

Online appendix

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

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Panel member expertise

Panel members	Expertise
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Francesco Bonella	Respiratory Medicine
Elisabeth Bendstrup	Respiratory Medicine
Marissa O'Callaghan	Respiratory Medicine
Clairelyne Dupin	Respiratory Medicine
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Raphael Borie	Respiratory Medicine
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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.

	Measure	Category	Level
BAL	Sensitivity & Specificity		Critical
	Safety	Adverse events	Critical
GM-CSF antibodies	Sensitivity & Specificity		Critical
	Safety	Adverse events	Important
WLL	Mortality	Adverse events	Critical
	Blood gas analysis	Lung function tests	Critical
	DLCO		Critical
	Safety	Adverse events	Critical
	HRCT	Scan	Critical
	Symptoms (dyspnoea)		Critical
	Exercise tolerance (6MWT)	Exercise capacity	Critical
GM-CSF treatment	Mortality	Adverse events	Critical
	Blood gas analysis	Lung function tests	Important
	DLCO		Critical
	Safety	Adverse events	Critical
	HRCT	Scan	Important
	Symptoms (dyspnoea)		Critical
	Exercise tolerance (6MWT)	Exercise capacity	Important
Rituximab	Mortality	Adverse events	Critical
	Blood gas analysis	Lung function tests	Important
	DLCO		Important
	Safety	Adverse events	Critical
	HRCT	Scan	Important
	Symptoms (dyspnoea)		Critical
	Exercise tolerance (6MWT)	Exercise capacity	Important
Plasmapheresis	Mortality	Adverse events	Critical
	Blood gas analysis	Lung function tests	Important
	DLCO		Important
	Safety	Adverse events	Critical
	HRCT	Scan	Important
	Symptoms (dyspnoea)		Critical
	Exercise tolerance (6MWT)	Exercise capacity	Important

Lung transplantation	Mortality		Critical
	Safety	Adverse events	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 histopathology[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" OR "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)

Main studies considered by the panel.

1. Deleanu OC, Zaharie AM, Șerbescu A, Nițu FM, Mihălțan 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 <u>BAL</u> for cytology analysis?	
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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input checked="" type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know	<p>Available data: Eight observational studies, mainly correlating and comparing clinical, radiology and tissue histology¹⁻⁸.</p> <p>Methodology The technique and clinical utility of BAL for patients with ILD has been described in detail in the relevant ATS Clinical Practice Guidelines⁹.</p>	

	<p>Desirable effects</p> <p>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 BAL¹. 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}.</p>	
<p>Undesirable Effects</p> <p>How substantial are the undesirable anticipated effects?</p>		
<p>JUDGEMENT</p>	<p>RESEARCH EVIDENCE</p>	<p>ADDITIONAL CONSIDERATIONS</p>
<p>● Trivial</p> <p>○ Small</p> <p>○ Moderate</p> <p>○ Large</p> <p>○ Varies</p> <p>○ Don't know</p>	<p>Available data: As above</p> <p>Undesirable effects: We did not find any studies reporting on the safety of BAL in patients with PAP or suspected PAP.</p>	<p>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 failure¹⁰. This meta-analysis revealed an integrated frequency of death of 0.000% [0.000-0.045%] after BAL¹⁰. 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.</p>

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Very low <input checked="" type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies 	<p>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.</p>	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty or variability <input checked="" type="radio"/> No important uncertainty or variability 	<p>No specific studies were identified to answer this question</p>	<p>The panel, including patient representatives, felt that the risks associated with bronchoalveolar lavage are trivial and acceptable for acquiring a confident diagnosis that will allow potentially life-saving, evidence-based treatment for patients with suspected PAP</p>

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● 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 	<p>BAL has a high diagnostic yield and a low risk of complications.</p>	<p>The panel, including patient representatives feel that BAL is a well tolerated procedure.</p>

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know 	<p>No specific studies were identified to answer this question.</p>	<p>Bronchoscopy and bronchoalveolar lavage 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.</p>

Certainty of evidence of required resources

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input checked="" type="radio"/> No included studies 	<p>No specific studies were identified to answer this question.</p>	

Cost effectiveness

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input checked="" type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> No included studies 	<p>No specific studies were identified to answer this question.</p>	<p>Bronchoscopy and bronchoalveolar lavage 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.</p>

Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Reduced <input type="radio"/> Probably reduced <input checked="" type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know	No specific studies were identified to answer this question.	Access 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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	No specific studies were identified to answer this question.	The panel, including patient representatives, feel that BAL is a safe and well tolerated procedure that would be available to patients with suspected PAP, given the high likelihood of establishing the diagnosis.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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

PROBLEM	JUDGEMENT						
	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 ●
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Recommendation

We recommend BAL should 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?

Search Strategy

See NQ1a (combined search strategy)

Main studies and documents considered by the panel.

1. Korevaar DA, Colella S, Fally M, Camuset J, Colby TV, Hagemeyer 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 transbronchoscopic 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 <u>lung biopsy</u> 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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	<p>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.</p>	
Desirable Effects		
How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Trivial <input type="radio"/> Small <input checked="" type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know	<p>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}.</p> <p>Methodology</p>	

	<p>Tissue can be obtained using endoscopic transbronchial biopsy (TBB), cryobiopsy (CTBLB) and surgical (video assisted or open) lung biopsy (SLB).</p> <p>Desirable effects:</p> <p>Five studies described the findings of biopsy in specifically in patients with PAP^{1,15,18-20}. A significant limitation of both transbronchial and surgical lung biopsy is the limited sensitivity due to the patchy involvement of the lung parenchyma¹⁸. 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 biopsy¹. 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 biopsy¹². Similarly, Sharp et al quantified the diagnostic yield of transbronchial cryobiopsy (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.</p>	
<p>Undesirable Effects How substantial are the undesirable anticipated effects?</p>		
<p>JUDGEMENT</p>	<p>RESEARCH EVIDENCE</p>	<p>ADDITIONAL CONSIDERATIONS</p>
<p>○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know</p>	<p>Available data: As above</p> <p>As previously described (see desirable effects), an important undesirable effect is a non-diagnostic biopsy^{1,12,18}.</p> <p>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 studies¹². 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 procedures¹³. Tomassetti et al revealed a higher risk of pneumothorax (33%, 19/58 participants), among patients undergoing bronchoscopic lung cryobiopsy for diffuse parenchymal lung disease⁹. Azuma et al, assessed the safety of bronchoscopy with transbronchial biopsy in 86 patients with PAP and did not report any serious adverse events¹. Pneumothorax was observed in 3.5% of the participants,</p>	

	<p>but no drainage was required¹. Minimal bleeding was noted in 7% of participants¹. None of the patients experienced uncontrollable hypoxemia or fever during or after the bronchoscopy¹.</p> <p>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 biopsy⁹. Hewitt et al quantified the safety of surgical lung biopsy among 24 children with ILD¹⁷. More specifically, one child (4.2%) died within 24 hours of the lung biopsy, and another one developed a serious complication, namely pneumothorax requiring drainage¹⁷. Less serious adverse events included small pleural effusions that resolved spontaneously (12.5%) and subcutaneous surgical emphysema (12.5%)¹⁷.</p>	
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Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Very low <input type="radio"/> Low <input checked="" type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies 	<p>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.</p>	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input checked="" type="radio"/> Probably no important uncertainty or variability <input type="radio"/> No important uncertainty or variability 	<p>No specific studies were identified to answer this question</p>	<p>The panel, including patient representatives, felt 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 significantly improve the diagnostic yield of the combination of bronchoalveolar lavage findings with multidisciplinary assessment.</p>

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input checked="" type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>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. Overall, in view of the high diagnostic yield of the combination of BAL and multidisciplinary diagnostic approach, biopsy does not appear to significantly add to the diagnostic process.</p>	

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Large costs <input checked="" type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>No specific studies to answer this question.</p>	<p>Some centers do not have access to tissue sampling, expert interventional pneumologists/endoscopists /thoracic surgeons and expert lung pathologist</p>

Certainty of evidence of required resources

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input checked="" type="radio"/> No included studies 	<p>No specific studies to answer this question.</p>	

Cost effectiveness

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input checked="" type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> No included studies 	<p>No specific studies were identified to answer this question.</p>	<p>While the cost of a transbronchial biopsy is not very resource intensive, the limited evidence of benefit suggests this diagnostic test is not cost-effective. Surgical biopsy is associated with more significant side effects but still imperfect diagnostic yield.</p>

Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Reduced <input checked="" type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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 ILD. 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
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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

PROBLEM	JUDGEMENT						
	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 ○
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Recommendation

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

NQ 2: Should patients with PAP syndrome undergo GM-CSF antibody testing for diagnosing primary 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 antibody*" [Title/Abstract] OR "anti-granulocyte macrophage colony stimulating factor antibody*" [Title/Abstract] OR "anti-gm-csf antibody*" [Title/Abstract] OR "gm-csf antibody*" [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 antibody*':ti,ab OR 'anti-granulocyte-macrophage colony-stimulating factor antibody*':ti,ab OR 'anti-granulocyte macrophage colony stimulating factor antibody*':ti,ab OR 'anti-gm-csf antibody*':ti,ab OR 'gm-antibody':ti,ab OR 'gm-csf antibody*':ti,ab OR 'gm csf antibody*':ti,ab OR 'gmcsf antibody*':ti,ab OR 'autoantibody'/exp OR 'antibody'/exp OR autoantibod*:ti,ab OR antibody*:ti,ab OR 'auto antibody':ti,ab OR 'antibody, auto':ti,ab) NOT 'case report'/exp

Main studies considered by the panel.

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- CSF autoantibody levels in autoimmune pulmonary alveolar proteinosis. *Biomark Med.* 2018 Feb;12(2):151-159. doi: 10.2217/bmm-2017-0362.
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Evidence to decision framework

QUESTION

Should GM-CSF antibodies be tested for all patients with a clinical diagnosis of PAP for the purpose of 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
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>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.</p> <p>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.</p> <p>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.</p> <p>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,</p>	

	<p>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 significant 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.</p> <p>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.</p>	
<p>Desirable Effects How substantial are the desirable anticipated effects?</p>		
<p>JUDGEMENT</p>	<p>RESEARCH EVIDENCE</p>	<p>ADDITIONAL CONSIDERATIONS</p>
<p>○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know</p>	<p>Available data: (i) Multiple real-world observational studies (such as Bonella 2011, Trapnell 2003, McCarthy 2019, McCarthy 2022)^{2,18,21,22}, including a systematic review of 248 patients (Inoue 2008)²³. (ii) Three leading methodology papers (Kitamura 1999, Kitamura 2000, Uchida 2014)²⁴⁻²⁶.</p> <p>Desirable effects: GM-CSF deficient mice were found to accumulate surfactant in the lungs and cause a PAP-like disease²¹. Next GM-CSF antibodies were found in the bronchoalveolar lavage (BAL) fluid from patients with what was known at the time as 'idiopathic' PAP²⁶. The terminology of autoimmune PAP was coined when GM-CSF antibodies were consistently isolated from the serum of patients with idiopathic PAP²⁵.</p> <p>Inoue 2008 described the use of GM-CSF antibody testing in 248 patients with a tissue biopsy confirmed diagnosis of PAP²³. 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 PAP². 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 Japan²⁷.</p>	

	<p>The reference ranges used for test result interpretation (normal, ≤ 3.1 $\mu\text{g/ml}$; indeterminate, >3.1 to <10.2 $\mu\text{g/ml}$; and abnormal, ≥ 10.2 $\mu\text{g/ml}$) were determined by the Clinical and Laboratory Standards Institute on the basis of results for 153 healthy individuals (median, 0.33 $\mu\text{g/ml}$; 90% confidence interval [CI], 0.3–0.4 $\mu\text{g/ml}$) and 339 patients with autoimmune PAP (median, 84 $\mu\text{g/ml}$; 90% CI, 10.2–499 $\mu\text{g/ml}$). 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 involvement¹⁸. Furthermore, it described the significant procedure-related morbidity associated with transbronchial and surgical lung biopsies.</p>	
<h3>Undesirable Effects</h3> <p>How substantial are the undesirable anticipated effects?</p>		
<p>JUDGEMENT</p>	<p>RESEARCH EVIDENCE</p>	<p>ADDITIONAL CONSIDERATIONS</p>
<ul style="list-style-type: none"> ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know 	<p>Available data: As above</p> <p>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 assay²⁵. 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 PAP²⁴. 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 $\mu\text{g/ml}$, respectively²⁸. 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.</p>	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ○ Low ● Moderate ○ High ○ No included studies 	<p>1. 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}.</p> <p>2. 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 GM-CSF antibodies directly cause PAP (Sakagami 2010)²⁹.</p>	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability 	<p>No specific studies were identified to answer this question</p>	<p>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.</p>

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favours the comparison <input type="radio"/> Does not favour either the intervention or the comparison <input type="radio"/> Probably favours the intervention <input checked="" type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>A non-invasive test outweighs benefit of NOT testing for autoimmune PAP using this test.</p>	

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Large costs <input type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input checked="" type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>No specific studies to answer this question. However, a blood test is far cheaper than an invasive tissue biopsy. This stands to be true whether referring to an open lung biopsy or a transbronchial biopsy.</p>	<p>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.</p>

Certainty of evidence of required resources

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input checked="" type="radio"/> No included studies 	<p>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.</p>	<p>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.</p>

Cost effectiveness

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input checked="" type="radio"/> No included studies 	<p>No specific studies were identified to answer this question</p>	<p>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.</p>

Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Reduced <input type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input checked="" type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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

PROBLEM	JUDGEMENT						
	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 ●
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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: Should patients with clinical symptoms and/or functional impairment due to PAP undergo 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

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>.
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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.

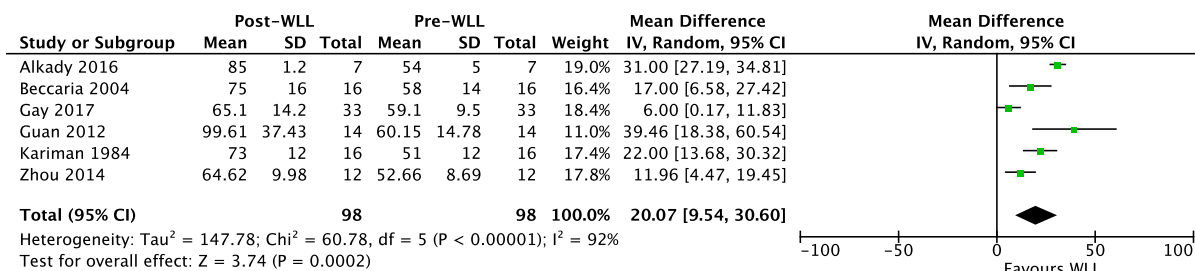
Studies	Indications of WLL	Unilateral/ Bilateral	Lavage volume
Alkady 2016	Symptomatic, NYHA class III-IV.	Bilateral, 2-3 days interval.	3L per cycle, an average of 15-18L per lung, warmed.
Athayde 2018	Not reported.	Not reported.	Not reported.
Badiozaman 2013 (children)	Advanced PAP.	Some had bilateral, 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)O ₂ 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 PaO ₂ <60mmHg or SatO ₂ <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 PaO ₂ , 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 $\geq 5\%$ in SatO ₂ 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] O ₂ 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.

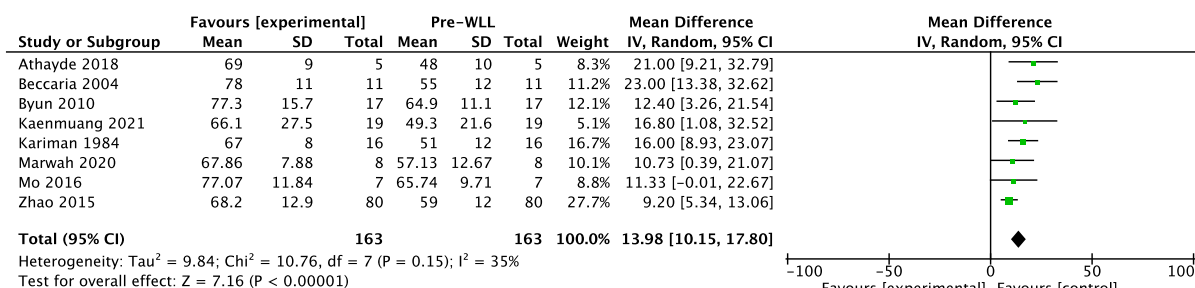
Perez 2004	Clinical and physiologic criteria, not further defined.	Bilateral. Unclear if single procedure.	45-60L per lung, warmed.
Selecky 1977	Progressive, severe exertional dyspnoea.	Bilateral. 2-3 day intervals	1-1.8L per cycle. Total of 15-18L per lung. Warmed
Smith 2019	ASA \geq II.	90% bilateral,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

Meta-analyses: Forest plots

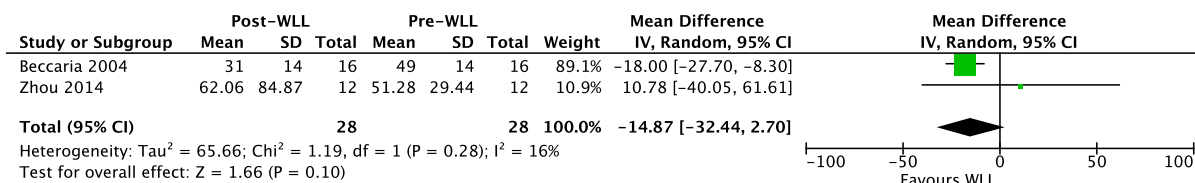
PaO₂ within one month post-WLL compared to pre-procedure



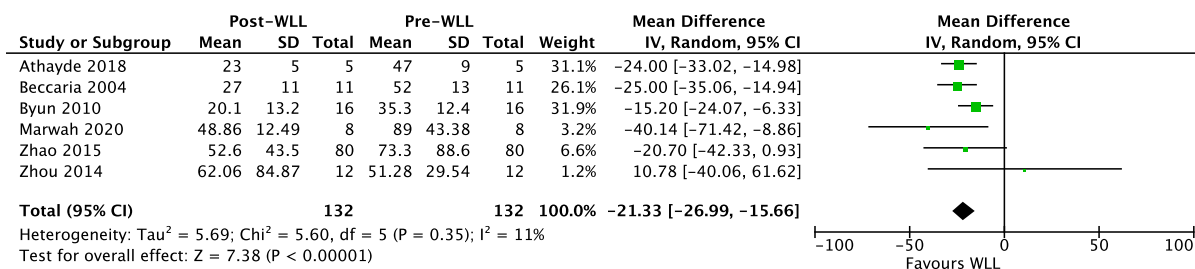
PaO₂ months to years post-WLL compared to pre-procedure



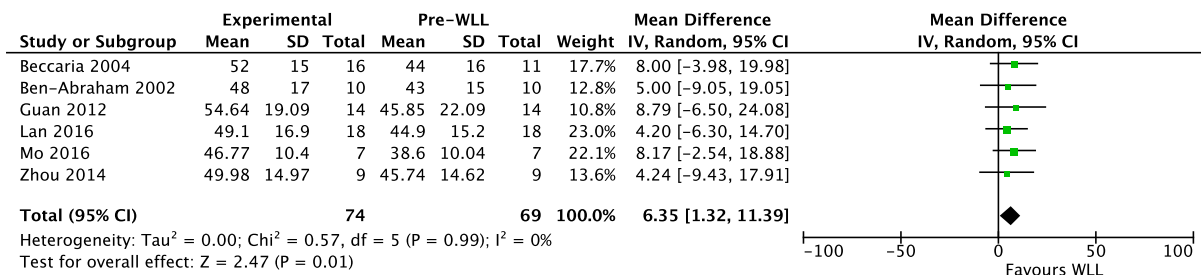
A-a (DO₂) within one month post-WLL compared to pre-procedure



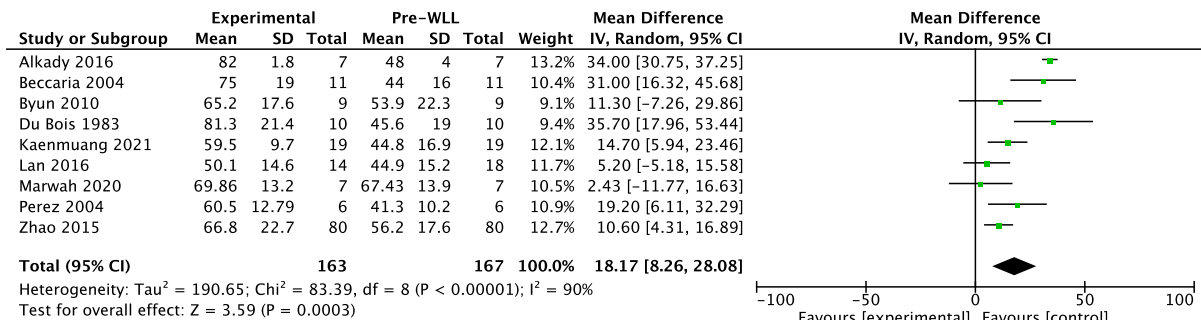
A-a (DO₂) months to years post-WLL compared to pre-procedure



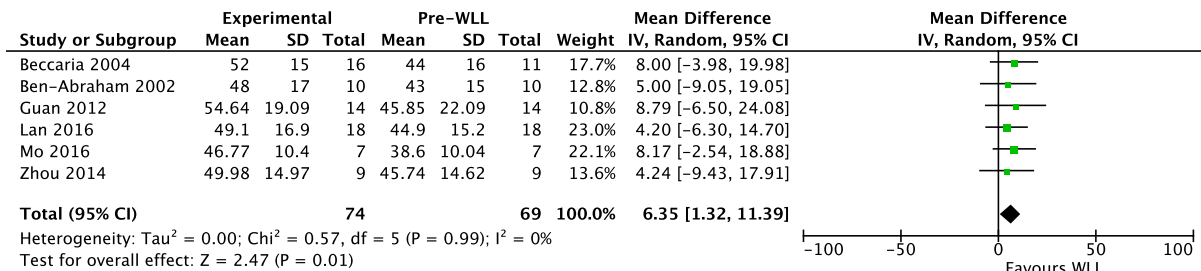
DLCO within one month post-WLL compared to pre-procedure



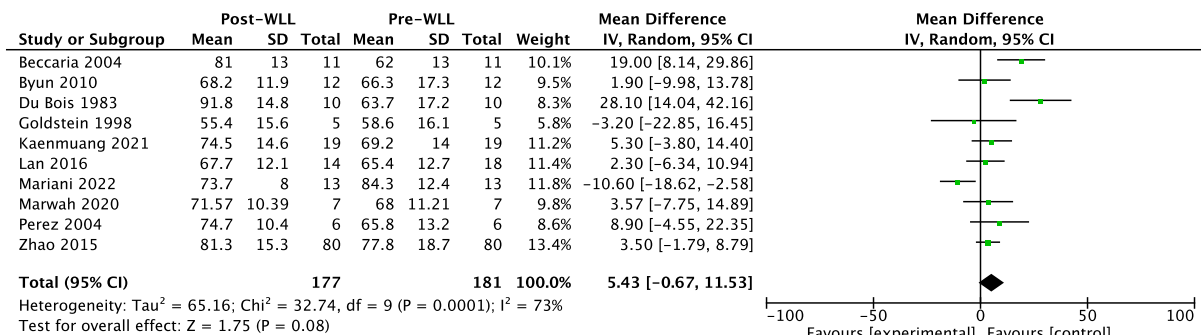
DLCO months to years post-WLL compared to pre-procedure



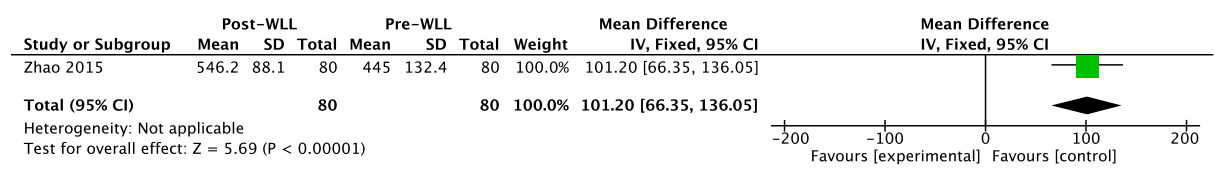
FVC within one month post-WLL compared to pre-procedure



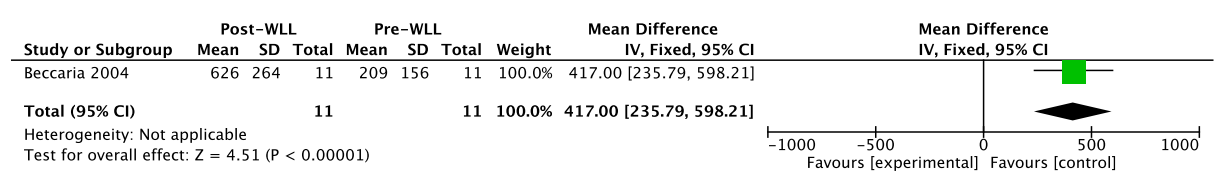
FVC months to years post-WLL compared to pre-procedure



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



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



Evidence to decision framework

QUESTION

Should Whole Lung Lavage (WLL) vs. Before WLL be used for Auto-Immune Pulmonary Alveolar Proteinosis?	
POPULATION:	Auto-Immune Pulmonary Alveolar Proteinosis
INTERVENTION:	Whole Lung Lavage (WLL)
COMPARISON:	Before WLL
MAIN OUTCOMES:	A-a DO ₂ ; PaO ₂ ; 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
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>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.</p>	
Desirable Effects		
How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Trivial <input type="radio"/> Small <input checked="" type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>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 case series described the clinical characteristics and laboratory results of patients pre- and post- WLL and compared laboratory values pre- and post-WLL.</p>	

	<p>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.</p> <p>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.</p> <p>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).</p> <p>Low certainty evidence suggests improved PaO₂ within a month from WLL (20.07 mmHg [95% CI 9.54, 30.60], I²=92%) and at longer follow-up, months to years from the WLL (13.98 mmHg [95% CI 10.15, 17.80], I²= 35%). Moreover, a trend over improved A-a DO₂ was observed post-WLL (-14.87 mmHg [-32.44, 2.70], I²=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], I²=11%, low certainty). No clear improvement was observed in FVC% predicted at short (8.54% [-8.22, 25.29], I² = 96%), or longer follow-up (5.43% [-0.67, 11.53]), low certainty.</p>	
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Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Trivial <input type="radio"/> Small <input checked="" type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Available data: As above</p> <p>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.</p> <p>A small number of mortalities were reported in a number of studies:</p> <ul style="list-style-type: none"> - Badiozaman 2013: One patient (out of 9) due to complications of general anaesthesia prior to WLL³² - Byun 2010: One patient (out of 26) died “soon after the WLL”, no further explanation given³⁵. - Diaz-Mendoza 2021: One patient (out of 13) died within one year post-WLL, but no cause of death was given³⁷. - 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 insufficiency³⁹. - Kiani 2018: One patient (out of 45) died five months after WLL because of respiratory insufficiency⁴⁵. - Zhao 2015: Three patients (out of 40) died within one year following WLL⁵³. <p>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.</p>	<p>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 WLL³⁰. Ben-Abraham 2002 reported a hospital stay of 2-3 days for unilateral WLL³⁴. 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.</p>

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input checked="" type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies 	<p>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, before-after studies 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.</p> <p>Overall, the certainty of evidence is low or very low. There are serious concerns around the methodological limitations of the included studies that were single arm and not controlled.</p>	

	<p>Moreover, there are serious concerns around imprecision, since the available studies were very underpowered.</p> <p>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.</p>	
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Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input checked="" type="radio"/> Probably no important uncertainty or variability <input type="radio"/> No important uncertainty or variability 	<p>No specific studies were identified to answer this question</p>	<p>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 severe symptoms and hypoxia that are refractory to other treatments outweigh the potential risks.</p>

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>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) DO₂.</p> <p>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.</p>	

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know 	<p>No specific studies were identified to answer this question</p>	<p>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.</p>

Certainty of evidence of required resources

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ● No included studies 	<p>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.</p>	

Cost effectiveness

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input checked="" type="radio"/> 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
<ul style="list-style-type: none"> <input checked="" type="radio"/> Reduced <input type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> 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 significant problem.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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 low or 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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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

	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 <input type="radio"/>	Conditional recommendation against the intervention <input type="radio"/>	Conditional recommendation for either the intervention or the comparison <input type="radio"/>	Conditional recommendation for the intervention <input type="radio"/>	Strong recommendation for the intervention <input checked="" type="radio"/>
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Recommendation

1. We recommend performing bilateral whole lung lavage in patients with primary 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 primary auto-immune 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)

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.
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.

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.

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.

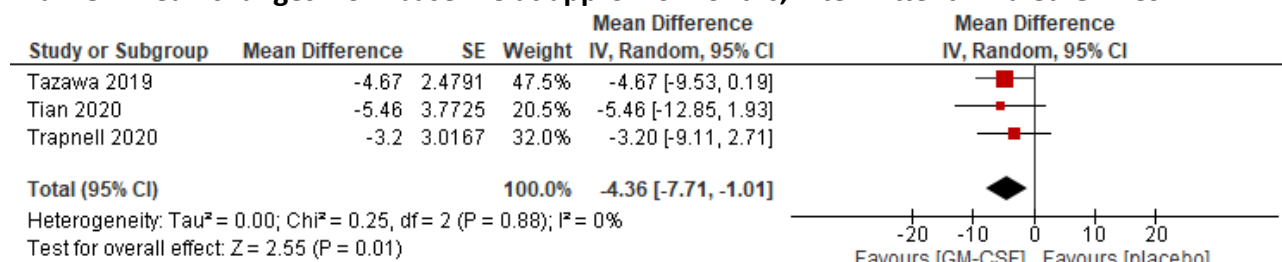
8. Papiris SA, Tsigotis P, Kolilekas L, Papadaki G, Papaioannou AI, Triantafillidou C, Papaportfyriou A, Karakatsani A, Kagouridis K, Griese M, Manali ED. Long-term inhaled granulocyte macrophage-colony-stimulating factor in autoimmune pulmonary alveolar proteinosis: effectiveness, safety, and lowest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

Risk of bias assessment

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Tazawa 2019	+	+	+	+	?	+	-
Tian 2020	+	-	-	-	-	+	+
Trapnell 2020	+	+	+	+	?	+	-

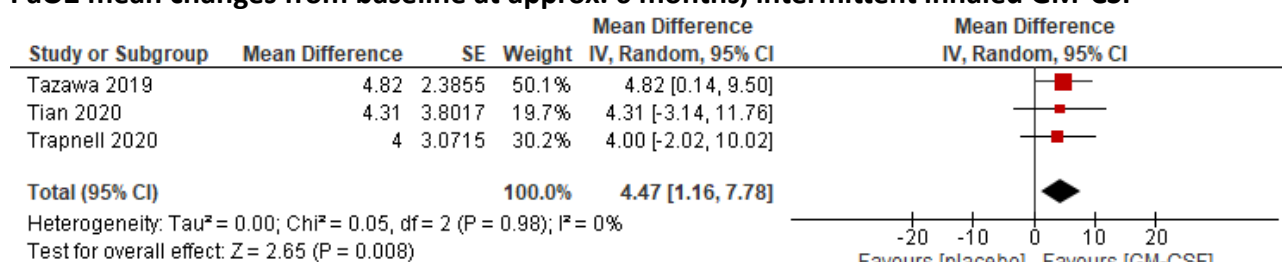
Meta-analyses: Forest plots

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



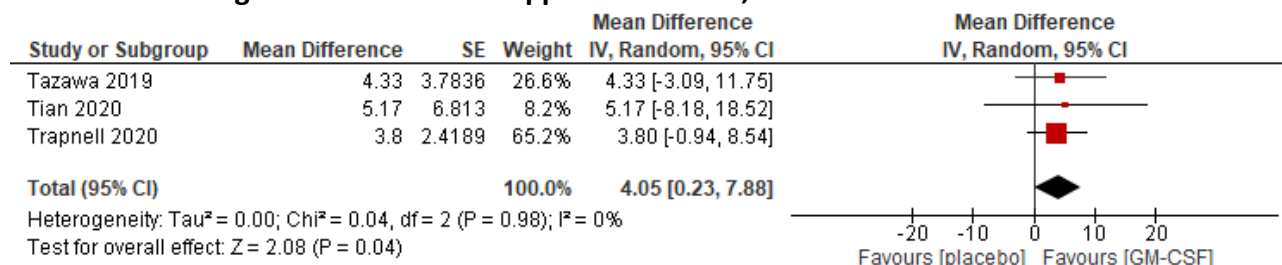
Additional evidence from observational trials and case series:

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



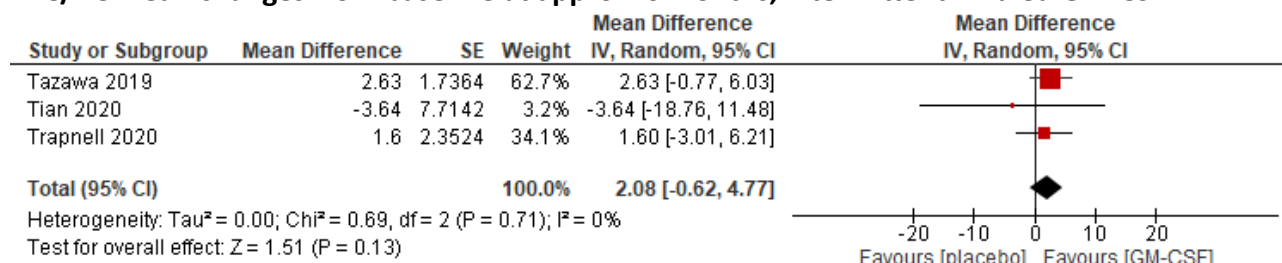
Additional evidence from observational trials and case series:

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



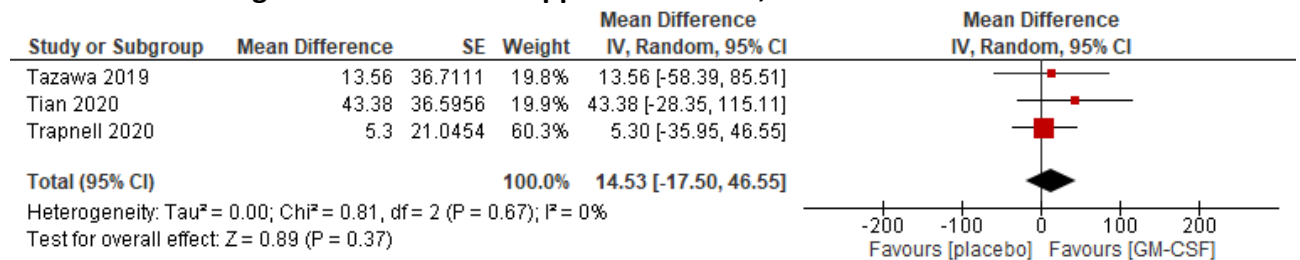
Additional evidence from observational trials and case series:

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



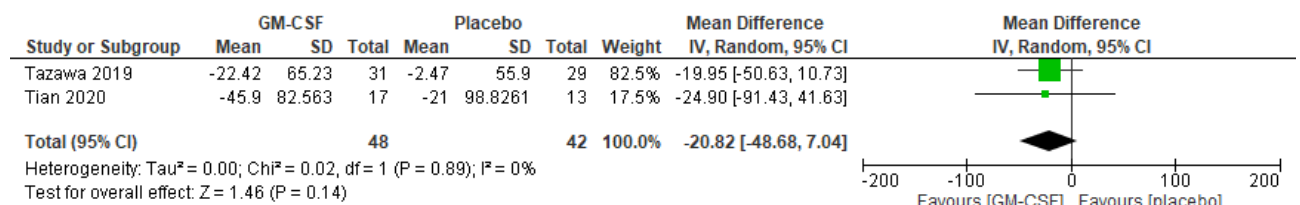
Additional evidence from observational trials and case series:

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



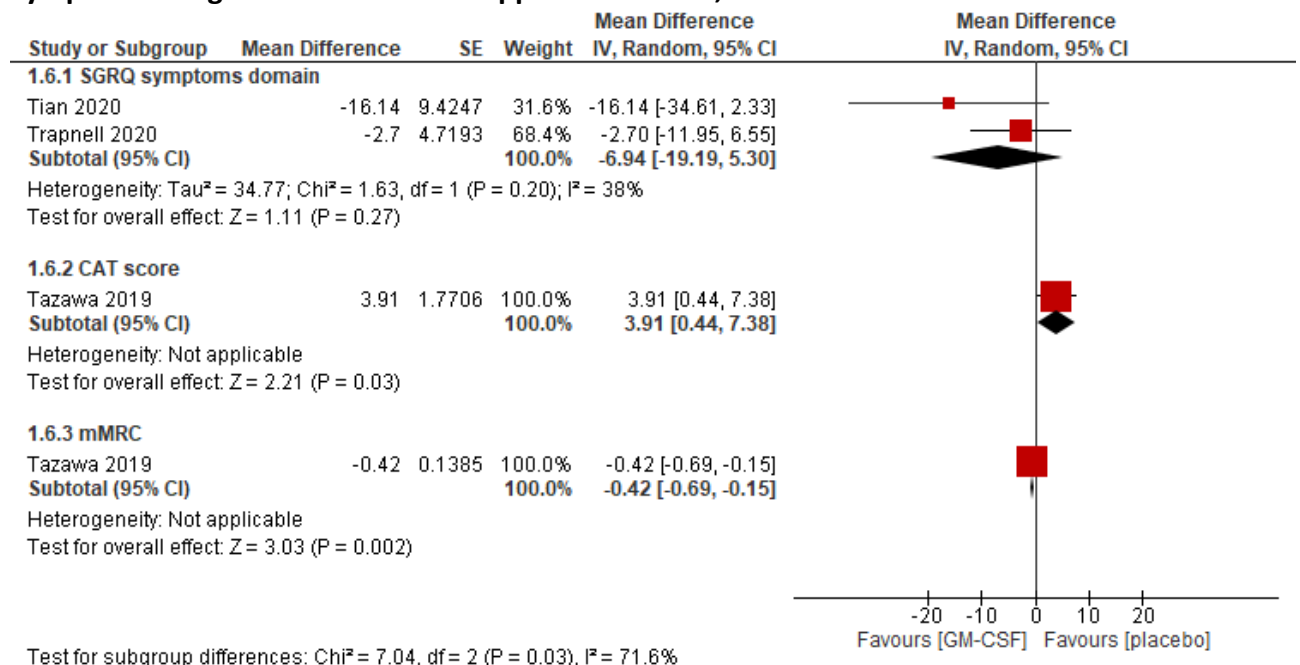
Additional evidence from observational trials and case series:

Lung density mean changes from baseline at approx. 6 months



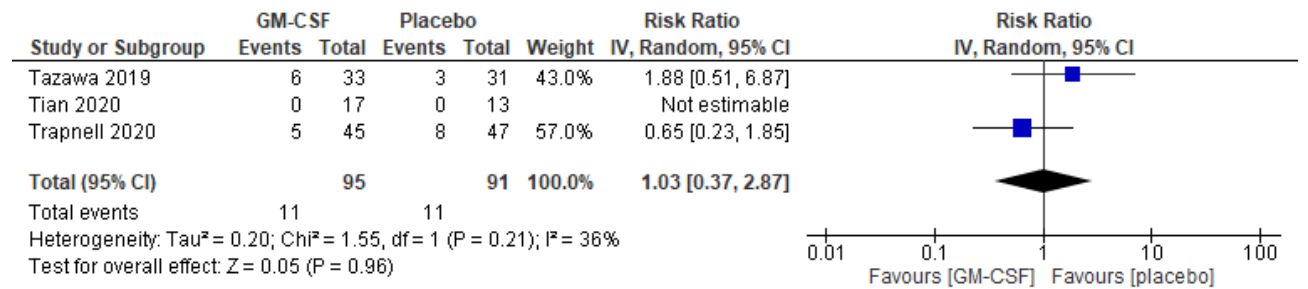
Additional evidence from observational trials and case series:

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



Additional evidence from observational trials and case series:

Serious adverse events at 24-42 wks.



Evidence profile

Certainty assessment							No of patients		Effect		Certainty	Importance
No 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 ^a	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 ^a	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 ^{e,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 ^a	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 ^a	none	48	42	-	MD 22.82 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 ^a	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

- Downgraded by 1 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.
- Probably not important to patients (a surrogate outcome).
- Downgraded by 1 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).
- Downgraded by 1 due to small sample size and the resulting wide CI.
- Downgraded by 2 because (1) the effect size includes beneficial and non-beneficial values and (2) the small sample size.
- Downgraded by 1 because of small sample size and no events.
- Downgraded by 1 because the questionnaire is not disease-specific.
- Downgraded by 1 because of incomplete outcome data.
- Downgraded by 1 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.
- Downgraded by 1 because the studies used different techniques to automatically calculate lung density.

Evidence to decision framework

QUESTION

Should GM-CSF vs. placebo be used in Pulmonary Alveolar Proteinosis?	
POPULATION:	Autoimmune Pulmonary Alveolar Proteinosis (PAP)
INTERVENTION:	Exogenous GM-CSF
COMPARISON:	Placebo
MAIN OUTCOMES:	Alveolar arterial oxygen difference, A-aDO ₂ (Critical) Exercise: Treadmill (Critical) Exercise: 6-minute walk test, 6MWT (Critical) Mortality (Critical) Partial concentration of oxygen measured on room air, PaO ₂ (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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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 safer and more cost-effective treatments for this burdensome disease.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know 	<p>Available data:</p> <ul style="list-style-type: none"> (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 <p>The three RCTs⁵⁷⁻⁵⁹ 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.</p> <p>Desirable effects:</p> <p>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) %.</p> <p>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).</p> <p>The were no mortality events in the RCTs. No RCT evaluated the outcome "Exercise: Treadmill".</p>	<p>Overall, the clinical magnitude of the effects is uncertain, as minimal important clinical differences (MICD) for the clinical outcomes are not established for PAP.</p> <p>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.</p> <p>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.</p> <p>Tazawa 2014 was an observational study estimating long term effects of intermittent inhaled GM-CSF during a 30-month observation after another observational trial⁶¹. 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 results⁶².</p>

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know 	<p>Available data: As above</p> <p>Undesirable effects: There 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).</p>	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Very low ○ Low ○ Moderate ○ High ○ No included studies 	<p>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 blinding⁵⁸. All three RCTs had either unclear or high risk of bias regarding incomplete outcome data⁵⁷⁻⁵⁹.</p> <p>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.</p> <p>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.</p> <p>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.</p>	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important 	<p>No specific studies were identified to answer this question.</p>	<p>Overall, the clinical magnitude of the effects is uncertain, as minimal important clinical differences (MICD) for the outcomes are not established for PAP.</p>

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 DO ₂ , PaO ₂ , DLCO, VC/FVC and HRCT surrogate outcomes that probably are not important for patients.
<h3>Balance of effects</h3> <p>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</p>		
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 significant effect on some outcomes. However, due to these outcomes being surrogate outcomes, we suggest that the results only probably favours the intervention.	
<h3>Resources required</h3> <p>How large are the resource requirements (costs)?</p>		
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.	<p>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.</p> <p>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 period⁵⁸.</p> <p>Tazawa 2014 was an observational study estimating long term effects of intermittent inhaled GM-CSF during a 30-month observation after another observational trial⁶¹. The results demonstrated that inhaled GM-CSF sustained remission of PAP in more than one-half of cases. A</p>

		<p>case series of 6 patients with PAP also showed similar promising results⁶²</p> <p>Altogether, inhaled GM-CSF might prevent the amount of WLL necessary, and the costs connected to this procedure.</p>
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Certainty of evidence of required resources

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ● No included studies 	<p>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.</p>	

Cost effectiveness

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input checked="" type="radio"/> 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
<ul style="list-style-type: none"> <input type="radio"/> Reduced <input type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input checked="" type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> 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
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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.

Feasibility		
Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	No specific studies were identified to answer this question.	We believe that the intervention is feasible to implement without major logistical issues.

SUMMARY OF JUDGEMENTS

PROBLEM	JUDGEMENT						
	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 ○
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Recommendation

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

PICO 5: Should patients with confirmed primary autoimmune pulmonary alveolar proteinosis be treated with rituximab?

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)

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.

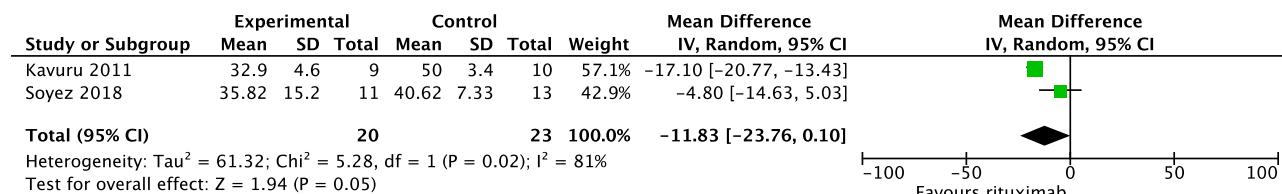
Risk of bias assessment

Table 3. Risk of bias assessment of the included studies.

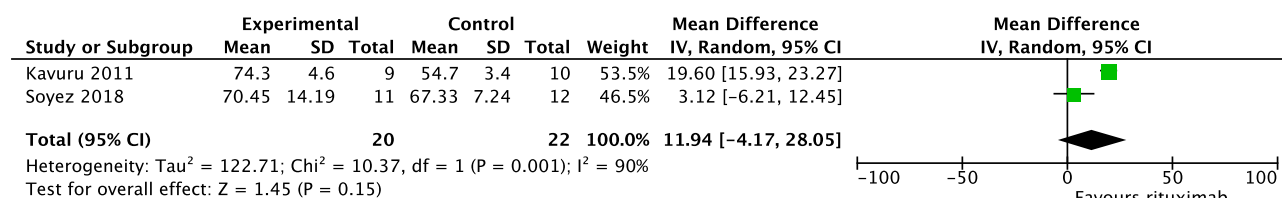
Bias domains	Kavuru 2011 ⁶⁷	Soyez 2018 ⁶⁸
Study design	Single arm interventional	Single arm observational
Bias caused by confounding	Serious	Serious
Bias caused by selection of participants	Low	Low
Bias caused by classification of interventions	Low	Low
Bias caused by deviations from intended interventions	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

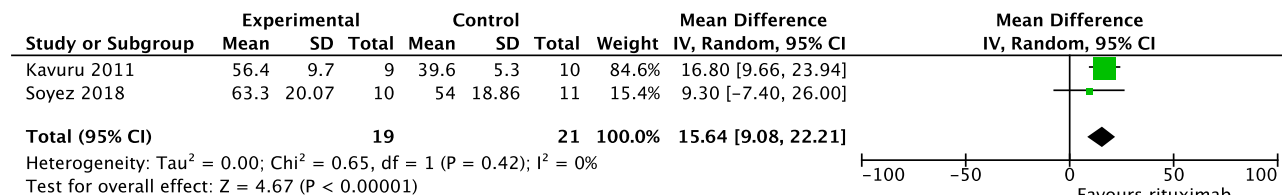
A-a DO2 6-12 months post-rituximab, compared to baseline



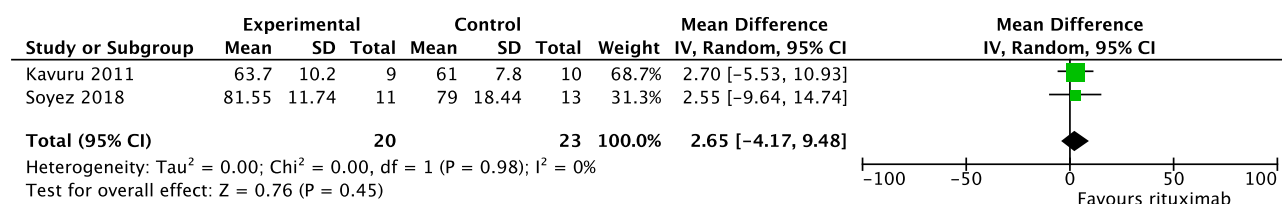
PaO₂ 6-12 months post-rituximab, compared to baseline



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



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



Evidence profile

Table 4. 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)												
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												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	Before Rituximab	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: confidence interval; MD: mean difference

Explanations

- a. Confounding and attrition bias.
- b. Inconsistent results, I² = 81%
- c. Small sample size

Case reports

Table 5. 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 6. 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.	<ul style="list-style-type: none"> ✓ 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: <ul style="list-style-type: none"> ✓ Oxygen therapy stopped. ✓ 6MWT: 562m (previously 330m). ✓ Improved FEV₁, 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.	<ul style="list-style-type: none"> ✓ 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	<ul style="list-style-type: none"> ✓ 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.	<ul style="list-style-type: none"> ✓ At one year: Improved FEV₁ (69% from 56% predicted), FVC (72% from 63%) and FEV₁/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	<ul style="list-style-type: none"> ✓ Radiologic improvement. ✓ Oxygen therapy stopped. ✓ Returned to her work and activities of daily living. 	Not reported

Evidence to decision framework

QUESTION

Should Rituximab vs. Before rituximab be used for Auto-Immune Pulmonary Alveolar Proteinosis?	
POPULATION:	Auto-Immune Pulmonary Alveolar Proteinosis
INTERVENTION:	Rituximab
COMPARISON:	Before rituximab
MAIN OUTCOMES:	A-a DO ₂ ; PaO ₂ ; 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
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>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.</p>	
Desirable Effects		
How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Trivial <input type="radio"/> Small <input checked="" type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Available data:</p> <ul style="list-style-type: none"> (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 reports⁶⁹⁻⁷⁵. <p>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</p>	

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 dose⁶⁸.

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, I² = 81% and improve the partial concentration of oxygen measured on room air (MD 11.94 [-4.17, 28.05] mmHg, I² =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, I² =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 WLL⁶⁷. 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 baseline⁶⁸. 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 2011⁶⁷ 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
<ul style="list-style-type: none"> ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know 	<p>Available data: As above</p> <p>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.</p>	<p>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 arthritis⁷⁶. 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]).</p> <p>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])</p> <p>The safety of rituximab in children at a dose of 1-4 infusions of 375mg/m² has been assessed in more detail in a meta-analysis evaluating rituximab for childhood steroid-dependent nephrotic syndrome⁷⁷. 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 low⁷⁸.</p> <p>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.</p>

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Very low ○ Low ○ Moderate ○ High ○ No included studies 	<p>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.</p> <p>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.</p> <p>All available data are from adult studies. We did not find any data around the safety and efficacy of rituximab in children and adolescents.</p>	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability 	<p>No specific studies were identified to answer this question</p>	<p>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.</p>

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>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.</p>	

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Large costs <input type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input checked="" type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>No specific studies were identified to answer this question</p>	<p>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.</p>

Certainty of evidence of required resources

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input checked="" type="radio"/> No included studies 	<p>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.</p>	

Cost effectiveness

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input checked="" type="radio"/> No included studies 	<p>No specific studies were identified to answer this question</p>	<p>As above. Rituximab may improve symptoms and hypoxia and prevent or delay the frequency of WLL, which is a costly procedure.</p>

Equity		
What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Reduced <input type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input checked="" type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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 ○
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Recommendation

We suggest considering 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: Should patients with confirmed primary autoimmune pulmonary alveolar proteinosis be treated with 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)

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 plasmaphérese 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 8. 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	Luisiatti 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

Table 9. 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	<ul style="list-style-type: none"> ✓ 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.	<ul style="list-style-type: none"> ✓ 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.

					<ul style="list-style-type: none"> ✓ Reduced need for WLL 	
Griese 2022 ⁸⁰	15, Male, NR	Malnourishment (BMI <14 kg/m ² , <3 rd 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 FiO ₂ 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.	<ul style="list-style-type: none"> ✓ 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/m²). ✓ 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 3 rd WLL, but another relapse led to 4 th 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	<ul style="list-style-type: none"> x Plasmapheresis was not effective <ul style="list-style-type: none"> ✓ 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	<ul style="list-style-type: none"> ✓ 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	<ul style="list-style-type: none"> ✓ 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:	<ul style="list-style-type: none"> ✓ 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 to decision framework

QUESTION

Should Rituximab vs. Before rituximab be used for Auto-Immune Pulmonary Alveolar Proteinosis?	
POPULATION:	Auto-Immune Pulmonary Alveolar Proteinosis
INTERVENTION:	Plasmapheresis
COMPARISON:	Before plasmapheresis
MAIN OUTCOMES:	A-a DO ₂ ; PaO ₂ ; 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
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>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.</p>	
Desirable Effects		
How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Trivial <input type="radio"/> Small <input checked="" type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Available data: 9 case reports ^{71,72,79-85}</p> <p>Desirable effects: No significant clinical benefits were observed in three of the reported cases (Jezequel 2016, Keske 2002, Vis 2020)^{72,81,84}.</p>	

	<p>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 later⁸⁵. 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 plasmapheresis⁸³.</p> <p>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}.</p> <p>A significant reduction in the GM-CSF antibody titres was reported in 5/9 cases.</p> <p>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.</p> <p>The plasmapheresis regimen is not standardised but it appears that higher intensity regimens that successfully suppress anti-GM-CSF antibodies offer clinical benefits.</p>	
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Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Trivial <input checked="" type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Available data: As above</p> <p>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 fully⁷¹. However, it is not clear whether the remaining cases did not have any plasmapheresis complications or whether these were just not recorded.</p>	<p>The safety of plasmapheresis was evaluated in detail in a Cochrane meta-analysis of the safety and efficacy of plasmapheresis for Guillain-Barre disease⁸⁶. 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.</p> <p>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.</p> <p>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 avoided⁸⁸. Complications were reported in 15%</p>

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

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Very low ○ Low ○ Moderate ○ High ○ No included studies 	<p>The certainty of evidence is very low. Our only evidence come 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.</p> <p>Only one case report described the use of plasmapheresis in an adolescent with PAP, while all other cases were adults.</p>	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability 	<p>No specific studies were identified to answer this question</p>	<p>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.</p>

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Available data of very low certainty support a potential benefit of plasmapheresis in some patients with auto-immune PAP.</p>	<p>Indirect evidence support the safety of plasmapheresis.</p>

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Large costs <input type="radio"/> Moderate costs <input checked="" type="radio"/> Negligible costs and savings <input type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>No specific studies were identified to answer this question</p>	<p>The costs of plasmapheresis varies significantly across the world⁸⁹. 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€.</p> <p>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 WLL⁹⁰. 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.</p>

Certainty of evidence of required resources

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input checked="" type="radio"/> No included studies 	<p>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.</p>	

Cost effectiveness

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input checked="" type="radio"/> No included studies 	<p>No specific studies were identified to answer this question</p>	<p>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.</p>

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Reduced <input checked="" type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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 ○
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Recommendation

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

PICO 7: Should patients with progressive pulmonary alveolar proteinosis despite whole lung lavage or pharmacological treatment be considered for 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)

Included studies

Case reports and case series

1. Lawi D, Dubruc E, Gonzalez M, Aubert JD, Soccac 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.
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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.istage.jst.go.jp/article/amn/57/1/57_25/pdf

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Case reports and case series

Table 10. 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 11. 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 <i>CSF2RB</i> 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 <i>CSF2RA</i> 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 Diamond-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 LDLT 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

Evidence to decision framework

QUESTION

When should patients with progressive PAP despite whole lung lavage or pharmacological treatment be considered for 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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	<p>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.</p> <p>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.</p> <p>Lung transplantation is an established procedure to treat chronic end-stage respiratory failure with no options to cure by other treatments, both in children¹⁰³ 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^{f104-107}.</p>	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know 	<p>Desirable effects: The desirable effect of lung transplantation is to cure the underlying lung disease by replacing one or the 2 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.</p> <p>Available data: *Data are available from 14 distinct case reports, among which 8 adults and 6 children⁹¹⁻¹⁰². 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 given¹⁰². *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).</p> <p>Outcomes : - 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.</p>	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Trivial <input type="radio"/> Small <input checked="" type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Available data: As above</p> <p>Undesirable effects:</p> <ul style="list-style-type: none"> - 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) <p>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.</p> <ul style="list-style-type: none"> - 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. 	<p>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.</p>

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input checked="" type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies 	<p>The certainty of evidence is very low because:</p> <ul style="list-style-type: none"> - 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
<ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability 	<p>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 QOL¹⁰⁸. Indeed, many patients consider lung transplantation for palliation of symptoms and improvement of QOL even when extended survival is not assured¹⁰⁸. However, there are always some people who reject an offer of transplant and wish palliative care.</p>	<p>A systematic review of health-related quality of life and psychological outcomes after lung transplantation¹⁰⁹.</p>
Balance of effects		
Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ 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 	<p>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.</p>	<p>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 derived¹¹⁰. 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 recipients¹¹¹.</p>

Resources required

How large are the resource requirements (costs)?¹¹

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Large costs <input checked="" type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>No specific studies were identified to answer this question.</p> <p>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 transplantation¹¹².</p>	<p>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.</p>

Certainty of evidence of required resources

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Very low <input type="radio"/> Low <input checked="" type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies 	<p>No studies specific for LT because of PAP to answer this question. Generally for lung transplant in adults, costs are</p> <p>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 year¹¹².</p>	

Cost effectiveness

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input checked="" type="radio"/> Favors the intervention <input type="radio"/> Varies No included studies 	See review above ¹¹² .	.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Reduced <input checked="" type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> 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
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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

PROBLEM	JUDGEMENT						
	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			Don't know
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	Don't know

	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 <input type="radio"/>	Conditional recommendation against the intervention <input type="radio"/>	Conditional recommendation for either the intervention or the comparison <input type="radio"/>	Conditional recommendation for the intervention <input checked="" type="radio"/>	Strong recommendation for the intervention <input type="radio"/>
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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 catheter¹¹³. 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 cylinder⁵⁶. This cycle of instillation and drainage is repeated several times until the returned fluid is clear, using an average of 15.4 litre per lung⁵⁵. 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≥70mm Hg; 2=symptomatic and PaO₂≥70mm Hg; 3=60≤PaO₂<70mm Hg; 4=50≤PaO₂<60mm Hg; 5=PaO₂<50mm 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/m² for children. The intervals of rituximab could be tailored to the individual patient requirements, following established regimes from other disease areas. The European Medicines 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

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