patients reported by ISHLT and lung transplanted all were successfully transplanted and 58 were alive at the end of the observation period.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Available data:** As above **Undesirable effects:** - Mortality: 2/14 (14%), median duration of follow-up [min;max]: 3 [0.2;7] years - Safety : ° Infectious adverse events: 9/14 (64%), including 7 episodes of pyogenous pneumonia, 3 invasive aspergillosis, 3 EBV reactivation among which 1 with lymphoproliferative disease, 2 CMV reactivation, 1 organized pneumonia. All episodes were cured. ° BOS 2/14 (17%), post-transplant lymphoproliferative disease 1x. ° **Recurrence of PAP on lung graft** : 3/14 (21%) (1: 9 months post-LT, CSF2RB mutations; died. 2: 18 months post-LT, lysinuric protein intolerance, died. 3: 3 years post-LT, unknown cause, alive) Due to lack of evaluating the aetiology of PAP and the diagnostic tests used the cause of PAP was not described in 5 cases. Post-intervention condition is described as good by the authors without any further detail in 3 cases and is missing in 2 cases. It is likely that the risk of disease recurrence depends on the cause of PAP: macrophage related diseases (CSF2RA or B receptor defects, lysinuric protein intolerance) may have the highest risk. - Of 101 patients reported by ISHLT and lung transplanted 43 had died at the end of the observation period. In none of the patients the diagnosis “GRAFT FAILURE: RECURRENT DISEASE” was noted.	PAP caused by systemic diseases involving the macrophages (CSF2RA or CSF2RB defects, lysinuric protein intolerance, OAS1 defects, etc) may be primarily treated with stem cell transplant (SCT), as long as the lung has no fibrotic non-reversible damage. One case of end-stage lung disease, due to CSF2RA defect was first lung transplanted, followed by SCT (Beeckmans 2022)[94].

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of evidence is very low because: - Data came from 10 single case-reports and one small series of 3 cases among which 2 patients underwent lung transplantation for PAP, and a cumulative report on the outcome of 12 (of 190) children with PAP after lung transplantation with no details given on the group of PAP patients. - Among this small number of case reports data on safety and post-intervention condition are missing for respectively 33% and 17% of cases - Median follow-up duration is 3 years. In ISHLT registry, there is 2 time-points assessments (1 year and 5 year). It would have been desirable to have data at 5 years post-LT for all cases in order to compare the 5-y survival of those cases to that from the ISHLT registry (5-y survival for IPF 68% in the 2008-2013 era). - Significant re-assuring evidence comes from the 101 patients reported by ISHLT. However reporting bias by the submitting centers must be considered.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ●Probably no important uncertainty or variability ○ No important uncertainty or variability	This is a situation of end-stage lung disease, likely death within few years, or transplant of an organ and further on life-long medication and medical treatment/surveillance. Patients, clinicians, and investigators recognize that a primary clinical aim of lung transplantation is to improve QOL[108]. Indeed, many patients consider lung transplantation for palliation of symptoms and improvement of QOL even when extended survival is not assured[108]. However, there are always some people who reject an offer of transplant and wish palliative care.	A systematic review of health-related quality of life and psychological outcomes after lung transplantation[109].

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Available data of very low certainty favour the safety of lung transplantation because there was only 2 deaths and 2 BOS, and all other adverse events were cured or stabilised. Lung transplantation allows curing the patients from chronic respiratory failure. The 2 deaths occurred in the setting of recurrence of PAP on the lung graft. When lung transplantation is being considered in a patient with PAP, we highly recommend making sure that a complete etiological assessment of the PAP has been performed to avoid lung transplantation in patients with a high risk of recurrence such as PAP caused by CSF2R defects.	Regarding the risk of recurrence of PAP on the lung graft in hereditary PAP, 2 previous articles studied the persistence of alveolar donor macrophages in human lung transplants recipients. By studying samples from 15 lung transplant recipients, Nayak et al found that up to 3.5 years post-LTx the majority of AMs (>87%) was donor derived[110]. Eguíluz-Gracia et al found a stable mixed chimerism between donor and recipient AMFs after performing sequential transbronchial biopsies from LT to 2 years post-LT in 10 lung transplant recipients[111].

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No specific studies were identified to answer this question. The best available cost-utility estimates for lung transplant versus waitlist may represent cost-effectiveness under some circumstances, but high-quality evidence is lacking. Further cost-utility analyses, with sufficient methodologic rigour, are required to overcome the observed variation in results and confirm cost-effectiveness of the current standard of care in lung transplantation[112].	The costs of care for patients with end-stage lung disease and chronic respiratory insufficiency should be balanced with the costs of care of hospitalization for LT including stays in surgery and ICU and lifelong costs for medications and care.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low○ Moderate High ● **No included studies**	No studies specific for LT because of PAP to answer this question. Generally for lung transplant in adults, costs are high. A scoping review based on a systematic search of MEDLINE, EMBASE, NHS EED, and EconLit identified studies involving lung transplantation for adults that measured costs, cost-effectiveness, or which described themselves as economic evaluations. Risk of bias was assessed in included studies using the ECOBIAS and CHEC-list tools. The results identified 28 studies eligible as base. Cost-utility estimates of lung transplant versus waitlist, from the healthcare payer perspective and a time-horizon of at least 10-years ranged between $42,459 and $154,051 per quality-adjusted life year[112].	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention**○ Favors the intervention ○ Varies No included studies	See review above[112].	.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No specific studies were identified to answer this question	LT is not available worldwide.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No specific studies for PAP were identified to answer this question; however for lung transplant for end-stage lung disease, overall the intervention is widely accepted by all stakeholders. Some eligible people may choose palliative care. Both health-related quality of life and mental health improve after lung transplantation[109].	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Referral of end-stage lung disease people to established lung transplant centers for assessment is established standard in high-income countries.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	**No included studies**

	JUDGEMENT						
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Recommendation

We suggest considering lung transplantation for patients with PAP progressing despite whole lung lavage and/or pharmacological treatment, who fulfil the International Society for Heart and Lung Transplantation (ISHLT) criteria for patients with interstitial lung disease. (Very low certainty of evidence, conditional recommendation)

Supplementary Details

WLL Procedure

In short, WLL is done under general anaesthesia and intubation is performed using a double lumen endotracheal tube in order ventilate one lung while washing the other through a blocked catheter[113] . Volumes of fluid instilled into the washed lung varies between 500 and 1000ml per cycle. Afterwards gravitational force is used to drain the fluid out into a lower positioned measuring cylinder[56]. This cycle of instillation and drainage is repeated several times until the returned fluid is clear, using an average of 15.4 litre per lung[55]. Both lungs could be washed during the same session and same anaesthesia, however it is more common to wash the lungs a few days apart. For children AH it is not always the case to use a double lumen tube, in some cases a bronchoscope is inserted into the tube and the child is ventilated on this tube manually, and it is also possible to insert the bronchoscope next to the tube. There are multiple articles addressing the technical aspects of WLL, providing guidance on position of the patient during treatment, amount of washing fluid used, chest percussion during the WLL and how to monitor fluid turbidity, however it is beyond the scope of the guidelines to provide recommendations.

Additional GM-CSF therapy studies

One study included five patients previously treated with inhaled GM-CSF. The protocol consisted of a 12-week induction phase with intermittent, inhaled GM-CSF (125ug BD every other week), followed by 12-week maintenance phase (125µg OD for 4 days, followed by no treatment for 10 days). A single patient had undergone WLL prior to GM-CSF initiation. The benefits of GM-CSF included better functional outcomes, radiographic outcomes, a reduction in morbidity and patient-reported symptoms without any adverse events or safety issues

reported [114,115]. In another study, five patients with intractable aPAP (no significant response to GM-CSF inhalation before WLL or subsequent medication with ambroxol hydrochloride after WLL) were treated with intermittent inhaled GM-CSF. The protocol consisted of a 12-week induction phase (125µg BD for 8 days, followed by no treatment for 6 days), followed by 12-week maintenance phase (125µg OD for 4 days, followed by no treatment for 10 days) [114,115] GM-CSF inhalation therapy after WLL was reported to be effective in all patients (decrease of AaDO2 by >10 mm Hg) and to reinforce the efficiency of WLL in patients with severe aPAP [86]. Paediatric studies reported beneficial effects in 5/7 children and young adolescents treated with inhaled GM-CSF either alone (n=1) or in combination with WLL (n=4). Treatment with inhaled GM-CSF was not available or approved by insurance for 2 out of 7 children reported in the studies [80,116-118]. There is no specific reason to expect a difference in response to inhaled GM-CSF in aPAP between subjects older or younger than 18 years and evidence suggests similar responses in adolescents as in young adults.

Disease Severity Score

DSS categories include: 1 = asymptomatic and PaO2 ≥ 70 mm Hg; 2 = symptomatic and PaO2 ≥ 70 mm Hg; 3 = 60 ≤ PaO2 < 70 mm Hg; 4 = 50 ≤ PaO2 < 60 mm Hg; 5 = PaO2 < 50 mm Hg. The patients can be stratified into mild (DSS 1–2), moderate (DSS 3), and severe (DSS 4–5)

Rituximab Administration

At first, two doses of intravenous rituximab can be offered two weeks apart. Maintenance dose of intravenous rituximab should be offered six monthly to patients that experience a beneficial response, defined as a significant improvement in their symptoms, hypoxia and/or supplemental oxygen needs. We suggest 1,000mg of rituximab per dose for adults and 375

mg/m^2 for children. The intervals of rituximab could be tailored to the individual patient requirements, following established regimes from other disease areas. The EuropeanMedicines Agency reported that the most common adverse events to rituximab are related to infusion (fever, chills, and shivering), while most common adverse events are infusion reactions, infections, and cardiac-related problems

List of Experienced Laboratories Testing for GM-CSF Antibody titres

Japan, Niigata, Medical and Dental School, Koh Nakata
Japan, Osaka, National Hospital Center, Yoshikazu Inoue
China, Beijing, Peking Union Medical College, Kai-Feng Xu
United States, Denver, National Jewish Health, Vijaya Knight
United States, Cincinnati, Cincinnati Children's Hospital, Bruce Trapnell

REFERENCES

1. Azuma K, Takimoto T, Kasai T, et al. Diagnostic yield and safety of bronchofiberscopy for pulmonary alveolar proteinosis. Respir Investig 2021;59(6):757-765. DOI: 10.1016/j.resinv.2021.03.012.
2. Bonella F, Bauer PC, Griese M, Ohshimo S, Guzman J, Costabel U. Pulmonary alveolar proteinosis: new insights from a single-center cohort of 70 patients. Respir Med 2011;105(12):1908-16. (Research Support, Non-U.S. Gov't) (In eng). DOI: 10.1016/j.rmed.2011.08.018.
3. Danel C, Israel-Biet D, Costabel U, Rossi GA, Wallaert B. The clinical role of BAL in alveolar proteinosis. Eur Respir J 1990;3(8):950-1, 961-9. (https://www.ncbi.nlm.nih.gov/pubmed/2292299).
4. Deleanu OC, Zaharie AM, Serbescu A, NiTu FM, MihalTan FD, Arghir OC. Analysis of bronchoalveolar lavage fluid in a first Romanian pulmonary alveolar proteinosis cohort. Rom J Morphol Embryol 2016;57(2 Suppl):737-743. (https://www.ncbi.nlm.nih.gov/pubmed/27833966).
5. Enaud L, Hadchouel A, Coulomb A, et al. Pulmonary alveolar proteinosis in children on La Reunion Island: a new inherited disorder? Orphanet J Rare Dis 2014;9:85. DOI: 10.1186/1750-1172-9-85.
6. Ilkovich YM, Ariel BM, Novikova LN, Bazhanov AA, Dvorakovskaya IV, Ilkovich MM. Pulmonary alveolar proteinosis: a long way to correct diagnosis: problems of diagnostics and therapy in routine practice. Ann Clin Lab Sci 2014;44(4):405-9. (https://www.ncbi.nlm.nih.gov/pubmed/25361924).
7. Maygarden SJ, Iacocca MV, Funkhouser WK, Novotny DB. Pulmonary alveolar proteinosis: a spectrum of cytologic, histochemical, and ultrastructural findings in bronchoalveolar lavage fluid. Diagn Cytopathol 2001;24(6):389-95. DOI: 10.1002/dc.1086.
8. Xu Z, Jing J, Wang H, Xu F, Wang J. Pulmonary alveolar proteinosis in China: a systematic review of 241 cases. Respirology 2009;14(5):761-6. DOI: 10.1111/j.1440-1843.2009.01539.x.
9. Tomassetti S, Wells AU, Costabel U, et al. Bronchoscopic Lung Cryobiopsy Increases Diagnostic Confidence in the Multidisciplinary Diagnosis of Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2016;193(7):745-52. DOI: 10.1164/rccm.201504-0711OC.
10. Anan K, Oshima Y, Ogura T, et al. Safety and harms of bronchoalveolar lavage for acute respiratory failure: A systematic review and meta-analysis. Respir Investig 2022;60(1):68-81. DOI: 10.1016/j.resinv.2021.07.008.
11. Korevaar DA, Colella S, Fally M, et al. European Respiratory Society guidelines on transbronchial lung cryobiopsy in the diagnosis of interstitial lung diseases. Eur Respir J 2022;60(5). DOI: 10.1183/13993003.00425-2022.
12. Dhooria S, Sehgal IS, Aggarwal AN, Behera D, Agarwal R. Diagnostic Yield and Safety of Cryoprobe Transbronchial Lung Biopsy in Diffuse Parenchymal Lung Diseases: Systematic Review and Meta-Analysis. Respir Care 2016;61(5):700-12. DOI: 10.4187/respcare.04488.
13. Sharp C, McCabe M, Adamali H, Medford AR. Use of transbronchial cryobiopsy in the diagnosis of interstitial lung disease-a systematic review and cost analysis. QJM 2017;110(4):207-214. DOI: 10.1093/qjmed/hcw142.
14. Chuang MT, Raskin J, Krellenstein DJ, Teirstein AS. Bronchoscopy in diffuse lung disease: evaluation by open lung biopsy in nondiagnostic transbronchial lung biopsy. Ann Otol Rhinol Laryngol 1987;96(6):654-7. DOI: 10.1177/000348948709600607.

15. Fisher M, Roggli V, Merten D, Mulvihill D, Spock A. Coexisting endogenous lipoid pneumonia, cholesterol granulomas, and pulmonary alveolar proteinosis in a pediatric population: a clinical, radiographic, and pathologic correlation. Pediatr Pathol 1992;12(3):365-83. DOI: 10.3109/15513819209023316.
16. Han Q, Luo Q, Chen X, Xie J, Wu L, Chen R. The evaluation of clinical usefulness of transbrochoscopic lung biopsy in undefined interstitial lung diseases: a retrospective study. Clin Respir J 2017;11(2):168-175. DOI: 10.1111/crj.12318.
17. Hewitt CJ, Hull D, Keeling JW. Open lung biopsy in children with diffuse lung disease. Arch Dis Child 1974;49(1):27-35. DOI: 10.1136/adc.49.1.27.
18. McCarthy C, Carey B, Trapnell BC. Blood Testing for Differential Diagnosis of Pulmonary Alveolar Proteinosis Syndrome. Chest 2019;155(2):450-452. DOI: 10.1016/j.chest.2018.11.002.
19. Prakash UB, Barham SS, Carpenter HA, Dines DE, Marsh HM. Pulmonary alveolar phospholipoproteinosis: experience with 34 cases and a review. Mayo Clin Proc 1987;62(6):499-518. DOI: 10.1016/s0025-6196(12)65477-9.
20. Rubinstein I, Mullen JB, Hoffstein V. Morphologic diagnosis of idiopathic pulmonary alveolar lipoproteinosis-revisited. Arch Intern Med 1988;148(4):813-6. (https://www.ncbi.nlm.nih.gov/pubmed/3355301).
21. Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. N Engl J Med 2003;349(26):2527-39. DOI: 10.1056/NEJMra023226.
22. McCarthy C, Avetisyan R, Carey BC, Chalk C, Trapnell BC. Prevalence and healthcare burden of pulmonary alveolar proteinosis. Orphanet J Rare Dis 2018;13(1):129. DOI: 10.1186/s13023-018-0846-y.
23. Inoue Y, Trapnell BC, Tazawa R, et al. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. Am J Respir Crit Care Med 2008;177(7):752-62. DOI: 10.1164/rccm.200708-1271OC.
24. Uchida K, Nakata K, Carey B, et al. Standardized serum GM-CSF autoantibody testing for the routine clinical diagnosis of autoimmune pulmonary alveolar proteinosis. J Immunol Methods 2014;402(1-2):57-70. DOI: 10.1016/j.jim.2013.11.011.
25. Kitamura T, Uchida K, Tanaka N, et al. Serological diagnosis of idiopathic pulmonary alveolar proteinosis. Am J Respir Crit Care Med 2000;162(2 Pt 1):658-62. DOI: 10.1164/ajrccm.162.2.9910032.
26. Kitamura T, Tanaka N, Watanabe J, et al. Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. J Exp Med 1999;190(6):875-80. DOI: 10.1084/jem.190.6.875.
27. McCarthy C, Carey BC, Trapnell BC. Autoimmune Pulmonary Alveolar Proteinosis. Am J Respir Crit Care Med 2022;205(9):1016-1035. DOI: 10.1164/rccm.202112-2742SO.
28. Han X, Uchida K, Jurickova I, et al. Granulocyte-macrophage colony-stimulating factor autoantibodies in murine ileitis and progressive ileal Crohn's disease. Gastroenterology 2009;136(4):1261-71, e1-3. DOI: 10.1053/j.gastro.2008.12.046.
29. Sakagami T, Uchida K, Suzuki T, et al. Human GM-CSF autoantibodies and reproduction of pulmonary alveolar proteinosis. N Engl J Med 2009;361(27):2679-81. DOI: 10.1056/NEJMc0904077.
30. Aklady H, Ali HF, Saber A, Mahmoud AF, Adel M. Whole lung lavage in comparison with bronchoscopic lobar lavage using the rigid bronchoscope in patients with pulmonary alveolar proteinosis: Is it time to change strategy? Journal of the Egyptian Society of Cardio-Thoracic Surgery 2016;24(4):330-7.

31. Athayde RAB, Arimura FE, Kairalla RA, Carvalho CRR, Baldi BG. Characterization and outcomes of pulmonary alveolar proteinosis in Brazil: a case series. J Bras Pneumol 2018;44(3):231-236. DOI: 10.1590/S1806-37562017000000168.
32. Badiozaman R, Tahereh P, Shideh D, Mohammadreza B, Ahmadreza A, Seyyedahmad T. Whole lung lavage of nine children with pulmonary alveolar proteinosis: experience in a tertiary lung center. Iran J Pediatr 2013;23(1):95-9. (https://www.ncbi.nlm.nih.gov/pubmed/23550265).
33. Beccaria M, Luisetti M, Rodi G, et al. Long-term durable benefit after whole lung lavage in pulmonary alveolar proteinosis. Eur Respir J 2004;23(4):526-31. DOI: 10.1183/09031936.04.00102704.
34. Ben-Abraham R, Greenfeld A, Rozenman J, Ben-Dov I. Pulmonary alveolar proteinosis: step-by-step perioperative care of whole lung lavage procedure. Heart Lung 2002;31(1):43-9. DOI: 10.1067/mhl.2002.119831.
35. Byun MK, Kim DS, Kim YW, et al. Clinical features and outcomes of idiopathic pulmonary alveolar proteinosis in Korean population. J Korean Med Sci 2010;25(3):393-8. DOI: 10.3346/jkms.2010.25.3.393.
36. Casanova S, Puglisi S, Gurioli C, et al. Whole lung lavage: our experience in pulmonary alveolar proteinosis and in type B Niemann Pick disease. Rassegna di Patologia dell'Apparato Respiratorio 2021;36(3):158-65.
37. 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;21(1):358. DOI: 10.1186/s12890-021-01734-w.
38. Du Bois RM, McAllister WA, Branthwaite MA. Alveolar proteinosis: diagnosis and treatment over a 10-year period. Thorax 1983;38(5):360-3. DOI: 10.1136/thx.38.5.360.
39. Gay P, Wallaert B, Nowak S, et al. Efficacy of Whole-Lung Lavage in Pulmonary Alveolar Proteinosis: A Multicenter International Study of GELF. Respiration 2017;93(3):198-206. DOI: 10.1159/000455179.
40. Goldstein LS, Kavuru MS, Curtis-McCarthy P, Christie HA, Farver C, Stoller JK. Pulmonary alveolar proteinosis: clinical features and outcomes. Chest 1998;114(5):1357-62. DOI: 10.1378/chest.114.5.1357.
41. Guan Y, Zeng Q, Yang H, et al. Pulmonary alveolar proteinosis: quantitative CT and pulmonary functional correlations. Eur J Radiol 2012;81(9):2430-5. DOI: 10.1016/j.ejrad.2011.05.005.
42. Holbert JM, Costello P, Li W, Hoffman RM, Rogers RM. CT features of pulmonary alveolar proteinosis. AJR Am J Roentgenol 2001;176(5):1287-94. DOI: 10.2214/ajr.176.5.1761287.
43. Kaenmuang P, Navasakulpong A. Efficacy of whole lung lavage in pulmonary alveolar proteinosis: a 20-year experience at a reference center in Thailand. J Thorac Dis 2021;13(6):3539-3548. DOI: 10.21037/jtd-20-3308.
44. Kariman K, Kylstra JA, Spock A. Pulmonary alveolar proteinosis: prospective clinical experience in 23 patients for 15 years. Lung 1984;162(4):223-31. DOI: 10.1007/BF02715650.
45. Kiani A, Parsa T, Adimi Naghan P, et al. An eleven-year retrospective cross-sectional study on pulmonary alveolar proteinosis. Adv Respir Med 2018;86(1):7-12. DOI: 10.5603/ARM.2018.0003.
46. Lan L, Cen Y, Chen D, Ouyang B. Does higher lavage height improve lavage effect for pulmonary alveolar proteinosis patients. International Journal of Clinical and Experimental Medicine 2016;9(7):13802-10.

47. Mariani F, Salvaterra E, Lettieri S, et al. A mini-whole lung lavage to treat autoimmune pulmonary alveolar proteinosis (PAP). Respir Res 2022;23(1):60. DOI: 10.1186/s12931-022-01982-2.
48. Marwah V, Katoch CDS, Singh S, et al. Management of primary pulmonary alveolar proteinosis: A multicentric experience. Lung India 2020;37(4):304-309. DOI: 10.4103/lungindia.lungindia_401_19.
49. Mo Q, Wang B, Dong N, et al. The Clinical Clues of Pulmonary Alveolar Proteinosis: A Report of 11 Cases and Literature Review. Can Respir J 2016;2016:4021928. DOI: 10.1155/2016/4021928.
50. Perez At, Rogers RM. Enhanced alveolar clearance with chest percussion therapy and positional changes during whole-lung lavage for alveolar proteinosis. Chest 2004;125(6):2351-6. DOI: 10.1378/chest.125.6.2351.
51. Selecky PA, Wasserman K, Benfield JR, Lippmann M. The clinical and physiological effect of whole-lung lavage in pulmonary alveolar proteinosis: a ten-year experience. Ann Thorac Surg 1977;24(5):451-61. DOI: 10.1016/s0003-4975(10)63440-6.
52. Smith BB, Torres NE, Hyder JA, et al. Whole-lung Lavage and Pulmonary Alveolar Proteinosis: Review of Clinical and Patient-centered Outcomes. J Cardiothorac Vasc Anesth 2019;33(9):2453-2461. DOI: 10.1053/j.jvca.2019.03.047.
53. Zhao YY, Huang H, Liu YZ, Song XY, Li S, Xu ZJ. Whole Lung Lavage Treatment of Chinese Patients with Autoimmune Pulmonary Alveolar Proteinosis: A Retrospective Long-term Follow-up Study. Chin Med J (Engl) 2015;128(20):2714-9. DOI: 10.4103/0366-6999.167295.
54. Zhou X, Lu G, Yu Z, Gao F, Bian T. Long-term follow-up of whole lung lavage in patients with pulmonary alveolar proteinosis. Exp Ther Med 2014;8(3):763-768. DOI: 10.3892/etm.2014.1788.
55. Campo I, Luisetti M, Griese M, et al. Whole lung lavage therapy for pulmonary alveolar proteinosis: a global survey of current practices and procedures. Orphanet J Rare Dis 2016;11(1):115. DOI: 10.1186/s13023-016-0497-9.
56. Awab A, Khan MS, Youness HA. Whole lung lavage-technical details, challenges and management of complications. J Thorac Dis 2017;9(6):1697-1706. DOI: 10.21037/jtd.2017.04.10.
57. Tazawa R, Ueda T, Abe M, et al. Inhaled GM-CSF for Pulmonary Alveolar Proteinosis. N Engl J Med 2019;381(10):923-932. DOI: 10.1056/NEJMoa1816216.
58. Tian X, Yang Y, Chen L, et al. Inhaled granulocyte-macrophage colony stimulating factor for mild-to-moderate autoimmune pulmonary alveolar proteinosis - a six month phase II randomized study with 24 months of follow-up. Orphanet J Rare Dis 2020;15(1):174. DOI: 10.1186/s13023-020-01450-4.
59. Trapnell BC, Inoue Y, Bonella F, et al. Inhaled Molgramostim Therapy in Autoimmune Pulmonary Alveolar Proteinosis. N Engl J Med 2020;383(17):1635-1644. DOI: 10.1056/NEJMoa1913590.
60. Tazawa R, Trapnell BC, Inoue Y, et al. Inhaled granulocyte/macrophage-colony stimulating factor as therapy for pulmonary alveolar proteinosis. Am J Respir Crit Care Med 2010;181(12):1345-54. DOI: 10.1164/rccm.200906-0978OC.
61. Tazawa R, Inoue Y, Arai T, et al. Duration of benefit in patients with autoimmune pulmonary alveolar proteinosis after inhaled granulocyte-macrophage colony-stimulating factor therapy. Chest 2014;145(4):729-37. DOI: 10.1378/chest.13-0603.
62. Papiris SA, Tsirigotis P, Kolilekas L, et al. Long-term inhaled granulocyte macrophage-colony-stimulating factor in autoimmune pulmonary alveolar proteinosis: effectiveness, safety, and lowest effective dose. Clin Drug Investig 2014;34(8):553-64. DOI: 10.1007/s40261-014-0208-z.

63. Zhang F, Weng D, Su Y, et al. Therapeutic effect of subcutaneous injection of low dose recombinant human granulocyte-macrophage colony-stimulating factor on pulmonary alveolar proteinosis. Respir Res 2020;21(1):1. DOI: 10.1186/s12931-019-1261-1.
64. Venkateshiah SB, Yan TD, Bonfield TL, et al. An open-label trial of granulocyte macrophage colony stimulating factor therapy for moderate symptomatic pulmonary alveolar proteinosis. Chest 2006;130(1):227-37. DOI: 10.1378/chest.130.1.227.
65. Seymour JF, Presneill JJ, Schoch OD, et al. Therapeutic efficacy of granulocyte-macrophage colony-stimulating factor in patients with idiopathic acquired alveolar proteinosis. Am J Respir Crit Care Med 2001;163(2):524-31. DOI: 10.1164/ajrccm.163.2.2003146.
66. Zhen G, Li D, Jiang J, Weng Y. Granulocyte-Macrophage Colony-Stimulating Factor Inhalation Therapy for Severe Pulmonary Alveolar Proteinosis. Am J Ther 2020;28(2):e171-e178. DOI: 10.1097/MJT.0000000000001053.
67. Kavuru MS, Malur A, Marshall I, et al. An open-label trial of rituximab therapy in pulmonary alveolar proteinosis. Eur Respir J 2011;38(6):1361-7. DOI: 10.1183/09031936.00197710.
68. Soyez B, Borie R, Menard C, et al. Rituximab for auto-immune alveolar proteinosis, a real life cohort study. Respir Res 2018;19(1):74. DOI: 10.1186/s12931-018-0780-5.
69. Amital A, Dux S, Shitrit D, Shpilberg O, Kramer MR. Therapeutic effectiveness of rituximab in a patient with unresponsive autoimmune pulmonary alveolar proteinosis. Thorax 2010;65(11):1025-6. DOI: 10.1136/thx.2010.140673.
70. Bird D, Evans J, Pahoff C. Rituximab rescue therapy for autoimmune pulmonary alveolar proteinosis. Respir Med Case Rep 2022;37:101637. DOI: 10.1016/j.rmcr.2022.101637.
71. Garber B, Albores J, Wang T, Neville TH. A plasmapheresis protocol for refractory pulmonary alveolar proteinosis. Lung 2015;193(2):209-11. DOI: 10.1007/s00408-014-9678-2.
72. Keske A, Destrampe EM, Barksdale B, Rose WN. Pulmonary Alveolar Proteinosis Refractory to Plasmapheresis and Rituximab despite GM-CSF Antibody Reduction. Case Reports Immunol 2022;2022:2104270. DOI: 10.1155/2022/2104270.
73. F.A. M, S.K. F, M.B. Z, M. B. A rare case report. J Clin Diagn Res 2018;12(4):OD07-8. DOI: 10.7860/JCDR/2018/32371.11419.
74. Hunt S, Miller AL, Schissel S, Ross JJ. A crazy cause of dyspnea. N Engl J Med 2010;363(25):e38. DOI: 10.1056/NEJMimc1008281.
75. Nagasawa J, Kurasawa K, Hanaoka R. Rituximab improved systemic lupus erythematosus-associated pulmonary alveolar proteinosis without decreasing anti-GM-CSF antibody levels. Lupus 2016;25(7):783-4. DOI: 10.1177/0961203315627204.
76. Lopez-Olivo MA, Amezaga Urruela M, McGahan L, Pollono EN, Suarez-Almazor ME. Rituximab for rheumatoid arthritis. Cochrane Database Syst Rev 2015;1:CD007356. DOI: 10.1002/14651858.CD007356.pub2.
77. Liu S, Gui C, Lu Z, Li H, Fu Z, Deng Y. The Efficacy and Safety of Rituximab for Childhood Steroid-Dependent Nephrotic Syndrome: A Systematic Review and Meta-Analysis. Front Pediatr 2021;9:728010. DOI: 10.3389/fped.2021.728010.
78. Kamei K, Ogura M, Sato M, Ito S, Ishikura K. Infusion reactions associated with rituximab treatment for childhood-onset complicated nephrotic syndrome. Pediatr Nephrol 2018;33(6):1013-1018. DOI: 10.1007/s00467-018-3900-z.

79. Bonfield TL, Kavuru MS, Thomassen MJ. Anti-GM-CSF titer predicts response to GM-CSF therapy in pulmonary alveolar proteinosis. Clin Immunol 2002;105(3):342-50. DOI: 10.1006/clim.2002.5301.
80. Griese M, Panagiotou P, Manali ED, et al. Autoimmune pulmonary alveolar proteinosis in children. ERJ Open Res 2022;8(1). DOI: 10.1183/23120541.00701-2021.
81. Jezequel A, Kerjouan M, Lederlin M, et al. [Plasmapheresis failure in the treatment of auto-immune pulmonary alveolar proteinosis]. Rev Mal Respir 2017;34(3):240-243. DOI: 10.1016/j.rmr.2016.06.002.
82. Kavuru MS, Bonfield TL, Thomassen MJ. Plasmapheresis, GM-CSF, and alveolar proteinosis. Am J Respir Crit Care Med 2003;167(7):1036; author reply 1036-7. DOI: 10.1164/ajrccm.167.7.950.
83. Luisetti M, Rodi G, Perotti C, et al. Plasmapheresis for treatment of pulmonary alveolar proteinosis. Eur Respir J 2009;33(5):1220-2. DOI: 10.1183/09031936.00097508.
84. Vis DC, Kelly MM, De Heuvel E, MacEachern PR. Reduction in Alveolar Macrophage Size in Refractory Autoimmune Pulmonary Alveolar Proteinosis After Treatment With Pioglitazone. J Bronchology Interv Pulmonol 2020;27(3):219-222. DOI: 10.1097/LBR.0000000000000686.
85. Yu H, Sun X, Wang Y, Xu Z, Huang H. Whole lung lavage combined with Granulocyte-macrophage colony stimulating factor inhalation for an adult case of refractory pulmonary alveolar proteinosis. BMC Pulm Med 2014;14:87. DOI: 10.1186/1471-2466-14-87.
86. Chevret S, Hughes RA, Annane D. Plasma exchange for Guillain-Barre syndrome. Cochrane Database Syst Rev 2017;2(2):CD001798. DOI: 10.1002/14651858.CD001798.pub3.
87. Mokrzycki MH, Kaplan AA. Therapeutic plasma exchange: complications and management. Am J Kidney Dis 1994;23(6):817-27. DOI: 10.1016/s0272-6386(12)80135-1.
88. Eyre M, Hacohen Y, Barton C, Hemingway C, Lim M. Therapeutic plasma exchange in paediatric neurology: a critical review and proposed treatment algorithm. Dev Med Child Neurol 2018;60(8):765-779. DOI: 10.1111/dmcn.13925.
89. Klemencic Kozul T, Yudina A, Donovan C, Pinto A, Osman C. Cost-minimisation analysis of plasma exchange versus IVIg in the treatment of autoimmune neurological conditions. BMC Health Serv Res 2022;22(1):904. DOI: 10.1186/s12913-022-08210-z.
90. Morgan C. The benefits of whole lung lavage in pulmonary alveolar proteinosis. Eur Respir J 2004;23(4):503-5. DOI: 10.1183/09031936.04.00016704.
91. Lawi D, Dubruc E, Gonzalez M, Aubert JD, Soccal PM, Janssens JP. Secondary pulmonary alveolar proteinosis treated by lung transplant: A case report. Respir Med Case Rep 2020;30:101108. DOI: 10.1016/j.rmcr.2020.101108.
92. Liang J, Chen Y, Zheng M, et al. Single lung transplantation for idiopathic pulmonary alveolar proteinosis with intraoperative veno-venous extracorporeal membrane oxygenation support. Transpl Immunol 2022;74:101627. DOI: 10.1016/j.trim.2022.101627.
93. Takaki M, Tanaka T, Komohara Y, et al. Recurrence of pulmonary alveolar proteinosis after bilateral lung transplantation in a patient with a nonsense mutation in CSF2RB. Respir Med Case Rep 2016;19:89-93. DOI: 10.1016/j.rmcr.2016.06.011.
94. Beeckmans H, Ambrocio GPL, Bos S, et al. Allogeneic Hematopoietic Stem Cell Transplantation After Prior Lung Transplantation for Hereditary Pulmonary Alveolar

Proteinosis: A Case Report. Front Immunol 2022;13:931153. DOI: 10.3389/fimmu.2022.931153.
95. Kobayashi K, Ohkouchi S, Sasahara Y, et al. Improvement of native pulmonary alveolar proteinosis after contralateral single living-donor lobar lung transplantation: A case report. Pediatr Transplant 2020;24(2):e13659. DOI: 10.1111/petr.13659.
96. Santamaria F, Brancaccio G, Parenti G, et al. Recurrent fatal pulmonary alveolar proteinosis after heart-lung transplantation in a child with lysinuric protein intolerance. J Pediatr 2004;145(2):268-72. DOI: 10.1016/j.jpeds.2004.04.047.
97. Tagawa T, Yamasaki N, Tsuchiya T, et al. Living-donor lobar lung transplantation for pulmonary alveolar proteinosis in an adult: report of a case. Surg Today 2011;41(8):1142-4. DOI: 10.1007/s00595-010-4411-0.
98. Murata H, Hara T, Matsumoto S, Inoue H, Yamashita H, Sumikawa K. Anesthetic management of a patient with a double inferior vena cava and pulmonary alveolar proteinosis who underwent bilateral living-donor lobar lung transplantation. J Anesth 2009;23(4):583-6. DOI: 10.1007/s00540-009-0803-y.
99. Parker LA, Novotny DB. Recurrent alveolar proteinosis following double lung transplantation. Chest 1997;111(5):1457-8. DOI: 10.1378/chest.111.5.1457.
100. Ono M, Saito R, Tominaga J, Okada Y, Ohkouchi S, Takemura T. Pathological features of explant lungs with fibrosis in autoimmune pulmonary alveolar proteinosis. Respirol Case Rep 2017;5(5):e00255. DOI: 10.1002/rcr2.255.
101. Rahimi N, Matilla JR, Lang G, et al. Simultaneous pectus excavatum correction and lung transplantation-A case series. Am J Transplant 2021;21(1):410-414. DOI: 10.1111/ajt.16180.
102. Huddleston CB, Bloch JB, Sweet SC, de la Morena M, Patterson GA, Mendeloff EN. Lung transplantation in children. Ann Surg 2002;236(3):270-6. DOI: 10.1097/00000658-200209000-00003.
103. Iablonskii P, Carlens J, Mueller C, et al. Indications and outcome after lung transplantation in children under 12 years of age: A 16-year single center experience. J Heart Lung Transplant 2022;41(2):226-236. DOI: 10.1016/j.healun.2021.10.012.
104. Divithotawela C, Apte SH, Tan ME, De Silva TA, Chambers DC. Pulmonary alveolar proteinosis after lung transplantation. Respirol Case Rep 2020;8(5):e00566. DOI: 10.1002/rcr2.566.
105. Gal AA, Bryan JA, Kanter KR, Lawrence EC. Cytopathology of pulmonary alveolar proteinosis complicating lung transplantation. J Heart Lung Transplant 2004;23(1):135-8. DOI: 10.1016/s1053-2498(03)00032-9.
106. Kawana S, Miyoshi K, Tanaka S, et al. Pulmonary alveolar proteinosis after lung transplantation: Two case reports and literature review. Respirol Case Rep 2023;11(6):e01160. DOI: 10.1002/rcr2.1160.
107. Philippot Q, Cazes A, Borie R, et al. Secondary pulmonary alveolar proteinosis after lung transplantation: a single-centre series. Eur Respir J 2017;49(2). DOI: 10.1183/13993003.01369-2016.
108. Singer JP, Singer LG. Quality of life in lung transplantation. Semin Respir Crit Care Med 2013;34(3):421-30. DOI: 10.1055/s-0033-1348470.
109. Seiler A, Klaghofer R, Ture M, Komossa K, Martin-Soelch C, Jenewein J. A systematic review of health-related quality of life and psychological outcomes after lung transplantation. J Heart Lung Transplant 2016;35(2):195-202. DOI: 10.1016/j.healun.2015.07.003.
110. Nayak DK, Zhou F, Xu M, et al. Long-Term Persistence of Donor Alveolar Macrophages in Human Lung Transplant Recipients That Influences Donor-Specific Immune Responses. Am J Transplant 2016;16(8):2300-11. DOI: 10.1111/ajt.13819.

111. Eguiluz-Gracia I, Schultz HH, Sikkeland LI, et al. Long-term persistence of human donor alveolar macrophages in lung transplant recipients. Thorax 2016;71(11):1006-1011. DOI: 10.1136/thoraxjnl-2016-208292.
112. Peel JK, Keshavjee S, Krahn M, Sander B. Economic evaluations and costing studies of lung transplantation: A scoping review. J Heart Lung Transplant 2021;40(12):1625-1640. DOI: 10.1016/j.healun.2021.08.007.
113. Reiter K, Schoen C, Griese M, Nicolai T. Whole-lung lavage in infants and children with pulmonary alveolar proteinosis. Paediatric anaesthesia 2010;20(12):1118-23. (In eng). DOI: 10.1111/j.1460-9592.2010.03442.x.
114. Livingstone C, Corallo C, Siemienowicz M, Pilcher D, Stirling RG. Nebulised sargramostim in pulmonary alveolar proteinosis. British journal of clinical pharmacology 2022;88(7):3523-3528. (In eng). DOI: 10.1111/bcp.15266.
115. Ohkouchi S, Akasaka K, Ichiwata T, et al. Sequential Granulocyte-Macrophage Colony-Stimulating Factor Inhalation after Whole-Lung Lavage for Pulmonary Alveolar Proteinosis. A Report of Five Intractable Cases. Annals of the American Thoracic Society 2017;14(8):1298-1304. (In eng). DOI: 10.1513/AnnalsATS.201611-892BC.
116. Yamamoto H, Yamaguchi E, Agata H, et al. A combination therapy of whole lung lavage and GM-CSF inhalation in pulmonary alveolar proteinosis. Pediatric pulmonology 2008;43(8):828-30. (In eng). DOI: 10.1002/ppul.20856.
117. Price A, Manson D, Cutz E, Dell S. Pulmonary alveolar proteinosis associated with anti-GM-CSF antibodies in a child: successful treatment with inhaled GM-CSF. Pediatric pulmonology 2006;41(4):367-70. (In eng). DOI: 10.1002/ppul.20347.
118. Gajewska ME, Sritharan SS, Santoni-Rugiu E, Bendstrup EM. Autoimmune pulmonary alveolar proteinosis in an adolescent successfully treated with inhaled rhGM-CSF (molgramostim). Respiratory medicine case reports 2018;23:167-169. (In eng). DOI: 10.1016/j.rmcr.2018.02.005.