European Respiratory Society guidelines for the diagnosis and management of pulmonary alveolar proteinosis

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Shareable abstract (@ERSpublications)
The diagnosis of PAP is based on CT and BAL cytology or histology, whereas the diagnosis of a specific PAP-causing disease requires GM-CSF antibody testing and/or genetic analysis. Inhaled GM-CSF appears to be a promising option for autoimmune PAP. https://bit.ly/3YLJR6j

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Abstract

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

Methods A European Respiratory Society Task Force composed of clinicians, methodologists and patients with experience in PAP developed recommendations in accordance with the ERS Handbook for Clinical

Practice Guidelines and the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach. This included a systematic review of the literature and application of the GRADE approach to assess the certainty of evidence and strength of recommendations. The Task Force formulated five PICO (Patients, Intervention, Comparison, Outcomes) questions and two narrative questions to develop specific evidence-based recommendations.

Results The Task Force developed recommendations for the five PICO questions. These included management of PAP with WLL, GM-CSF augmentation therapy, rituximab, plasmapheresis and lung transplantation. Also, the Task Force made recommendations regarding the use of GM-CSF antibody testing, diagnostic BAL and biopsy based on the narrative questions. In addition to the recommendations, the Task Force provided information on the hierarchy of diagnostic interventions and therapy.

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

Scope and objectives

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

Introduction

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

Primary PAP is driven by disruption of signalling by granulocyte–macrophage colony-stimulating factor (GM-CSF) resulting in dysfunction of alveolar macrophages and neutrophils, while secondary PAP occurs

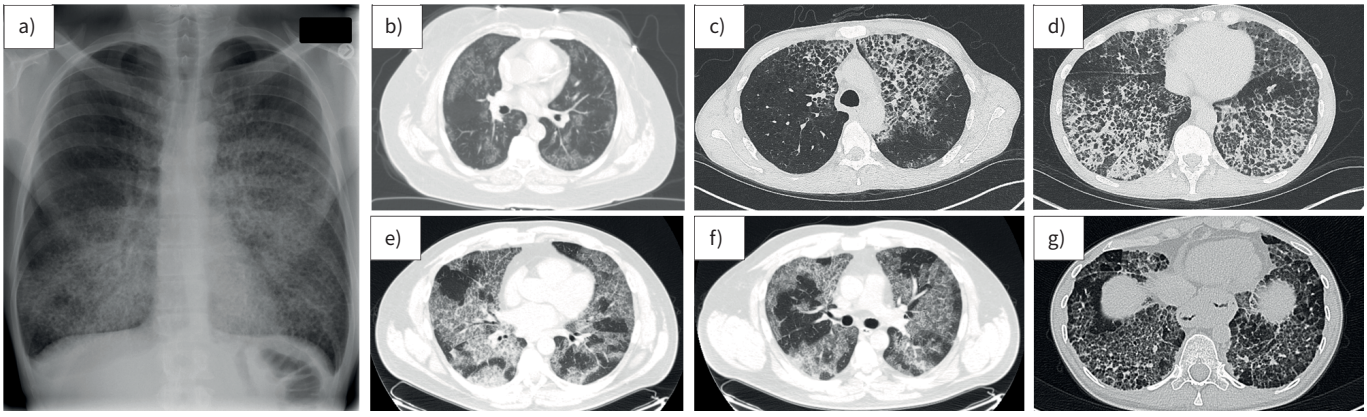

FIGURE 1 Radiological findings in pulmonary alveolar proteinosis (PAP). Representative images from a) chest radiography and b–g) computed tomography (CT) of the thorax demonstrating the diversity of radiographic findings in PAP. b) Ground-glass infiltrates in a mild case of autoimmune PAP (aPAP) without interlobular septal thickening. c–f) CT images demonstrating varying degrees of involvement with the distinctive pattern of interlobular septal thickening superimposed on ground-glass opacification, referred to as "crazy paving". c, e, f) Clearly demarcated differences in the degree of involvement between adjacent lobes. g) aPAP complicated by pulmonary fibrosis 15 years after initial diagnosis of aPAP: CT demonstrates parenchymal distortion, honeycombing and traction bronchiectasis.

TABLE 1 Classification of pulmonary alveolar proteinosis (PAP)-causing diseases

Disorders of surfactant clearance	
Primary PAP (GM-CSF signalling disruption)	
Autoimmune PAP	Mediated by autoantibodies to GM-CSF
Hereditary PAP	GM-CSF signalling disruption due to GM-CSF receptor mutations (*CSF2RA* or *CSF2RB*) or *STAT5B* mutations
Secondary PAP (reduced alveolar macrophage function or number)	
Haematological conditions	Acute lymphocytic leukaemia, acute myeloid leukaemia, aplastic anaemia, chronic lymphocytic leukaemia, chronic myeloid leukaemia, myelodysplastic syndromes, multiple myeloma, lymphoma, Waldenstrom's macroglobulinaemia, GATA2 deficiency
Non-haematological malignancies	Adenocarcinoma, glioblastoma, melanoma
Immune deficiency and chronic inflammatory conditions	AIDS, amyloidosis, Fanconi's syndrome, agammaglobulinaemia, juvenile dermatomyositis, renal tubular acidosis, severe combined immunodeficiency disease
Occupational and environmental exposures	Aluminium, cement, silica, titanium, indium, flour, fertiliser, sawdust, chlorine fumes, cleaning products, gasoline/petroleum fumes, nitrogen dioxide, paint fumes, synthetic plastic fumes, varnish
Chronic infections	Cytomegalovirus, *Mycobacterium tuberculosis*, *Nocardia*, *Pneumocystis jirovecii*
Others including mutations affecting mononuclear phagocytes	Lysinuric protein intolerance, mutations in methionyl-tRNA synthetase (*MARS*)
Disorders of surfactant production	
Pulmonary surfactant metabolic dysfunction disorders	
Mutations in *SFTPB*, *SFTPC*, *ABCA3*, *NKX2.1*	Surfactant homeostasis affected due to mutations causing surfactant protein deficiency, lipid transporter deficiency or mutations that affecting lung development

because of an underlying disease or condition that reduces the numbers and/or functions of alveolar macrophages. Disorders of surfactant production or pulmonary surfactant metabolic dysfunction disorders are caused by mutations in genes encoding surfactant proteins or genes involved in surfactant production or lung development [1]. The prevalence of autoimmune PAP (aPAP) is estimated at 6.7–6.9 per million in the general population [2, 3]. Advances over the last 20 years have improved the understanding of PAP and resulted in novel methods for diagnosis and treatment. With established and emerging therapies and better understanding of the underlying pathogenesis, clinical practice guidelines are needed [1, 4].

Methodology

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

Questions and outcomes

The guidelines address seven clinically pertinent questions on the diagnosis and management of PAP that were selected by consensus. Following ERS processes [5], we formulated five questions using the PICO (Patients, Intervention, Comparison, Outcomes) format and two narrative questions. For every question, relevant outcomes were selected based on their importance for clinical practice, in line with the GRADE approach. Only outcomes that were rated critical or important by a majority of panel members were considered for the development of recommendations (supplementary material). PICO questions were informed by formal systematic reviews, meta-analyses and appraisal of the available evidence, while narrative questions were informed by systematic literature searches.

Literature searches and systematic literature review

An independent librarian designed systematic searches for all questions in collaboration with the chairs and methodologists of the Task Force (supplementary material). Each question was informed by systematic

searches of three online databases: PubMed, Embase and Cochrane Central. Searches were carried out during 13–19 May 2022 and subsequently updated on 9 August 2022. We considered interventional and observational studies addressing any of the PICO and narrative questions. We included all comparative studies and single-arm studies including at least five participants. In addition, in anticipation of a weaker evidence base for children and for PICO questions 5–7, we included case series irrespective of their study populations and case reports. Additional studies such as informative case reports or mechanistic studies that the panel members considered relevant for any of the PICO and narrative questions but did not fulfil the eligibility criteria are described in the "Additional considerations" sections of the Evidence-to-Decision (EtD) frameworks (supplementary material).

Study screening at a title-abstract and full-text level was independently conducted in Rayyan [7] by at least two members of the Task Force using predefined inclusion and exclusion criteria. Relevant information about study design, baseline characteristics of the participants, characteristics of interventions or index tests of interest, as well as the outcomes of interest, were extracted in a prospectively designed data extraction form by one and cross-checked by a second panel member for accuracy. Risk of bias of randomised controlled trials (RCTs) was appraised using the Cochrane Risk of Bias tool [8], while the ROBINS-I (risk of bias in non-randomised studies of interventions) tool was used for observational and non-comparative interventional studies [9], and for case series or reports we used the Joanna Briggs Institute's risk of bias tool for case reports [10]. In line with a protocol that had been prospectively submitted to the ERS Guidelines Working Group, meta-analyses were performed using random effects models when it was considered meaningful, for PICO questions. The random effects model was selected because of the expected heterogeneity among the included studies. Data from RCTs or quasi-RCTs, comparative observational studies and non-comparative studies were not pooled. Data for the narrative questions were described, in line with the ERS Handbook for Clinical Practice Guidelines [5].

Assessing the certainty of evidence and strength of recommendations

GRADE Evidence profiles were generated for PICO questions informed by comparative studies and EtD frameworks were generated for all PICO questions, while only EtDs were generated for narrative questions (supplementary material). For PICO questions, the certainty of the body of evidence informing each outcome was appraised using GRADE methodology as very low, low, moderate or high certainty. Judgements around certainty were informed by the assessment of the risk of bias of the included studies, inconsistency, indirectness, imprecision and publication bias across the included studies. For narrative questions, in accordance with the updated ERS guidelines [5], the approach was narrative. EtD frameworks were used by the panel to formulate recommendations and strength by consensus and/or voting. The recommendations were graded as strong or conditional. In line with GRADE terminology [6], the term "we recommend" was used for strong recommendations and the term "we suggest" was used for conditional recommendations.

A strong recommendation was made for an intervention when the panel was certain that the desirable consequences of the intervention outweighed the undesirable consequences and a strong recommendation against an intervention was made when the opposite was observed in the evidence. A strong recommendation indicates that most patients and healthcare providers would choose to recommend, or not to recommend, the intervention. A conditional recommendation for an intervention was made when the panel was uncertain that the desirable consequences of an intervention outweighed the undesirable consequences in most patients and a conditional recommendation against an intervention was made when the opposite was observed in the evidence. A conditional recommendation indicates that different patients and healthcare providers may make different choices regarding an intervention. In addition to the recommendations, specific considerations were made regarding individual PICO questions. These considerations reflect the Task Force members current practice and describe their clinical experience. Evidence supporting these comments was provided for each PICO question. All recommendations, comments and algorithms were reviewed and approved by the full panel.

Recommendation development

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

a conditional recommendation, while an agreement of at least 70% of the participants was required for issuing a strong recommendation.

Panel meetings

For developing these clinical practice guidelines, the Task Force panel organised four face-to-face meetings (Barcelona, ERS Congress 2022; Essen, October 2022; Paris, July 2023; Milan, ERS Congress 2023) and four videoconferences. The first two meetings were focused on finalising the methodology, PICO questions, outcomes selection and search strategies. During the latter meetings, the results of systematic reviews and EtD frameworks were discussed and recommendations were finalised. These meetings were complemented by several online meetings of groups focusing on specific questions or tasks. Teams consisting of at least two PAP experts, one methodologist and one patient representative were assigned to each clinical question. Teams met virtually and during physical meetings to address the topics. Detailed minutes/notes were taken at all meetings and subsequently distributed to all members of the Task Force.

Definitions of disease activity, severity and progression

General considerations

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

Disease activity

PAP is characterised by progressive accumulation of surfactant in pulmonary alveoli resulting in hypoxaemic respiratory insufficiency or failure. PAP is considered active in the presence of 1) continuous or progressive symptom(s) such as dyspnoea, cough, sputum production, chest pain or weight loss, and/or 2) lung function decline in forced vital capacity (FVC) or diffusing capacity of the lung for carbon monoxide (D_{LCO}), and/or 3) hypoxaemia measured by arterial blood gas (arterial oxygen tension (P_{aO_2}), arterial oxygen saturation (S_{aO_2}), alveolar–arterial oxygen tension difference (P_{A-aO_2} or AaD_{O_2}), and/or 4) new or worsening PAP-characteristic infiltrates on high-resolution CT (HRCT), including but not limited to ground-glass and “crazy paving”. Alternative causes or complications such as respiratory infections, pulmonary embolism, pulmonary hypertension and congestive cardiac failure should be excluded.

Disease severity

A disease severity score was proposed in 2008 [2] and is based on symptoms and P_{aO_2} levels [11]. This score is easy to calculate and has been used to stratify patients in clinical trials [12, 13]. Further scores which include smoking status and HRCT findings have been proposed and showed good correlation with prognosis [14]. It remains unclear whether opportunistic infections should be considered an indicator of disease severity or simply a complication [1]. A second opinion from a PAP reference centre can be of assistance in patient assessment, determining if the disease is active and to ascertain management options.

Disease progression

There is no standard definition of disease progression for PAP; however, it is widely considered to be the worsening of respiratory symptoms, decline in lung function tests (FVC and D_{LCO}), onset or worsening of respiratory failure including need for oxygen treatment and worsening of PAP-related CT findings after careful exclusions of other causes. Based on previous observational studies [15–17] and clinical trials [12, 13], D_{LCO} and AaD_{O_2} maybe the most sensitive markers of disease progression [1, 18]. Due to the paucity of data, specific thresholds for decline in lung function tests or blood gas parameters to define disease progression are not available. The reduction of time interval between subsequent whole lung lavage (WLL) procedures has also been used as an indicator of disease progression in PAP [16, 17]. Disease progression should always be confirmed by HRCT and to ensure no alternative processes are ongoing. Pulmonary fibrosis, which occurs at varying frequency but can affect up to 20% of PAP patients [19], should be considered as a sign of progressive disease. In this case, disease progression can tentatively be further assessed by using the progressive pulmonary fibrosis definition from the 2022 international clinical practice guideline [20]; however, the use of these criteria for PAP awaits validation.

Recommendations

The search strategies, PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagrams, included studies, risk of bias assessments, meta-analyses, evidence profiles and EtD frameworks for all questions are available in the supplementary material. Recommendations around individual interventions and the evidence supporting these are presented first (summarised in table 2), together with a proposed algorithm for the differential diagnosis of PAP (figure 2) and a hierarchy of treatment in aPAP (figure 3).

TABLE 2 Narrative and PICO (Patients, Intervention, Comparison, Outcomes) questions and recommendations

Question	Recommendation
NQ 1a: When should patients with clinical and radiological features consistent with a diagnosis of PAP undergo BAL?	We recommend that BAL be performed as part of the diagnostic work up of patients with suspected PAP. BAL should include differential cell count, periodic acid–Schiff (PAS) staining and microbiology. *(Strong recommendation, very low certainty of evidence.)*
NQ 1b: When should patients with clinical and radiological features consistent with a diagnosis of PAP undergo lung biopsy for histological analysis?	We suggest to not routinely perform lung biopsy as part of the diagnostic work up of patients with suspected PAP. *(Conditional recommendation, moderate certainty of evidence.)*
NQ 2: When should patients with clinical and radiological features consistent with PAP undergo GM-CSF antibody testing for diagnosing autoimmune PAP?	We recommend GM-CSF antibody testing for diagnosing autoimmune PAP for all patients with suspected or confirmed PAP syndrome. *(Strong recommendation, moderate certainty of evidence.)*
PICO 3: In patients with clinical symptoms and/or functional impairment due to PAP should WLL be used *versus* no WLL?	We recommend performing bilateral WLL in patients with autoimmune PAP with evidence of gas exchange impairment and either symptoms or functional impairment. *(Strong recommendation, very low certainty of evidence.)* No recommendation for or against WLL in other PAP types can be made due to lack of evidence. We suggest seeking advice from an expert centre on an individual case basis.
PICO 4: In patients with confirmed autoimmune PAP should exogenous GM-CSF be used *versus* no exogenous GM-CSF?	We recommend inhaled GM-CSF for symptomatic patients with confirmed autoimmune PAP. *(Strong recommendation, very low certainty of evidence.)*
PICO 5: In patients with confirmed autoimmune PAP should rituximab be used *versus* no immunosuppressive treatment?	We suggest the use of rituximab for patients with confirmed autoimmune PAP who remain significantly symptomatic, requiring supplemental oxygen, despite WLL therapy or exogenous GM-CSF treatment. *(Conditional recommendation, very low certainty of evidence.)*
PICO 6: In patients with confirmed autoimmune PAP should plasmapheresis be used *versus* no plasmapheresis?	We suggest the use of plasmapheresis for patients with confirmed autoimmune PAP who remain significantly symptomatic, requiring supplemental oxygen or two or more WLLs over a period of a year, despite receiving exogenous GM-CSF and rituximab, or having previously failed these treatments. *(Conditional recommendation, very low certainty of evidence.)*
PICO 7: In patients with PAP progressing despite WLL or pharmacological treatment should lung transplantation be considered *versus* no lung transplantation?	We suggest lung transplantation for patients with PAP progressing despite WLL and/or pharmacological treatment, who fulfil the International Society for Heart and Lung Transplantation (ISHLT) criteria [97] for patients with interstitial lung disease. *(Conditional recommendation, very low certainty of evidence.)*

NQ: narrative question; PAP: pulmonary alveolar proteinosis; BAL: bronchoalveolar lavage; GM-CSF: granulocyte–macrophage colony-stimulating factor; WLL: whole lung lavage.

Narrative question 1a

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

Recommendation

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

Justification of recommendations

The justification for the strong recommendation for BAL is based on the perceived benefit of a clear diagnosis on PAS staining without the need for more invasive tests and the low risk of complications. BAL is a low-risk technique that allows for the direct sampling of the cellular and acellular components in the distal airways and alveoli. The usefulness of BAL for identifying the presence of PAP has been reported in several studies. Ilkovich *et al.* [21] reported 68 patients with idiopathic PAP where BAL fluid (BALF) was reported as milky white, opalescent, with white material after sedimentation. Cytology revealed amorphous and granular eosinophilic masses mixed with alveolar macrophages. BALF cellularity in PAP patients is often increased with a predominance of lymphocytes, and cytological examination of the BALF shows foamy macrophages which contain eosinophilic granules and amorphic material that

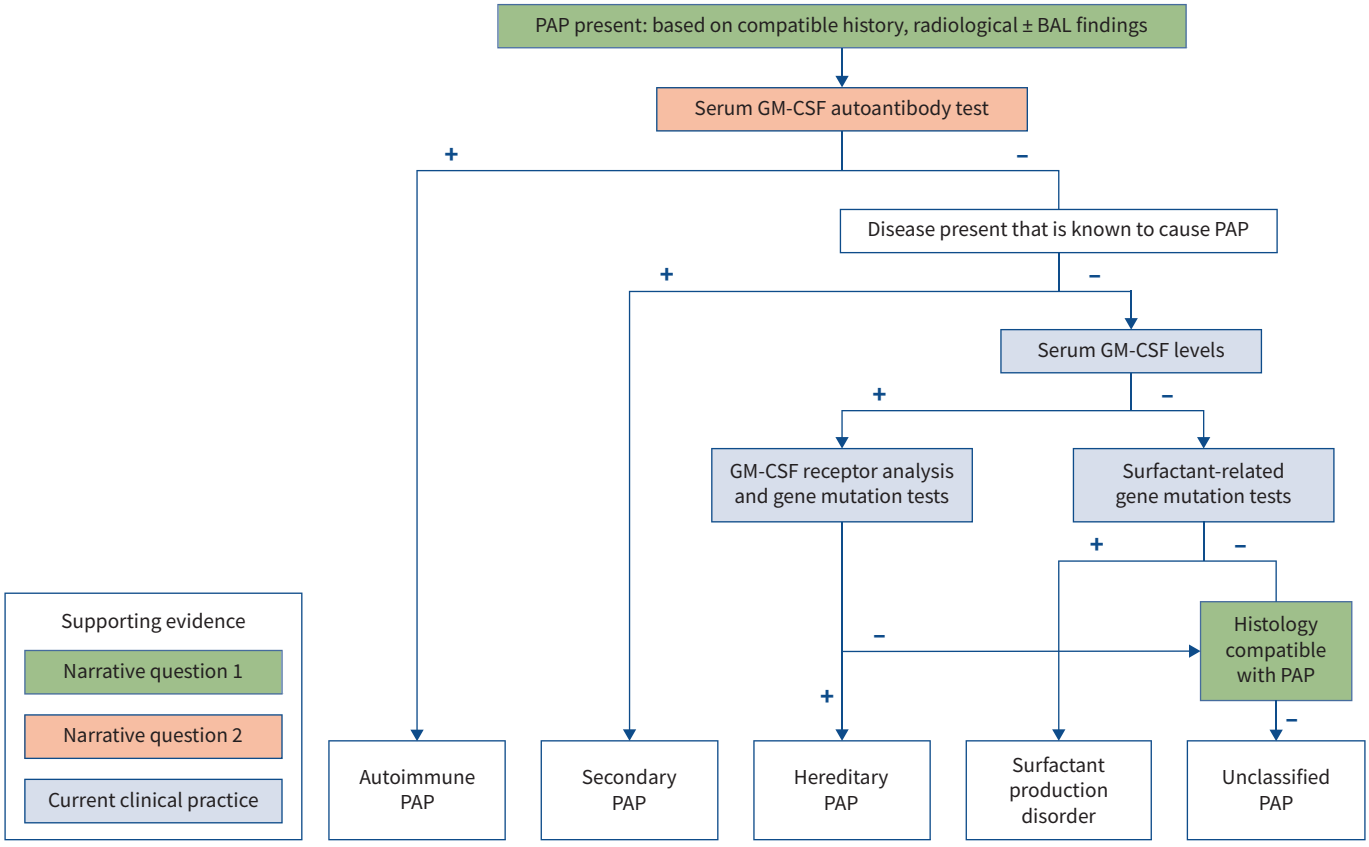

FIGURE 2 Algorithm for the differential diagnosis of pulmonary alveolar proteinosis (PAP). The presence of PAP is suspected when typical radiological findings and compatible history with or without bronchoalveolar lavage (BAL) findings. Granulocyte–macrophage colony-stimulating factor (GM-CSF) autoantibody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

stains PAS-positive; tubular myelin-like lamellar bodies are seen on electron microscopy [22]. Bonella *et al.* [23] reported on 70 patients where BAL was performed in 83%. In a study of 150 patients (86 with aPAP), Azuma *et al.* [24] reported diagnostic yields of 90.7% (78 out of 86) for BAL, 81.4% (70 out of 86) for transbronchial biopsy and 98.8% (85 out of 86) for the combination. In children, the yield of BAL to diagnose PAP is good; Enaud *et al.* [25] reported that the diagnosis was made by BALF examination for 15 children.

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

Practical considerations

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

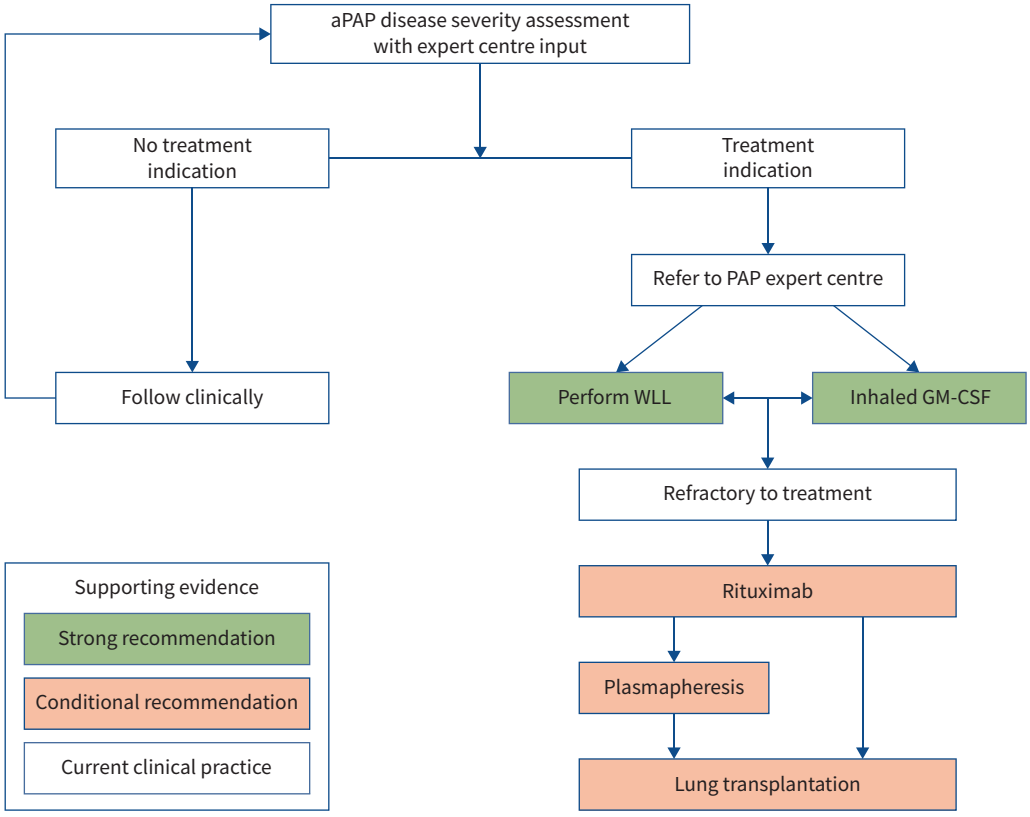

FIGURE 3 Hierarchy of treatments in autoimmune pulmonary alveolar proteinosis (aPAP). Treatment is indicated in patients with active or worsening disease. The appropriateness of treatment should be based on the degree of impairment of lung function, computed tomography (CT) imaging changes, blood oxygenation and symptoms. The treatment hierarchy was developed based on consensus among the Task Force panel members that was informed by 1) the strength of recommendations in PICO questions 3–7, with a focus on the potential benefits, risks and resources required for the corresponding interventions, 2) the certainty of evidence supporting those PICO questions, and 3) current clinical practice. Depending on immediacy of treatment need, either whole lung lavage (WLL) or inhaled granulocyte–macrophage colony-stimulating factor (GM-CSF) should be offered as first-line therapy (*Strong recommendation*). If these fail to show sustained benefit or in life-threatening respiratory failure, rituximab or plasmapheresis may be considered (*Conditional recommendations*). Lung transplantation remains an option for refractory cases (*Conditional recommendation*). The hierarchy algorithm is colour-coded based on the evidence supporting each step (see key).

Narrative question 1b

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

Recommendation

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

Justification of recommendations

The justification for the conditional recommendations is based on the known risk of side-effects and the perceived low benefit of a clear diagnosis from this invasive test. Rosen *et al.* [29] first described the lung histology in PAP and found preserved interalveolar septa with lipoproteinaceous material filling the alveoli and some bronchioles. Examination of surgical lung biopsies demonstrated preserved lung parenchyma with peribronchial lymphocytic infiltrations and alveoli filled with macrophages and amorphic eosinophilic PAS-positive material [30, 31]. Immunohistochemical staining of this material confirmed surfactant protein [30]. Lung biopsy was previously routinely used for diagnosis of PAP, although is not necessary in every patient [30]. Inoue *et al.* [2] reported that lung biopsy confirmed the diagnosis of PAP in 102 out of 223

cases. Where biopsy is needed, some case series have shown increasing use of transbronchial biopsy [24, 32–34] with a diagnostic yield of 81.4% [24]. Other studies reported higher use of surgical biopsy [21, 35, 36] and there are limited reports on the use of transbronchial cryobiopsy for diagnosing PAP [37].

While biopsy was previously considered the gold standard for diagnosing PAP, histological examination may also fail to identify the presence of PAP syndrome as seen in a study from the US National PAP Registry where histology was non-diagnostic in 28% of cases because of patchy involvement [35]. The authors concluded that any lung biopsy should only be performed in the rare situations in which the cause of PAP remains uncertain after completing BAL, non-invasive serological, blood-based and genetic tests [35].

Practical considerations

Lung biopsy is an invasive technique that may fail to diagnose PAP due to sampling error, has known risk of complications and a mortality risk [38]. Some hospitals do not have access to services providing lung biopsies. Patient representatives expressed a preference for a test that allowed for a quick diagnosis without the need for more invasive interventions. If lung biopsy is considered, benefits and limitations of the least invasive procedure should be discussed with patients, based on benefit/risk assessment and an expert PAP centre.

Narrative question 2

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

Recommendation

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

Summary of evidence

A systematic search of the available evidence revealed a large observational study comprising 248 patients [2], three methodology papers [39–41] and multiple real-world observational studies [4, 23, 30, 35, 42] focused on the use of GM-CSF autoantibody testing in PAP. Taken together, these studies established that GM-CSF autoantibodies can be measured in an objective and reproducible manner with a high accuracy for a diagnosis of aPAP, with a level of $\geqslant 10.2\ \mu g \cdot mL^{-1}$ the threshold of individual laboratory references (supplementary material) [4, 39, 41]. The largest study describes the use of GM-CSF autoantibody testing in 248 patients with a lung biopsy confirming a diagnosis of PAP [2]. Of this cohort, 89.9% of the patients had no underlying condition or cause to explain why they developed PAP and subsequently all these patients had elevated GM-CSF autoantibody levels [2]. In another observational study [23], GM-CSF autoantibody levels were described in 70 patients with PAP and were positive in the 64 individuals who had "idiopathic" PAP.

Justification of recommendations

The certainty of the available evidence has been ranked moderate despite the high sensitivity, specificity and reproducibility of GM-CSF autoantibody testing and its successful use in real-world cohorts [2, 4, 23, 35, 39, 41].

GM-CSF autoantibodies have been determined to be pathogenic of aPAP. Early data showed that GM-CSF-deficient mice were found to accumulate surfactant in the lungs and cause a PAP-like disease [43, 44], and GM-CSF autoantibodies were found in BALF from patients with what was known at the time as "idiopathic" PAP [40, 45]. It was also demonstrated that GM-CSF autoantibodies reproduced the molecular, cellular and histopathological features of PAP in healthy primates, demonstrating that GM-CSF autoantibodies directly cause PAP [46, 47]. GM-CSF autoantibody testing in the form of a simple blood test is pathognomonic for the diagnosis of aPAP, which accounts for almost 90% of all cases of PAP. More recently, studies have shown that a combination of GM-CSF antibody testing and genetic testing for hereditary causes can achieve a diagnosis in 95% of patients without a biopsy [41, 48, 49]. In these scenarios, this testing precludes the need for invasive lung biopsy. As further evidence of GM-CSF autoantibodies being the main mechanism of disease in aPAP, treatments acting on this specific mechanism such as inhaled GM-CSF and rituximab have successfully been used to treat this disease. This supports the testing of GM-CSF autoantibodies in all suspected patients with PAP. This non-invasive test with minimal risk outweighs the risk of not testing for aPAP.

Practical considerations

It is important to ensure that the appropriate test is performed to assess levels of GM-CSF antibody titres, and not just the presence of antibodies alone. A positive or negative antibody test is insufficient to

diagnose aPAP. Concentration should be reported, and this is best performed in experienced laboratories (supplementary material). All cases should be referred or discussed with a recognised PAP centre to get advice on which laboratory to test in and appropriate interpretation of results, especially before proceeding to more invasive procedures.

PICO question 3

In patients with clinical symptoms and/or functional impairment due to PAP should WLL be used versus *no WLL?*

Recommendation

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

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

Summary of evidence

Since WLL was first performed in 1964, it has been the most common treatment for patients with PAP [50]. There are no specific guidelines for the procedure itself and indications to perform a WLL vary between centres [51]. Briefly, WLL is done under general anaesthesia and intubation is performed using a double-lumen endotracheal tube to ventilate one lung while washing the other with several litres of saline (supplementary material) [51–53]. The main indications for WLL were decline in lung function and/or resting P_{aO_2} and an increase in respiratory symptoms or parenchymal abnormalities on CT. The most common complications reported were fever (18%), pneumonia (5%), fluid leakage (4%) and pneumothorax (0.8%). Extracorporeal membrane oxygenation (ECMO) can be used to support severely ill PAP patients undergoing WLL, as anecdotally reported [54].

Systematic searches identified 26 retrospective case series each describing five or more patients who had at least one unilateral or bilateral WLL (supplementary material). The median (interquartile range) study population in the 26 selected studies was 14 (8–21) patients. 20 series included adults only, five included both children and adults, and one study described the experience in children alone. Effects in children seemed similar to those observed in adults.

There was low certainty evidence suggesting that WLL improves respiratory symptoms when compared to pre-WLL symptom burden. Although we were not able to pool data from all of the included studies due to limitations, six of the 10 studies reporting on symptoms showed a moderate or significant symptomatic improvement in all participants [55–60], while the remaining four studies reported symptomatic improvement in 68–90% of participants [16, 17, 61, 62]. Two studies measuring exercise capacity reported increases in walking distance of 101 (95% CI 66.35–136.05) m in the 6-min walk test (6MWT) and 417 (95% CI 235–598) m using a treadmill. The certainty of evidence was low and very low, respectively. There was low certainty evidence to suggest an improvement in P_{aO_2} within 1 month of WLL (20.07 (95% CI 9.54–30.60) mmHg; I^2=92%) and within months to years of WLL (13.98 (95% CI 10.15–17.80) mmHg; I^2=35%). Moreover, a trend towards improved AaD_{O_2} was observed post-WLL (−14.87 (95% CI −32.44–2.70) mmHg; I^2=16%; very low certainty), with a clear improvement at longer follow-up (−21.33 (95% CI −26.99– −15.66) mmHg; I^2=11%; low certainty). No clear improvement was observed in FVC at short (8.54% (95% CI −8.22–25.29%); I^2=96%) or longer follow-up (5.43% (95% CI −0.67–11.53%)); low certainty of evidence.

Justification of recommendations

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

Practical considerations

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

PICO question 4

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

Recommendation

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

Summary of evidence

Systematic searches revealed three RCTs [12, 13, 63], one comparative observational study and seven observational, non-comparative studies on exogenous GM-CSF for patients with confirmed aPAP [15, 64–70]. All studies included adult patients with aPAP confirmed by the presence of high GM-CSF autoantibody titres. In the PAGE trial [12], 64 patients with mild-to-moderate aPAP were randomised to intermittent inhaled GM-CSF (sargramostim 125 µg twice daily every other week) or placebo for 25 weeks. Patients who underwent WLL within the previous 6 months or those who had severe disease (P_{aO_2} <50 mmHg) were excluded. In the IMPALA trial [13], 138 patients were randomised to continuous inhaled GM-CSF (molgramostim 300 µg once daily) or intermittent GM-CSF (300 µg once daily every other week) or placebo for 24 weeks. The 24-week intervention period was followed by an open-label treatment extension period with intermittent treatment. Patients who underwent WLL within the previous month were excluded. In an open-label RCT [63], 36 patients were randomised to intermittent inhaled GM-CSF (sargramostim 150 µg twice daily every other week for 3 months, then 150 µg once daily every other week for 3 months) or placebo for 26 weeks. Patients who had undergone WLL in the 3 months prior were excluded. The aforementioned RCTs were the main source of evidence, and data were pooled for intermittent, inhaled GM-CSF at ∼6 months after treatment initiation. Evidence suggests that compared to placebo, intermittent, inhaled GM-CSF reduces AaD_{O_2} with a mean difference (MD) of −4.36 (95% CI −7.71–1.01) mmHg, and improves P_{aO_2} with a MD of 4.47 (95% CI 1.16–7.78) mmHg and D_{LCO} with an absolute change (MD) of 4.05% (95% CI 0.23–7.88%). Further evidence is provided for either beneficial or no beneficial effects regarding 6MWT distance (MD 14.53 (95% CI −17.5–46.6) m), VC or FVC (MD 2.08% (95% CI −0.6–4.8%)), lung density in HRCT (MD −20.82 (95% CI −48.7–7.0) HU) and symptoms when measured by the St George's Respiratory Questionnaire symptoms domain (MD −6.94 (95% CI −19.2–5.3) points). The PAGE trial also assessed symptoms by measuring COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) Dyspnoea scale scores [15]. CAT was estimated to be higher in those treated with GM-CSF (MD 3.91 (95% CI 0.44–7.38) points) and mMRC was estimated to be lower (MD −0.4 (95% CI −0.7– −0.2) points). Trivial, adverse events were reported [12, 13, 63]. No mortality events were observed in any of the trials.

Eight observational studies with a total of 156 patients evaluating either inhaled [15, 65, 67, 69, 70] or subcutaneous [64, 66, 68] GM-CSF were included. In 2010, the first prospective, multicentre, phase II trial was published, examining 39 aPAP patients with P_{aO_2} <75 mmHg. The patients sequentially received a 12-week high-dose therapy with inhaled GM-CSF (sargramostim 250 µg for 8 days, no treatment for 6 days), followed by a 12-week low-dose therapy (125 µg for 4 days, no treatment for 10 days) and a follow-up period of 52 weeks [15]. Individuals were excluded if they had undergone WLL within 6 months prior to enrolment. The study demonstrated that the overall response rate was 62% at 6 months, response being defined as reduction in AaD_{O_2} by ⩾10 mmHg at the end of the low-dose period; the response was maintained in 83% of patients for 1 year without the need for additional therapy and treatment was safe [15]. Four years later, the long-term effects of intermittent inhaled GM-CSF during a 30-month observation period were reported in the same population [15, 70]. There was sustained remission of PAP in >50% of cases [70]. In 2014, a case series of six patients with PAP also showed promising long-term results by the application of the "as far as it takes protocol", minimising both disease burden and treatment costs in safety [67]. Finally, an observational study compared WLL alone with a combination of WLL followed by inhaled GM-CSF for 3 months in a total of 33 patients with severe aPAP [69]. The

GM-CSF/WLL group had significantly faster functional, exercise capacity and radiological improvement as well as reduction in the need for WLL compared with the WLL-alone group [69]. Additional studies include two case series in adult patients [71, 72] as well as four case series in children and young adolescents with documented aPAP (supplementary material) [73–76]. Paediatric studies reported beneficial effects in five out of seven children and young adolescents treated with inhaled GM-CSF either alone (n=1) or in combination with WLL (n=4).

Justification of recommendations

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

Practical considerations

GM-CSF administration may prevent or delay the next WLL, an expensive intervention that requires hospital admission and general anaesthesia. Patients with PAP often require regular WLL, sometimes monthly. The sustained benefits of inhaled GM-CSF for longer periods might minimise the need for repeated WLL, and the costs related to this procedure [63, 67, 70]. Serious adverse events were not more common in the GM-CSF arms compared to the placebo arms in the included RCTs. Treatment can therefore be considered safe and non-invasive, and we believe that acceptability will be high. Treatment with inhaled GM-CSF can potentially be administered at home or at local health institutions, which increases equity.

PICO question 5

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

Recommendation

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

Summary of evidence

A systematic search revealed a single-arm interventional study involving 10 patients [77], a retrospective case series of 13 patients [78] and seven case reports [79–85]. All studies and case reports evaluated adults with aPAP. Most patients included in the studies had undergone WLL and/or GM-CSF treatment prior to recruitment. Studies by both Kavuru *et al.* [77] and Soyez *et al.* [78] compared the clinical status of patients 6–12 months after rituximab treatment to baseline, hence the data were pooled together. Participants in both studies received two doses of rituximab 1000 mg, administered 15 days apart. One patient in the observational study only received a single dose, while three received an additional, maintenance dose. There was very low certainty of evidence suggesting that rituximab may reduce the AaD_{O_2} (MD −11.83 (95% CI −23.76–0.10) mmHg) and improve the partial concentration of oxygen measured on room air (MD 11.94 (95% CI −4.17–28.05) mmHg). In addition, very low certainty evidence suggests no substantial impact of rituximab on D_{LCO} (MD 15.64 (95% CI 9.08–22.21) % pred; I^2=0%), FVC (MD 2.65 (95% CI −4.17–9.48) % pred) or 6MWT distance (MD 19 (95% CI −93.47–131.47) m) [77, 78]. Kavuru *et al.* [77] reported that four out of seven patients that were observed for a mean±SD of 32±6 months did not require WLL. The remaining three patients required one WLL each during follow-up. Soyez *et al.* [78] reported four out of 11 patients showed significant improvement at 12 months compared to baseline. Improvement was defined as a decrease in the AaD_{O_2} by ⩾10 mmHg. Kavuru *et al.* [77] also reported a significant improvement in the HRCT scores (p=0.027), which was, however, not observed by Soyez *et al.* [78]. No deaths or serious adverse events were observed in these studies. However, the results should be interpreted carefully, as the sample size of the included studies was limited, and they were not controlled. Five out of seven case reports documented a clinically relevant improvement at various time-points after rituximab initiation (3–12 months) [79–82, 84]. Benefits included better oxygenation, improved exercise capacity, reduction in frequency of WLL and/or improvement in pulmonary function. Only one of the case reports addressed safety and it did not report any serious adverse events [79]. Two out of seven cases (28.6%) did not gain any benefits from rituximab [83, 85].

Justification of recommendation

The certainty of the available evidence is very low for all outcomes. There was very low certainty evidence suggesting that rituximab may reduce AaD_{O_2}, D_{LCO} or 6MWT distance. There are serious concerns around the methodological limitations of these small single-arm uncontrolled studies.

Practical considerations

While the safety of rituximab has not been adequately assessed in patients with aPAP, ample data are available from other disease areas. More specifically, the safety profile of rituximab at a similar dose (two doses of 1000 mg) in adults has been evaluated in more detail in a Cochrane review evaluating rituximab in rheumatoid arthritis (see supplementary material for details of dosing) [86]. The addition of rituximab was not associated with increased risk of serious adverse events, at 48–56 weeks of follow-up or at 104 weeks of follow-up. Rituximab was associated with a trend of increased discontinuation due to adverse events during the first 6 months; this trend disappeared at 1 year of follow-up and was reverted at longer follow-up. In children, the safety of rituximab at a dose of one to four infusions of 375 $mg \cdot m^{-2}$ has been assessed in more detail in a meta-analysis evaluating rituximab for childhood steroid-dependent nephrotic syndrome [87]. This meta-analysis did not reveal any increase in the risk of infections, or cardiovascular disease events, but found a trend for increased risk of infusion reactions. The authors reported that the rate of severe allergic reactions in children was very low [87].

PICO question 6

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

Recommendation

We suggest the use of plasmapheresis for patients with confirmed autoimmune PAP who remain significantly symptomatic, requiring supplemental oxygen or two or more WLLs over a period of a year, despite receiving exogenous GM-CSF and rituximab, or having previously failed these treatments. (Conditional recommendation, very low certainty of evidence.)

Summary of evidence

The systematic search included only nine case reports [75, 83, 84, 88–93] and no RCTs or observational studies on the role of plasmapheresis in aPAP. Only one case report described the use of plasmapheresis in an adolescent with aPAP, while all other cases were adults. The duration of the disease was variable: from 4 to 120 months (median 12 months). One of the patients was not tested for GM-CSF autoantibodies [92]. Patients all presented with severe disease: all but one was receiving supplemental oxygen therapy up to 8 $L \cdot min^{-1}$ and one patient was intubated receiving 60–75% inspiratory oxygen fraction. All had persisting symptoms and had undergone several WLLs prior to treatment with plasmapheresis. Four of nine patients had WLL and exogenous GM-CSF and one had WLL, exogenous GM-CSF and rituximab prior to plasmapheresis. Thus, plasmapheresis was used in patients with severe PAP, refractory to other treatments. No relevant clinical benefits were observed in three of the reported cases [83, 89, 93]. Yu *et al.* [92] reported improved clinical symptoms and radiological findings, which were, however, short-lived as relapse was observed 5 months later. Luisetti *et al.* [91] reported a reduced frequency of WLL after plasmapheresis, but no clear improvement in symptoms after plasmapheresis. Finally, four cases reported clear improvement in symptoms [75, 84, 88, 90], oxygenation, radiological findings and/or pulmonary function [75, 89]. A clear reduction in GM-CSF antibody titres was reported in five out of nine cases [77, 84, 88, 91]. Rituximab was also administered after completion of plasmapheresis in two case reports, which only reported effects after both treatments were administered [75, 84]. It appears that higher intensity plasmapheresis regimens successfully suppress GM-CSF autoantibodies and may offer clinical benefit.

Justification of recommendation

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

Practical considerations

The safety of plasmapheresis was evaluated in detail in a Cochrane review of the effectiveness of plasmapheresis for Guillain–Barré disease [94]. Based on data from three trials totalling 556 participants, plasmapheresis did not increase the risk of infection (risk ratio 0.91, 95% CI 0.73–1.13), blood pressure instability (risk ratio 0.88, 95% CI 0.64–1.22), cardiac arrhythmias (risk ratio 0.75, 95% CI 0.56–1.00) or pulmonary embolism (risk ratio 1.01, 95% CI 0.26–4.00). However, it should be noted that the included studies employed two to six sessions of plasmapheresis, a lower number compared to those

proposed for aPAP. The mortality associated with plasmapheresis has been estimated to be 0.05%, based on a systematic review meta-analysis of more than 15 500 patients, mainly adults [95]. The complications of over 4500 sessions of plasmapheresis in 593 children with neurological disease have been summarised in a narrative review that concluded that the intervention is well-tolerated and associated with adverse events that can be anticipated and avoided [96]. Complications were reported in 15% of plasmapheresis sessions and 70% of children. However, life-threatening complications were limited to 0.4% of treatment sessions and 2.4% of children. The patient representatives consider that potential prevention of WLL and improvement in the hypoxia may be considered important by patients with aPAP that is refractory to treatment and associated with a significant disease burden.

PICO question 7

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

Recommendation

We suggest lung transplantation for patients with PAP progressing despite WLL and/or pharmacological treatment, who fulfil the International Society for Heart and Lung Transplantation (ISHLT) criteria [97] for patients with interstitial lung disease. (Conditional recommendation, very low certainty of evidence.)

Summary of evidence

Data regarding lung transplantation in patients with PAP is derived from 14 individual case reports, nine adults and five children. Causes of PAP included graft *versus* host disease (two cases [98, 99]), aPAP (nine cases [100–103]), hereditary PAP (two cases [104, 105]) and lysinuric protein intolerance (*SLC7A7* mutation, one case [106]). Causes were not reported in five cases [107–110]. Median (range) duration of follow-up was 3 (0.2–7) years. Two patients died: one 4 years after lung transplantation in the context of recurrence of PAP, fungal infection and bronchiolitis obliterans syndrome (BOS) [105], and one 2 years after lung transplantation in the context of recurrence of PAP [106]. For the remaining patients with outcome data (n=11), the desirable effects of lung transplantation were quantified based on durable wean from oxygen, lung function and quality of life (QoL) at last follow-up. Nine patients were weaned from oxygen after transplantation, one was still on home oxygen and data were missing for one. Lung function among patients alive at last follow-up was reported to be improved in five, stable in one and not available in five. The reported QoL among alive patients was good in 10 out of 11. Among the 13 patients with post-lung transplantation data available, adverse events were mainly infections (nine out of 13), post-transplant lymphoproliferative disease was observed in two cases [102, 109] and BOS in two cases [105, 108]. Graft rejection was not reported. Recurrence of PAP on the transplant was reported in three cases. In these patients, the cause of the PAP was *CSF2RB* mutation in one, *SLC7A7* mutations in one and unknown in the last case. 12 additional paediatric cases were recorded in a report on the outcome of 190 children after lung transplantation; no causes of PAP and individual patient data were available. Survival and complications were not different from transplant for other diseases [111]. A query was made at the registry of the ISHLT. Of 101 patients reported by the ISHLT with different forms of PAP and lung transplant, 43 had died at the end of the observation period. In none of the patients was the diagnosis "Graft Failure: Recurrent Disease" noted. Thus, no relapses of PAP in the transplanted patients were noted leading to graft failure.

Justification of recommendation

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

Practical considerations

In treatment-refractory PAP, with or without pulmonary fibrosis and likely death within a few years, lung transplant associated with lifelong medication and medical treatment/surveillance is an alternative that can improve QoL [112]. Indeed, many patients consider lung transplantation for palliation of symptoms and improvement of QoL even when extended survival is not assured [112]. However, there are always few people who reject an offer of transplantation and wish palliative care [113]. A scoping review identified 28 studies in adults and made cost–utility estimates of lung transplantation *versus* waitlist, from the healthcare payer perspective. For a time-horizon of at least 10 years, costs ranged between USD 42 459 and 154 051 per quality-adjusted life-year [114]. The costs of care for patients with end-stage lung disease and chronic respiratory insufficiency should be balanced with the costs of care of hospitalisation for lung transplantation including stays in surgery and intensive care unit and lifelong costs for medications and care [114].

In patients with PAP progressing despite WLL and/or pharmacological treatment, an important issue is to estimate the risk of recurrence of PAP in the donor lung(s). However, it is not yet known if there is a correlation between the risk of disease recurrence and cause of PAP. In aPAP, the risk of recurrence exists as the production of GM-CSF autoantibodies may persist after lung transplantation. This might be balanced with the possible effect of immunosuppressive treatments required after organ transplantation on autoimmune processes. In genetically caused PAP, the replacement of donor macrophages in the transplanted lung by the host macrophages of patients with genetically caused PAP may increase recurrence risk of PAP in the donor lungs. Fortunately, the persistence of donor macrophages within the lungs has been reported in several cases with follow-up durations of up to 3.5 years post-lung transplantation [115]. Currently, the risk of recurrence of PAP on the graft is a difficult issue to address and not a contraindication for lung transplantation. Some rare genetically caused PAP (*CSF2RA* or *CSF2RB* defects, *OAS1* defects, *etc.*) may be treated with bone marrow transplant (BMT), if the lung has no fibrotic non-reversible damage (see supplementary material for specific details). In hereditary PAP due to mutations in the *CSF2RA* or *CSF2RB* genes and progressive PAP progressing despite all treatments, another theoretical possibility would be to consider the combination of lung transplantation and BMT.

Treatment hierarchy

Treatment is indicated in patients with active or worsening disease, as defined earlier. The appropriateness of treatment should be based on the degree of impairment of lung function, CT imaging changes, blood oxygenation and QoL. If no respiratory failure or life-threatening complications are present, and the patient still has an acceptable QoL, a "wait and see" strategy can be justified. In a survey of 20 PAP centres practising WLL, indications for WLL varied among centres [51]. Specific indications included an unspecified decline in lung function, a decline in resting P_{aO_2}, worsening of lung disease severity based on a comparison of serial chest imaging, decline in D_{LCO}, decline in FVC, decline in resting oxygen saturation on pulse oximetry or an increase in respiratory symptoms. The inclusion criteria in the RCTs of inhaled GM-CSF for aPAP were variable in terms of disease activity. In the PAGE trial, patients were eligible to receive treatment if P_{aO_2} was <70 mmHg after 5 min in the supine position while breathing ambient air or <75 mmHg and at least one symptom (cough, sputum production or exertional dyspnoea) was present [12]. In the IMPALA trial, inclusion criteria were stable or progressive aPAP during a minimum period of 2 months prior to the baseline visit, P_{aO_2} <75 mmHg at rest or desaturation of >4% in a 6MWT and AaD_{O_2} ⩾25 mmHg [13]. The Task Force panel recognises the need for more research in this field and of an international consensus on treatment indication criteria. The proposed hierarchy of treatment in aPAP, illustrated in figure 3, is based on consensus among the panel members that was informed by 1) the strength of recommendations in PICO questions 3–7, with a focus on the potential benefits, risks and resources required for the corresponding interventions, 2) the certainty of evidence supporting those PICO questions, and 3) current clinical practice.

Treatment response

There are no standard criteria defining treatment response. Treatment goals in PAP are to achieve either disease regression or long-term disease stabilisation, without the need for repeated WLL. In the reports on the efficacy of WLL, changes in blood gas parameters and radiological improvement have been used to assess response [51, 116]. In RCTs of GM-CSF, AaD_{O_2} while breathing room air was chosen as the primary outcome, whereas improvements in D_{LCO} and HRCT infiltrates were secondary outcomes [12, 13]. The magnitude of improvement in these, and other, RCT outcomes has been reviewed by the Task Force and is outlined in the summary of evidence in PICO question 2. Changes in QoL and/or symptoms of patients with a diagnosis of PAP have been anecdotally reported in retrospective studies and RCTs of inhaled GM-CSF [12, 13], although these studies rely on respiratory questionnaires which are non-specific for PAP. Although several circulating biomarkers, *e.g.* KL-6, SP-D, lactate dehydrogenase, YKL-40 and tumour tissue antigens [23, 64, 117–122], seem to be promising for assessing treatment response, validation studies are needed. The Task Force panel recognises the usefulness of lung function tests and blood gas parameters to define treatment response but does not indicate specific thresholds of decline or improvement. Beside functional assessment, a careful evaluation of symptoms and radiological changes over an appropriate follow-up (⩾6 months) is suggested.

Refractory disease

Refractory PAP can be defined by persistence or worsening of respiratory symptoms, lung function or gas exchange impairment and HRCT infiltrates despite adequate treatment and after appropriate follow-up (~6 months). Post-interventional complications should be excluded as a reason of treatment failure. The need for repeated WLL over time and the reduction of the time interval between two consecutive WLLs have been used as indicators of unresponsiveness to treatment [13, 123], but the studies are too

heterogeneous to draw conclusions. The same is true for circulating and genetic biomarkers [124]. The Task Force panel suggests a careful and close evaluation of the patients after treatment, aimed at assessing disease activity and to exclude immediate or long-term treatment complications or concomitant diseases as causes of treatment failure.

Discussion

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

In terms of disease outcome, ∼7% of patients diagnosed with PAP have spontaneous remission and never require treatment [1]. In these guidelines, we propose that patients are treated in cases of respiratory failure, lung function impairment or symptoms leading to disrupted QoL. Despite increasing evidence for D_{LCO}, HRCT infiltrates and blood gas parameters as treatment indicators, the Task Force strongly suggests considering multiple aspects at once, including patient needs. This concept has become readily accepted in clinical practice at expert centres [124]. For most PAP patients, treatment with WLL translates into rapid improvement of symptoms, gas exchange and radiology [125]. However, the paucity of data does not allow conclusions to be drawn regarding the long-term effects of WLL [126]. Similarly, the evidence for effectiveness of treatment, especially in relation to QoL, is weak, since no validated instruments for PAP patients exist [124]. The Task Force was able to provide a positive recommendation for WLL in adult patients with aPAP, since most studies have focused on adult disease [51, 127, 128]. Nonetheless, the Task Force included special considerations for the management of PAP in children, based on small and mostly single-centre observational studies or case series.

Inhaled GM-CSF, the only treatment investigated in RCTs of adult aPAP patients, received a strong recommendation, whereas the certainty of evidence was graded as very low. Due to the heterogeneous end-points and trial design, a head-to-head comparison of molgramostim and sargramostim is currently not feasible [12, 13]. For the sake of completeness, we mention that sargramostim for inhalation 250 µg has recently been approved in Japan to treat aPAP [129]. Beside the need for further long-term data on the efficacy of inhaled GM-CSF, the Task Force underscores the unmet need of PAP-specific end-points and more standardised administration protocols for clinical routine and future clinical trials. Despite the results of a recent trial [127] examining whether WLL and inhaled GM-CSF should be combined into specific protocols with *add-on* or sequential administration, this remains a question relevant to future studies.

The Task Force emphasises that strong recommendations are made on several questions despite low certainty of evidence; however, this is based on the observed effects and feasibility of the intervention studied. These guidelines have several limitations. First, the diagnostic recommendations provided refer to an ideal situation in which all procedures or tests are available. Few centres offer GM-CSF antibody measurement, GM-CSF signalling assessment or genetic testing, and early referral to a PAP expertise centre or network is mandatory. Second, despite the efforts of the Task Force to provide definitions of disease severity and progression, as well as treatment indications, they mostly remain based on a case-by-case approach and expert opinion. Third, measurements of response to treatments are still too heterogeneous across observational studies and RCTs, so that a consensus on clinically meaningful outcomes and best end-points is urgently needed. Fourth, the hierarchy of treatments provided (figure 3) should be considered at the individual level, and treatment decision depends on several factors, including local availability and reimbursement policies. Finally, these guidelines do not make specific recommendations regarding supportive treatments such as oxygen supplementation or pulmonary rehabilitation. In conclusion, the Task Force identified areas where there is sufficient information to make informed recommendations based on current evidence and clinical experience. While great progress has been made in understanding the pathogenesis and clinical progression of PAP syndrome, many questions remain unanswered and several recommendations for future research were proposed by the Task Force (table 3). Obviously, many of the research topics require international collaboration, such as consensus reports and international registries.

TABLE 3 Future research needs

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

BAL: bronchoalveolar lavage; PAP: pulmonary alveolar proteinosis; MCID: minimum clinically important difference; WLL: whole lung lavage; GM-CSF: granulocyte–macrophage colony-stimulating factor; aPAP: autoimmune PAP.

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

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