Summary for clinicians: ERS guidelines on pulmonary alveolar proteinosis

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Shareable abstract (@ERSpublications)
Pulmonary alveolar proteinosis is a rare but potentially debilitating lung disease caused by accumulation of proteinaceous material within alveolar spaces. We summarise the recently published ERS guidelines and highlight the best clinical approach. https://bit.ly/3DhG887

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Abstract

Pulmonary alveolar proteinosis (PAP) is a rare lung disease caused by accumulation of surfactant in the alveoli, leading to debilitating respiratory symptoms and impaired gas exchange. The recent European Respiratory Society guidelines provide evidence-based recommendations for its diagnosis and management. Autoimmune PAP (aPAP) is the most common form, driven by granulocyte–macrophage colony-stimulating factor (GM-CSF) autoantibodies. Recommended diagnostic tools include bronchoalveolar lavage and quantitative GM-CSF antibody testing. Whole lung lavage and inhaled GM-CSF are first-line treatments for symptomatic or progressive aPAP. Rituximab, plasmapheresis, and lung transplantation are options for refractory disease. Referral to expert centres is advised for diagnostic and therapeutic guidance. This case-based summary for clinicians highlights the best clinical approach to patients with suspicion or confirmation of PAP.

Introduction

Why and how were the guidelines created

Pulmonary alveolar proteinosis (PAP) is a rare lung disease and managing patients with PAP can be challenging. Recently, there have been significant developments in the understanding of the PAP disease process, as well as in diagnostic techniques and therapies. World PAP experts convened in conjunction with the European Respiratory Society (ERS) resulting in the approval of a task force in 2021, charged with producing evidence-based recommendations for the diagnosis and management of PAP [1].

Recommendations were developed following the methodology proposed by the ERS guidance for developing Clinical Practice Guidelines and the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach [2, 3]. The final guideline addresses seven PICO (Patient, Intervention, Comparison, Outcome) questions in relation to the diagnosis and management of PAP. This document offers a concise summary of the key recommendations from the guidelines, serving as a quick-reference guide for clinicians. The discussion is structured around two clinical cases that illustrate complex decision-making in the management of patients with suspected or confirmed PAP, helping to apply the recommendations to clinical practice.

What is PAP

Pulmonary alveolar proteinosis, or PAP, is a rare clinical syndrome that is characterised by progressive diffuse intra-alveolar accumulation of surfactant. This results in foamy macrophages filling the alveolar

spaces. Patients present with respiratory symptoms such as cough and dyspnoea and are often hypoxaemic. The disease progresses to respiratory insufficiency or failure in some patients. Classic radiological findings include patchy ground glass opacification in a geographical distribution with interlobular septal thickening. PAP typically results from an autoimmune disease affecting surfactant clearance but can also occur secondary to other diseases where there are deficiencies in surfactant production [4].

Autoimmune PAP (a form of primary PAP) is the major focus of the guideline due to its greater prevalence as opposed to secondary or hereditary PAP. Primary PAP is characterised by abnormal granulocyte–macrophage colony-stimulating factor (GM-CSF) signalling which causes alveolar macrophage and neutrophil dysfunction. The most frequent cause is autoimmune PAP (aPAP) in which GM-CSF directed autoantibodies block this action leading to deficiency in surfactant clearance [5, 6].

Secondary PAP results from conditions that reduce the number and/or function of alveolar macrophages. Some of these are caused by mutations in the genes that are involved in surfactant metabolism or genes that encode surfactant, others are caused by occupational exposures and secondary diseases such as lymphoproliferative disorders [4].

Table 1 outlines the classification of PAP causing diseases.

PAP activity, severity and progression

The definitions of "disease activity", "disease severity" and "disease progression" were agreed upon by the task force (TF) panel using definitions used in published studies and clinical experience.

PAP is considered "active" in the presence of:

- Continuous or progressive symptom(s) of dyspnoea, cough, sputum production, chest pain and/or weight loss; and/or lung function decline in forced vital capacity (FVC) or diffusing capacity of carbon monoxide (D_{LCO}); and/or
- Hypoxaemia measured by arterial blood gas (arterial oxygen tension (P_{aO_2}), arterial oxygen saturation, alveolar–arterial oxygen tension difference (P_{A-aO_2})); and/or
- New or worsening PAP-characteristic infiltrates on high resolution computed tomography (HRCT), including but not limited to ground glass opacification and crazy paving.

TABLE 1 The classification of PAP-causing diseases [1]

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)
Secondary PAP (reduced alveolar macrophage function or number)	
Haematological conditions	Acute lymphocytic leukaemia, acute myeloid leukaemia, aplastic anaemia, chronic lymphocytic leukaemia, chronic myeloid leukaemia, myelodysplastic syndromes, multiple myeloma, lymphoma, Waldenstrom's macroglobulinaemia, GATA2 deficiency
Non-haematological malignancies	Adenocarcinoma, glioblastoma, melanoma
Immune deficiency and chronic inflammatory conditions	Acquired immunodeficiency syndrome, amyloidosis, Fanconi's syndrome, agammaglobulinaemia, juvenile dermatomyositis, renal tubular acidosis, severe combined immunodeficiency disease
Occupational and environmental exposures	Aluminium, cement, silica, titanium, indium, flour, fertiliser, sawdust, chlorine fumes, cleaning products, gasoline/petroleum fume, nitrogen dioxide, paint fumes, synthetic plastic fumes, varnish
Chronic infections	Cytomegalovirus, *Mycobacterium tuberculosis*, *Nocardia*, *Pneumocystis jirovecii*
Others including mutations affecting mononuclear phagocytes	Lysinuric protein intolerance, mutations in methionyl-tRNA synthetase
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 affect lung development

PAP: pulmonary alveolar proteinosis; GM-CSF: granulocyte–macrophage colony-stimulating factor; CSFR2A: colony stimulating factor 2 receptor alpha; CSF2RB: colony stimulating factor 2 receptor beta; GATA2: GATA binding protein 2; SFTPB: surfactant protein b; SFTPC: surfactant protein c; ABCA3: ATP-binding cassette subfamily A member 3; NKX2.1: NK2 homeobox 1.

The TF panel advise that other important differential diagnoses should be excluded such as respiratory infections, pulmonary embolism, pulmonary hypertension and congestive cardiac failure.

PAP "disease severity" was defined using the 2008 Inoue severity score, based on symptoms and P_{aO_2} levels [6, 7]. The TF panel agree that other scoring systems that include smoking status and HRCT findings are good options too [8]. The presence of an opportunistic infection was not deemed sufficient to be used as a sign of severity. All TF panel members agreed that a second opinion from a PAP reference centre was always advisable.

"Disease progression" should be considered when: [9–13]

- There are worsening respiratory symptoms; and/or
- Decline of lung function tests (D_{LCO}); and/or
- Onset or worsening of respiratory failure (including the need for oxygen) (P_{A-aO_2}); and/or
- Worsening PAP related computed tomography (CT) findings after careful exclusion of alternative causes, or pulmonary fibrosis (PF) [14]; and/or
- Reduction of time interval between the need for subsequent whole lung lavage procedures [12, 15].

The TF panel advise that disease progression should always be confirmed by HRCT. With respect to PF, the definition used in the 2022 American Thoracic Society/ERS guidelines for progressive PF [16] could be applied, although this has not been validated for PAP.

Reaching the diagnosis of PAP

Case 1

A 40-year-old male is referred to the outpatient clinic with a 6-month history of shortness of breath and dry cough. He has no past medical history. On examination, bilateral crackles are heard over the lungs and room air peripheral oxygen saturation is 97%. A chest radiograph showed bilateral shadows, and follow-up HRCT shows bilateral crazy paving opacities (figure 1). You suspect that the patient has a diagnosis of PAP.
As per the ERS PAP guidelines, the following approach should be taken when considering diagnostic studies:

- Bronchoalveolar lavage (BAL): recommended as part of the diagnosis work up in patients with suspected PAP (See narrative question 1a).
- Generally, do not perform lung biopsy: biopsy is not recommended in most cases. It could however be considered in a patient with an uncertain diagnosis after completing BAL, non-invasive serologic testing and genetic tests. The benefits and limitations of a biopsy should be adequately discussed with the patient by an expert PAP centre (See narrative question 1b).
- Appropriate GM-CSF antibody testing: such tests should assess GM-CSF titres, not only their presence or absence alone (see narrative question 2).

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).

The committee justifies this recommendation as BAL can achieve a clear diagnosis of PAP without the need for more invasive tests. Typical BAL fluid findings include increased cellularity with a predominance of lymphocytes and foamy macrophages with eosinophilic granules and PAS-positive amorphic material on cytology [17]. BAL can yield a diagnosis of PAP in up to 90% of adults with PAP [18], and has been recommended in previous guidelines on this technique [19, 20]. The test is also helpful in children [21].

BAL is not only helpful for diagnosis but can also exclude pulmonary infections. Pulmonary infections account for up to 20% of disease mortality often due to opportunistic organisms [22]. *Nocardia*, Mycobacteria and fungi are specifically referred to in the ERS PAP guidelines [23].

The guidelines note that BAL is generally safe, even in acutely ill patients. Adverse events can be minimised by the use of standardised protocol [19, 20].

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

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

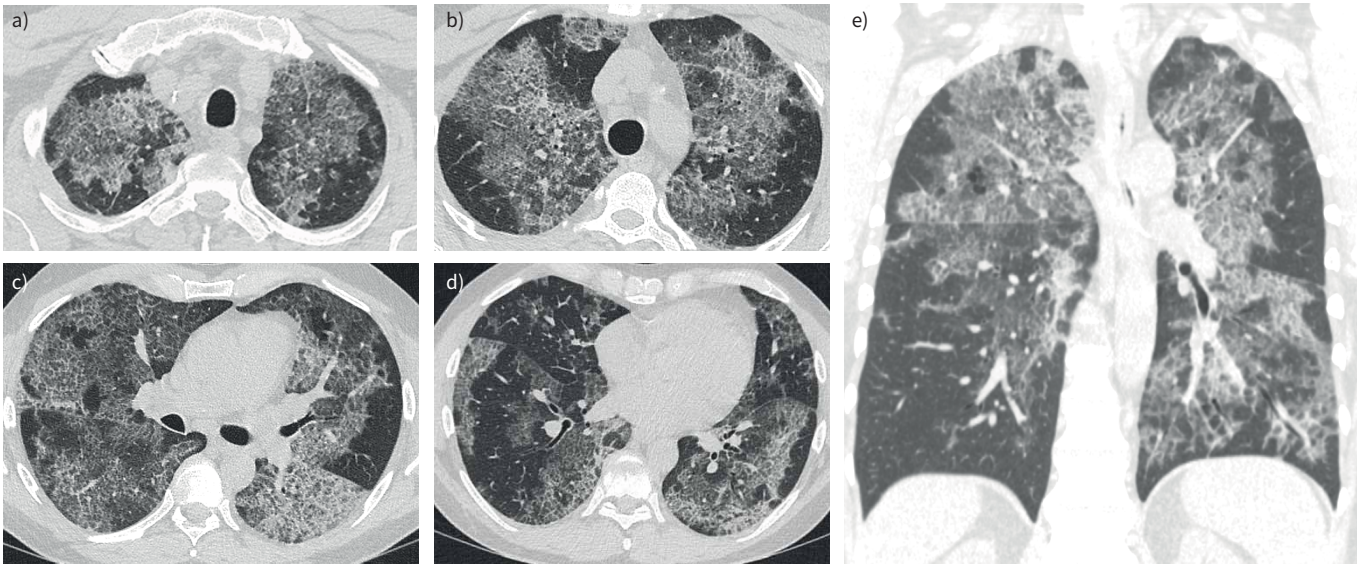

FIGURE 1 Computed tomography of the chest showing the radiographic findings in autoimmune pulmonary alveolar proteinosis in a 40-year-old man. Panels (a–d) show cross-sectional chest computed tomography (CT) images with ground glass opacification involving some but not all secondary lobules resulting in a distinctive "geographic" pattern. The distinctive pattern of interlobular septal thickening superimposed on ground glass opacification, often referred to as "crazy paving", is also demonstrated. There is relative sparing of the lower lobes of the lung. Panel e) shows a sagittal CT chest image of ground glass opacification in a patchy distribution with relative sparing of subpleural space and the costophrenic angles.

Surgical biopsy [24, 25], transbronchial biopsy [18] and transbronchial cryobiopsy [26] have all been described in the literature. However, lung biopsy by any of these methods is invasive and carries a risk of complications and mortality. Furthermore, non-diagnostic biopsies, possibly due to sampling errors, are common in PAP, reported in up to 28% of cases the US National PAP Registry [27]. The TF panel agree that lung biopsy can be considered in a patient where there is diagnostic uncertainty after completing BAL, non-invasive serologic testing and genetic tests, but the benefits and limitations should be adequately discussed with the patient by an expert PAP centre [27].

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).

GM-CSF antibody measurement is objective, reproducible and has high accuracy for diagnosing aPAP with a level of 10.2 $\mu g \cdot mL^{-1}$ or above the threshold of the individual laboratory references [28–30]. This test has been validated in real-world cohorts and consistently shown high sensitivity, specificity and reproducibility [6, 24, 27, 28, 31, 32]. The combined use of GM-CSF testing and genetic testing can reach a diagnosis of aPAP in 95% of patients without the need for biopsy (figure 2) [30, 33, 34].

The TF panel highlight that the test should be done in experienced laboratories that report GM-CSF antibody concentration results and not only their presence or absence alone. Patients should be referred or discussed with a recognised PAP centre to get advice on which laboratories to use and for appropriate interpretation of the results, especially before progressing to more invasive procedures.

Treatment of PAP

Case 2

A 34-year-old female is referred to your interstitial lung disease (ILD) centre with a 12-month history of progressive exertional dyspnoea. She is now out of breath on walking briskly. She was diagnosed with aPAP 3 years ago. The diagnosis was made by an ILD multidisciplinary team based on compatible imaging, BAL findings and raised GM-CSF antibodies of 26 $\mu g \cdot mL^{-1}$ (normal range $\leqslant 3$ $\mu g \cdot mL^{-1}$). On examination she is not in respiratory distress, has peripheral oxygen saturation of 92% on room air and crackles can be heard on auscultation. No clubbing is noted.

HRCT demonstrates worsening ground glass opacities throughout both lung fields with subpleural sparing when compared to CT thorax from 3 years before. Pulmonary function testing is remarkable for a FVC of 67% predicted, and a D_{LCO} of 57% predicted. Pulmonary function tests from 12 months prior showed FVC of 78% predicted and D_{LCO} of 64% predicted. You perform a careful assessment for infection, congestive cardiac failure, and other alternative explanations for the patient's symptoms, and you conclude that there is progression of aPAP.

What treatments should you consider for this patient (figure 3)?

- Bilateral whole lung lavage (WLL) if gas exchange is impaired AND symptoms OR lung function impairment are present. Get advice from an expert centre first (PICO Q3);
- Inhaled GM-CSF if symptomatic and confirmed aPAP. Get advice from an expert centre first (PICO Q4);
- Consider rituximab if they remain symptomatic, requiring supplemental oxygen, despite WLL or exogenous GM-CSF (PICO Q5);
- Consider plasmapheresis if they remain symptomatic, requiring high flow of supplemental oxygen ($\geqslant$4 L·min^{-1}), OR $\geqslant$2 WLL over a period of a year despite receiving exogenous GM-CSF and rituximab, OR having previously failed these treatments (PICO Q6);
- Consider referring for lung transplant if progressing despite WLL and/or pharmacological treatment AND fulfils the criteria of ILD from the ISHLT (PICO Q7).

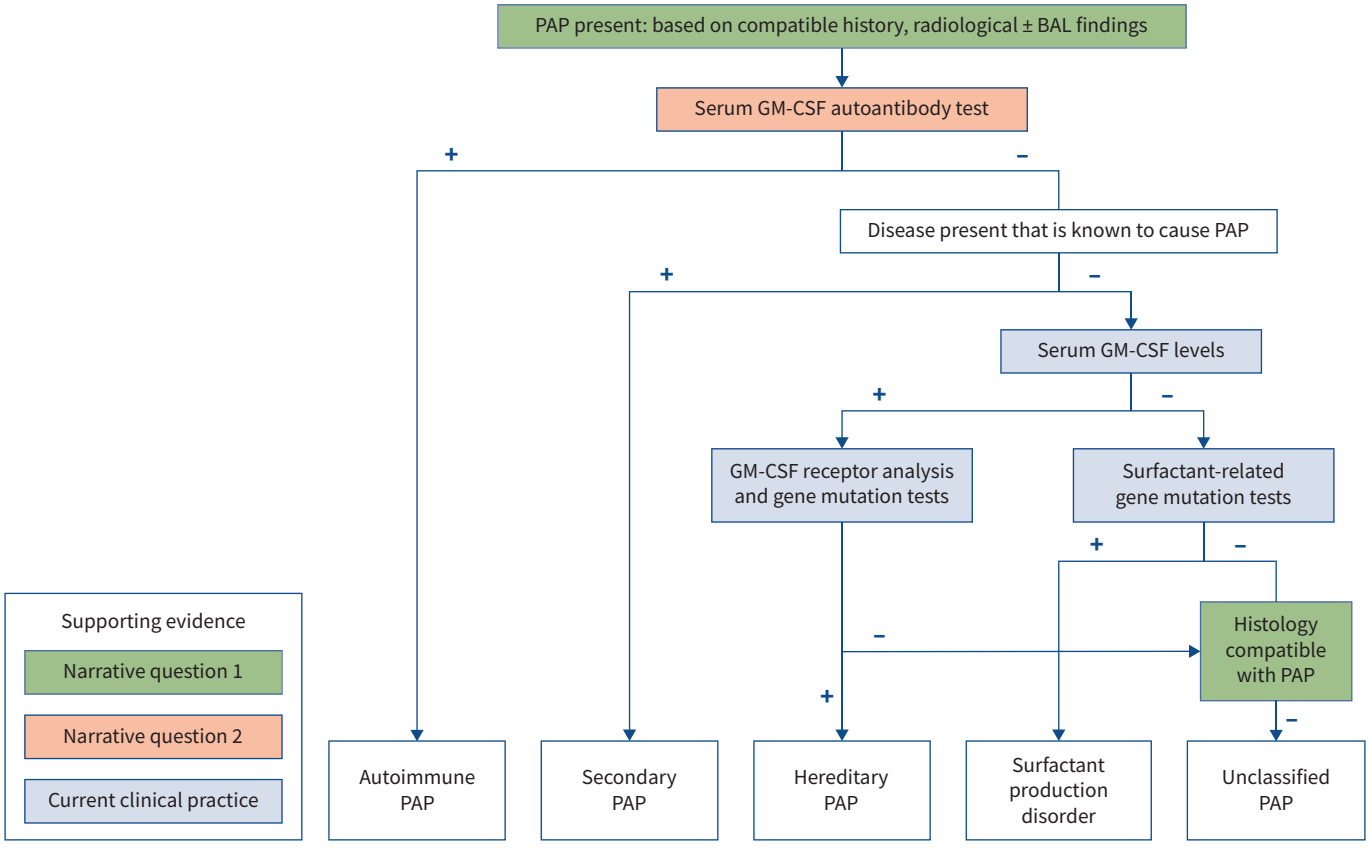

FIGURE 2 Recommended approach for working up a patient with suspected pulmonary alveolar proteinosis (PAP). PAP is suspected when there are typical radiological findings and a compatible history with or without described bronchoalveolar lavage (BAL) findings. Granulocyte–macrophage colony-stimulating factor (GM-CSF) antibody levels should be measured in an approved centre: raised levels >10.2 µg·mL^{-1} confirm the diagnosis of autoimmune PAP. Patients with normal GM-CSF antibody titres, or a negative test, and who have a disease known to cause PAP, can 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/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 a PAP-causing mutation is not identified, the patient is diagnosed with unclassified PAP and a lung biopsy may be needed to confirm diagnosis. Reproduced from [1] with permission.

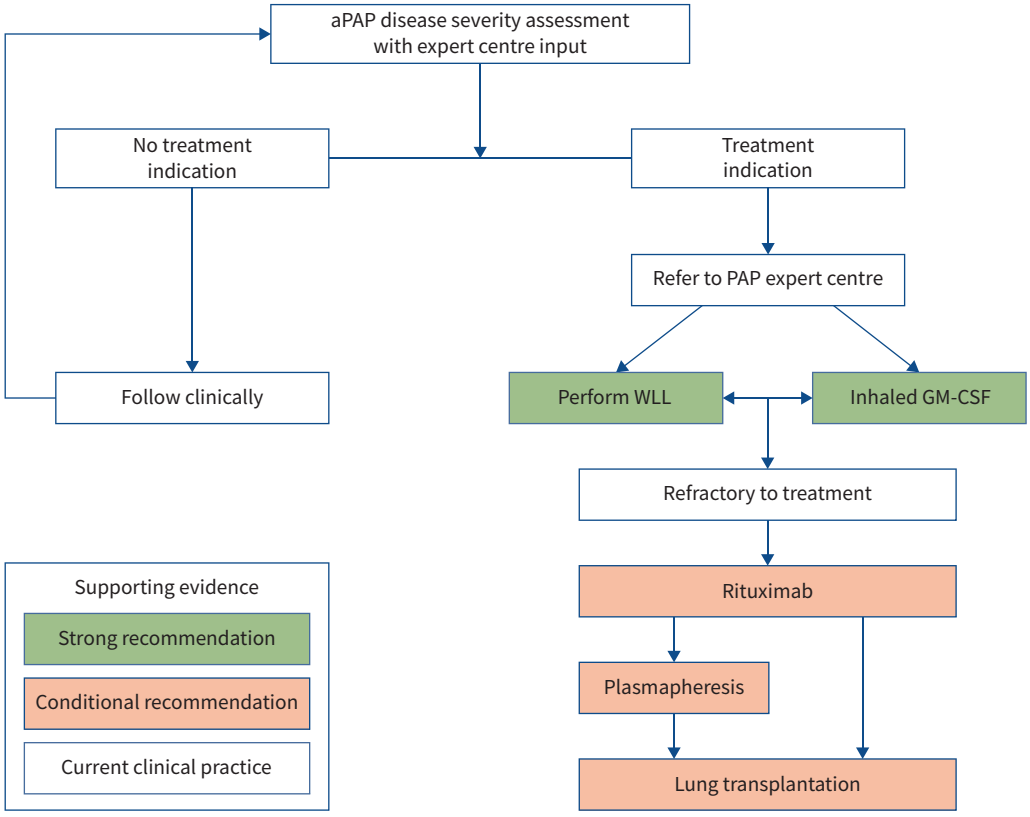

FIGURE 3 Algorithm to guide treatment decisions in patients with a diagnosis of autoimmune pulmonary alveolar proteinosis (aPAP). Treatment is indicated in patients with active or worsening disease. Whole lung lavage (WLL) and/or inhaled granulocyte–macrophage colony-stimulating factor (GM-CSF) should be offered as first line therapy (strong recommendation). If these fail to show sustained benefit or if there is life threatening respiratory failure, rituximab or plasmapheresis may be considered (conditional recommendations). Lung transplantation is an option for refractory cases (conditional recommendation). Reproduced from [1] with permission.

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 aPAP 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.

WLL is the most widely described and commonly used treatment for patients with PAP. WLL is performed under general anaesthesia with double lumen intubation, allowing for single lung ventilation while the other lung is washed with several litres of saline [35–37]. There is no standardised protocol for the procedure with respect to volume of saline nor the specifics of the washing technique. The procedure is generally indicated for patients with a decline in lung function and/or decrease in resting P_{aO_2}, worsening respiratory symptoms and parenchymal abnormalities on the HRCT.

There are no reported randomised controlled trials (RCTs) on the effect of WLL on symptoms or pulmonary function tests of patients with a diagnosis of PAP, so the guideline recommendation is based on a systematic review of 26 case series. There was no significant improvement in FVC at short or long term follow up after WLL, but a significant symptomatic improvement was reported. Furthermore, improvements in walking distance, a suggestion of improvement of P_{aO_2} and a trend toward improvement on P_{A-aO_2} were also seen following WLL [1].

The TF panel recommend that the indication and choice of treatment for PAP should be discussed with an expert centre before proceeding. Some of the advantages of WLL include the fact that it can be performed as a stand-alone treatment with reasonable quick recovery. Disadvantages include the need for admission, costs, the possible need for travel to an expert centre and the risk of fever, pneumonia, fluid leakage and pneumothorax. Bilateral WLL rather than unilateral WLL is recommended as the disease affects both lungs in almost all cases [4].

PICO question 4: In patients with confirmed aPAP should exogenous GM-CSF be used versus *no exogenous GM-CSF?*

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

This recommendation is based on the results from three RCTs and eight non-interventional studies. All studies administered exogenous GM-CSF in adult patients with a diagnosis of aPAP as confirmed by high GM-CSF antibody titres.

With respect to the RCTs, the PAGE trial included 64 patients with mild to moderate aPAP randomised to intermittently inhaled sargramostim 125 µg twice daily every other week or placebo for 25 weeks [12]. This trial excluded those patients that had a P_{aO_2} of under 50 mmHg or that required WLL in the previous six months. The IMPALA trial randomised 138 patients to continuously inhaled molgramostim, intermittent molgramostim or placebo [13]. This was followed by an open-label extension period where patients received intermittent molgramostim. Subjects that required WLL in the previous six months were excluded. In the third, open-label RCT reported by Tian *et al.* [38], 36 patients were randomised to intermittent inhaled sargramostim or placebo for 26 weeks. Patients were excluded if they required WLL within the prior three months.

Pooled results from these trials showed that intermittent inhaled GM-CSF reduced P_{A-aO_2} (mean difference (MD) −4.36 mmHg, 95% CI −7.71; 1.01), improved P_{aO_2} (MD 4.47 mmHg, 95% CI 1.16; 7.78) and improved D_{LCO} (MD absolute change of 4.05%, 95% CI 0.23; 7.88) at 6 months compared to placebo. The side-effects from treatment were considered to be trivial. There was no reported mortality.

The observational studies assessed a total of 156 patients subjected to either inhaled or subcutaneous GM-CSF. These studies report on the short-term and long-term effects of GM-CSF and demonstrate a good overall response rate at both time periods. The combination of WLL followed by inhaled GM-CSF led to more rapid improvement in lung function, exercise capacity, imaging and reduced the need for repeat WLL in one study [39]. Observational studies looking at efficacy in the paediatric population demonstrate benefits in five of seven children and young adolescents treated with inhaled GM-CSF either alone or in conjunction with WLL.

An important consideration is that inhaled GM-CSF can prevent or delay the need for WLL, and this effect may be sustained for long periods of time [38, 40, 41]. Overall, treatment with GM-CSF was considered safe and non-invasive with the potential to be administered at home or at local health institutions.

PICO question 5: In patients with confirmed aPAP should rituximab be used versus *no immunosuppressive treatment?*

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

Rituximab is a chimeric murine/human monoclonal immunoglobulin G1 antibody that targets CD20 activity. The suggestion to use rituximab in the treatment of patients with confirmed aPAP is based on a systematic search compiling results from a single arm interventional study (n=10) [42], a case-series (n=8) [43] and seven additional case reports (n=7) [44–50]. Most of these patients had previous treatment with WLL and/or GM-CSF treatment. Patients in the referenced interventional study and case-series received two doses of 1000 mg of rituximab 15 days apart [42], and outcomes measured 6–12 months later. Pooled analysis suggest rituximab may improve P_{A-aO_2} (MD −11.83 mmHg, 95% CI −23.76, 0.10) and P_{aO_2} on room air (MD 11.94 mmHg; 95% CI −4.17, 28.05). There was also a suggestion of improvement in D_{LCO}, FVC and 6-minute walk test distance. The safety data showed no serious adverse events or deaths on these studies.

The TF panel emphasises that these results should be interpreted carefully as the referenced studies were not controlled, and the sample sizes were small. We reference previous large, high powered studies on the

use of rituximab in adults with rheumatoid arthritis [51] and in children with steroid-dependent nephrotic syndrome [52] to demonstrate the generally accepted safety of using rituximab in both adults and children respectively. Common adverse effects reported in these studies include rituximab-induced infusion reactions and infections.

PICO question 6: In patients with confirmed aPAP should plasmapheresis be used versus *no plasmapheresis?*

Recommendation: We suggest the use of plasmapheresis for patients with confirmed aPAP who remain symptomatic, requiring high flow of supplemental oxygen ($\geqslant 4$ L $\cdot$min^{-1}) or two or more WLL over a period of a year, despite receiving exogenous GM-CSF and rituximab, or having previously failed these treatments (conditional recommendation, very low certainty).

For this PICO question, there were no RCTs or observational studies available, so the suggestion is based on case reports (n=9), eight adults and one adolescent patient. Subjects had severe and refractory disease with persisting symptoms despite numerous WLLs. In eight of nine cases, patients had an oxygen requirement. Plasmapheresis was effective in four cases where symptom, oxygenation, radiological or lung function improvements were described. Treatment was partially effective in two patients and non-effective in the remaining three. In two of the cases where treatment response was described, patients were also receiving rituximab therapy [49, 53]. Most patients (five of nine) had a reduction in GM-CSF antibody titres after plasmapheresis. There was some evidence suggesting enhanced benefits with higher intensity plasmapheresis regimens, resulting in improvements on GM-CSF antibody titres or symptoms [48, 49, 53–55].

Plasmapheresis has been deemed to be safe for use in one study of 556 adults with a diagnosis of Guillain–Barré disease [56], with no increase in infection risk. A meta-analysis that included mostly adult patients showed a plasmapheresis-associated mortality of 0.05% [57]. In children, life-threatening complications were observed in 0.4% of sessions and 2.4% of children [58].

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 for patients with ILD (conditional recommendation, very low certainty of evidence).

There is limited evidence on the benefit of lung transplantation in PAP. Data was pooled from available case reports (n=14), nine on adults and five on children [59–68]. Cases were heterogenous with lung transplantation for aPAP in four of the described cases, PAP secondary to graft *versus* host disease in two cases, hereditary PAP in two cases and PAP due to lysinuric protein intolerance in the final case. The median follow-up was 3 years and two of these patients died following a recurrence of PAP. 11 patients had follow-up data. 10 out of 11 patients had good quality of life post-transplant. While oxygen independence is not a direct measure of transplantation success, it was possible to wean oxygen in nine of the 11 patients post transplantation.

A cohort of paediatric lung transplant included 12 cases of PAP, and the survival was similar to other causes [69]. The ISHLT registry have records of 101 patients that underwent lung transplantation for PAP; 43 of whom had died at the end of the observation period. There we no noted reports of “Graft failure: Recurrent disease”, suggesting disease recurrence post transplantation was uncommon, albeit this is observational data. Other adverse events included recurrent infections, post-transplant lymphoproliferative disease and bronchiolitis obliterans syndrome. There were no instances of graft rejection.

The TF panel recommendations around lung transplantation for PAP are based on the benefits that a lung transplant may have for quality of life in patients with progressive PAP despite WLL and/or pharmacological treatments [70]. A major consideration is the possibility of the recurrence of PAP in the graft lung. It is unknown if the risk of relapse is related to the PAP-causing disease. For example, in aPAP, the production of GM-CSF antibodies may persist after transplantation, but this may be offset by the routine use of immunosuppressive medications in the post-transplantation period.

Discussion

The new ERS guidelines on PAP provide evidence-based recommendations for both the diagnosis and treatment of PAP, but like any recommendations, these should always be considered together with patients’ values and preferences, local clinical expertise, and the specific details of every individual patient.

The two clinical examples provided in this summary document for clinicians aim to help translate these comprehensive guidelines into clinical practice, but as in all cases, referral and discussion with an expert centre or clinician is still advisable. This may be especially relevant and important for patients with secondary or hereditary PAP, as many of the guidelines are limited to the most common form of PAP, which is autoimmune. Another consideration is the heterogenous availability, and reimbursement policies with respect to testing and treatment in different healthcare settings. And, of course, patient preference.

Many areas of uncertainty remain within the area of PAP and the need for further research is highlighted throughout the guideline document. A recurrent theme is the need to reach a consensus on meaningful clinical outcomes and endpoints for clinical trials in PAP. The TF panel propose specific research needs across areas such as biomarkers, outcomes, treatment strategies and registries. Ongoing international collaboration is needed to explore and address these topics.

Key points

- The new ERS PAP guidelines provide evidence-based recommendations for diagnosis and treatment of this rare disease.
- BAL and quantitative GM-CSF antibody test should be used for the diagnosis work up of PAP, supplemented, if necessary, by genetic tests and, in uncertain cases, lung biopsy.
- Treatment of PAP, when deemed necessary, should be performed in consultation with an expert centre, and may include WLL or inhaled GM-CSF (strong recommendations), while rituximab, plasmapheresis and lung transplantation may be used for refractory disease (conditional recommendations).

Self-evaluation questions

1. Which of the following is the most common cause of PAP?
    a) Hereditary PAP
    b) Congenital PAP
    c) Autoimmune PAP
    d) HIV related PAP
    e) Medication induced PAP
2. You suspect PAP in a patient with progressive dyspnoea and patchy ground glass opacification on chest CT with subpleural and basal sparing. You arrange a BAL. What other diagnostic test will you organise?
    a) Lung cryobiopsy
    b) No further tests are needed; chest CT and BAL are sufficient
    c) GM-CSF signalling blood test
    d) GM-CSF antibody titres
    e) Surgical lung biopsy
3. Your top differential in a patient with suspected PAP is pneumonia. The patient is not productive of sputum. You proceed to perform bronchoscopy and BAL. Which of the following would be suggestive of PAP rather than infection?
    a) Pas positive material on cytology
    b) Eosinophil predominant cell differential
    c) Pigmented macrophages
    d) *Streptococcus pneumoniae* growth on microbiology
    e) Atypical squamous cells on cytology
4. You confirm a diagnosis of aPAP. The patient is symptomatic, hypoxic and has had a deterioration in spirometry over a 6-month period and you decide treatment is appropriate. What is the first line treatment once other causes of deterioration are excluded?
    a) Antibiotics
    b) Intravenous methylprednisolone
    c) Lung transplantation work-up
    d) Whole lung lavage or inhaled Gm-CSF
    e) Plasmapheresis

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Suggested answers

1. c.
2. d.
3. a.
4. d.