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27

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1 **ABSTRACT**

2 Background

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

12

13 Methods

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

22 Results

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

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

3

4 Conclusions

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

9

10 **Take home message:**

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

15

16

17

18

1 **SCOPE AND OBJECTIVES**

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

13

14 **INTRODUCTION**

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

19

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

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

5 **METHODOLOGY**

6 The ERS Pulmonary Alveolar Proteinosis Clinical Practice Guidelines were developed by an ERS
7 Task Force (TF) following methodology proposed by the ERS guidance for developing Clinical
8 Practice Guidelines[5] and the GRADE (Grading of Recommendations, Assessment, Development
9 and Evaluation)[6] approach. The TF was chaired by C. McCarthy (Ireland), F. Bonella (Germany)
10 and E. Bendstrup (Denmark). The TF included respiratory medicine specialists, paediatricians, a
11 radiologist, pathologist, guideline methodologists and two lay representatives living with PAP. The
12 two lay representatives were full members of the TF and contributed to all recommendations.
13 Conflicts of interest were disclosed by all panel members and were managed in line with the ERS
14 policy. The TF met virtually and during physical meetings to define and discuss the methodological
15 details of the guideline, to discuss the evidence and develop recommendations.
16

17 **Questions and outcomes**

18 This Guideline addressed seven clinically pertinent questions on the diagnosis, characterisation, and
19 management of PAP that were selected by consensus. Following ERS processes [5], we formulated
20 five questions using the 'Patient, Intervention, Comparison, Outcome' (PICO) format, and two
21 narrative questions (NQ). For every question, relevant outcomes were selected based on their
22 importance for clinical practice, in line with the GRADE recommendations. Only outcomes that were
23 rated critical or important by a majority of panel members were considered for the development of
24 recommendations (See supplementary appendix). Systematic reviews (SR) were conducted to
25 answer these questions.
26

1 **Literature searches and systematic literature review**

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

14 Study screening at a title-abstract and full-text level were independently screened in Rayyan [7] by
15 at least two members of the TF using predefined inclusion and exclusion criteria. Relevant
16 information about study design, baseline characteristics of the participants, characteristics of
17 interventions, or index tests of interest, as well as the outcomes of interest were extracted in a
18 prospectively designed data extraction form by one and cross-checked by a second panel member
19 for accuracy. Risk of bias of randomised controlled trials (RCTs) was appraised using the Cochrane
20 Risk of Bias tool [8] while the Risk of bias in non-randomised studies of interventions (ROBINS-I)
21 tool was used for observational and non-comparative interventional studies [9] , and for case series
22 or reports we used the Joanna Brigg’s institute’s risk of bias tool for case reports[10]. In line with a
23 prospective protocol, meta-analyses were performed using random effect models when it was
24 considered meaningful, for PICO questions. Data from RCTs or quasi-RCTs, comparative
25 observational studies and non-comparative studies were not pooled. Data from the remaining
26 questions were described narratively, in line with the ERS Clinical Practice Guidelines[5]. GRADE

1 methodology was used for assessing the certainty of the body of evidence for every outcome of
2 every PICO and narrative question[11] (See supplementary appendix).

3 4 **Assessing the level of evidence and degree of recommendations**

5 Evidence profiles and Evidence-to-decision (EtD) frameworks were generated for each PICO
6 question, whilst only EtDs were generated for NQs (See supplementary appendix). For NQs, in
7 accordance with the updated ERS guidelines, the approach was narrative. EtD frameworks were
8 used by the panel to formulate recommendations and strength by consensus and/or voting. The
9 recommendations were graded as strong or conditional with key considerations summarised in
10 **Table 2.** In line with GRADE terminology [6], the term “we recommend” was used for strong
11 recommendations and “we suggest” for conditional ones.

12
13 A strong recommendation was made for an intervention when the panel was certain that the
14 desirable consequences of the intervention outweighed the undesirable consequences and a strong
15 recommendation against an intervention was made when the opposite was true. A strong
16 recommendation indicates that most patients and healthcare providers would choose to recommend,
17 or not to recommend, the intervention. A conditional recommendation for an intervention was made
18 when the panel was uncertain that the desirable consequences of an intervention outweighed the
19 undesirable consequences in most patients and a conditional recommendation against an
20 intervention was made when the opposite was true. Reasons for uncertainty included (very) low
21 certainty of evidence, a close balance between desirable and undesirable effects or patients’ values
22 and preferences. A conditional recommendation indicates that different patients and healthcare
23 providers may make different choices regarding an intervention. In addition to the recommendations,
24 specific considerations were made regarding individual PICOs. These considerations reflect the TF
25 members current practice and describe their clinical experience. Data supporting these comments
26 were provided for each PICO. All recommendations, comments and algorithms were reviewed and
27 approved by the full panel.

1

2 **Recommendation development**

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

12

13 **Panel meetings**

14 For developing this clinical practice guideline, the panel organised four face-to-face meetings
15 (Barcelona, ERS Congress 2022; Essen, October 2022; Paris, July 2023; Milan, ERS Congress
16 2023) and four videoconferences. The first two meetings were focused on finalising the methodology
17 PICO questions, outcomes selection, and search strategies. During the latter meetings, the results
18 of systematic reviews and EtD Frameworks were discussed, and recommendations were finalised.
19 These meetings were complemented by several online meetings of groups focusing on specific
20 questions or tasks.

21

22 **CLINICAL DEFINITION OF PAP**

23 General considerations

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

4

5 Disease activity and severity

6 PAP is characterised by progressive accumulation of surfactant in pulmonary alveoli resulting in
7 hypoxemic respiratory insufficiency or failure. PAP is considered active in the presence of (a)
8 continuous or progressive symptoms such as dyspnea, cough, sputum production, chest pain,
9 weight loss, and/or (b) lung function decline in forced vital capacity (FVC) or diffusing capacity of
10 carbon monoxide (DLco), and/or (c) hypoxaemia measured by arterial blood gas (PaO₂, SaO₂,
11 AaDO₂), and/or (d) new or worsening PAP-characteristic infiltrates on high resolution CT (HRCT),
12 including but not limited to ground glass and crazy paving. Alternative causes or complications like
13 respiratory infections, pulmonary embolism, pulmonary hypertension, and congestive cardiac failure
14 should be excluded. A disease severity score (DSS) was proposed in 2008 [2] and is based on
15 symptoms and PaO₂ levels. [12]. This score is easy to calculate and has been used to stratify
16 patients in clinical trials [13, 14]. Further scores which include smoking status and HRCT findings
17 have been proposed and showed good correlation with prognosis[15]. The reduction of time interval
18 between subsequent whole lung lavage procedures has also been used as an indicator of disease
19 progression in PAP (10, 12). It remains unclear whether opportunistic infections should be
20 considered an indicator of disease severity or simply a complication [1]. Agreed upon thresholds for
21 lung function tests or blood gas parameters are currently lacking to stratify patients for disease
22 severity. A second opinion from a PAP reference centre can be of assistance in patient assessment,
23 determining if the disease is active, and to ascertain treatment options.

24 Disease progression

25 There is no standard definition of disease progression for PAP, however it is widely considered to
26 be the worsening of respiratory symptoms, decline in lung function tests (FVC, DLco), onset or

1 worsening of respiratory failure including need for oxygen treatment, and worsening of PAP-related
2 CT findings after careful exclusions of other causes. Based on previous observational studies [16-
3 18] and clinical trials [13, 14], DLco and AaDO₂ maybe the most sensitive markers of disease
4 progression [1, 19]. Due to the paucity of data, specific thresholds for decline in lung function tests
5 or blood gas parameters to define disease progression are not available. Disease progression should
6 always be confirmed by HRCT and to ensure no alternative processes are ongoing. Pulmonary
7 fibrosis, which occurs at varying frequency but can affect up to 20% of PAP patients [20], should be
8 considered as a sign of progressive disease. In this case, disease progression can tentatively be
9 further assessed by using the progressive pulmonary fibrosis (PPF) definition from the 2022
10 ATS/ERS guidelines [21], however the use of these criteria for PAP awaits validation.

11

12 **RECOMMENDATIONS**

13 **Question 1a (NQ)**

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

16 Recommendation

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

20 Justification of recommendations

21 The justification for the strong recommendation for BAL is based on the perceived benefit of a clear
22 diagnosis on PAS staining without the need for more invasive tests and the low risk of complications.
23 BAL is a low-risk technique that allows for the direct sampling of the cellular and acellular
24 components in the distal airways and alveoli. The usefulness of BAL for identifying the presence of
25 PAP has been reported in several studies. Ilkovich reported 68 patients with idiopathic PAP where

1 BAL fluid (BALF) was reported as milky white, opalescent, with white material after sedimentation.
2 Cytology revealed amorphous and granular eosinophilic masses mixed with alveolar macrophages
3 [22]. BALF cellularity in PAP patients is often increased with a predominance of lymphocytes and
4 cytological examination of the BALF shows foamy macrophages which contain eosinophilic granules
5 and amorphous material that stains PAS-positive and tubular myelin like lamellar bodies are seen on
6 electron microscopy. [23] Bonella *et al* reported on 70 patients where BAL was performed in 83%.
7 [24] In a study of 150 patients (86 with aPAP), Azuma *et al* report diagnostic yields of 90,7% (78/86)
8 for BAL, 81.4% (70/86) for transbronchial biopsy (TBB) and 98.8% (85/86) for the combination. [25]
9 In children, the yield of BAL to diagnose PAP is good; Enaud *et al* reported that the diagnosis was
10 made by BALF examination for 15 children [26].

11 BAL is decisive to exclude pulmonary infections, which, along with systemic infections, can
12 complicate PAP of all forms, accounting for approximately 20% of mortality [27]. Opportunistic
13 infections (particularly *Nocardia* spp., *Mycobacteria*, and fungi) are associated with worse prognosis
14 and higher risk of mortality [28]. Most adverse events of BAL are closely related to endoscopic
15 technique, location, and extent of lavaged lung area, volume and temperature of instilled fluid [29].

16 Practical considerations

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

20

21 **Question 1b (NQ)**

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

24 Recommendation:

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

3 Justification of recommendations

4 The justification for the conditional recommendations is based on the known risk of side-effects and
5 the perceived low benefit of a clear diagnosis from this invasive test. Rosen *et al* first described the
6 lung histology in PAP, and found preserved interalveolar septa with lipoproteinaceous material filling
7 the alveoli and some bronchioles [30]. Examination of surgical lung biopsies demonstrated preserved
8 lung parenchyma with peribronchial lymphocytic infiltrations and alveoli filled with macrophages and
9 amorphous eosinophilic PAS-positive material [31, 32]. Immunohistochemical staining of this material
10 confirmed surfactant protein [31]. Lung biopsy was previously routinely used for diagnosis of PAP,
11 although is not necessary in every patient. [31] Inoue *et al* reported that tissue biopsy confirmed the
12 diagnosis of PAP in 102/223 cases [2]. Where biopsy is needed, some case series have shown
13 increasing use of TBB [33-36] with a diagnostic yield of 81.4% [36]. Other studies report higher use
14 of surgical biopsy [22, 37, 38] and there are limited reports on the use of transbronchial cryobiopsy
15 for diagnosing PAP [39].

16 While biopsy was previously considered the gold standard for diagnosing PAP, histological
17 examination may also fail to identify the presence of PAP syndrome as seen in a study from the US
18 National PAP Registry where histology was non-diagnostic in 28% of cases because of patchy
19 involvement [37]. The authors conclude that lung biopsy should only be performed on the rare
20 situations in which the cause of PAP remains uncertain after completing BAL, non-invasive serologic,
21 blood-based, and genetic tests [37].

22 Practical considerations

23 Lung biopsy is an invasive technique that may fail to diagnose PAP due to sampling error, has known
24 risk of complications and a mortality risk [40]. Some hospitals do not have access to services
25 providing lung biopsies. Patient representatives expressed preference for a test that allowed for a

1 quick diagnosis without the need of more invasive interventions. If tissue biopsy is considered,
2 benefits and limitations of the least invasive procedure should be discussed with patients, based on
3 benefit/risk assessment.

4

5 **Question 2 (NQ)**

6 *Should patients with PAP undergo GM-CSF antibody testing for diagnosing autoimmune PAP?*

7 Recommendation

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

10 Justification of recommendations

11 A systematic review of the available evidence revealed a large study comprising 248 patients [2],
12 three methodology papers [41-43], and multiple real-world observational studies [4, 31, 37, 44, 45]
13 focused on the use of GM-CSF autoantibody testing in PAP. Taken together these studies
14 established that GM-CSF autoantibodies can be measured in an objective and reproducible manner
15 with a high accuracy for a diagnosis of aPAP with a level of 10.2µg/ml or above [4, 41, 43]. The
16 largest study describes the use of GM-CSF autoantibody testing in 248 patients with a tissue biopsy
17 confirming a diagnosis of PAP. Of this cohort, 89.9% of the patients had no underlying condition or
18 cause to explain why they developed PAP and subsequently all these patients had elevated GM-
19 CSF autoantibody levels [2]. In another observational study [44], GM-CSF autoantibody levels were
20 described in 70 patients with PAP and was positive in the 64 individuals who had “idiopathic” PAP.
21 The certainty of the available evidence has been ranked moderate despite the high sensitivity,
22 specificity, and reproducibility of the GM-CSF autoantibody testing and its successful use in real-
23 world cohorts [2, 4, 37, 41, 43, 44].

24 GM-CSF autoantibodies have been determined to be pathogenic of aPAP. Early data showed that
25 GM-CSF deficient mice were found to accumulate surfactant in the lungs and cause a PAP-like

1 disease [46, 47] and GM-CSF autoantibodies were found in BALF from patients with what was known
2 at the time as “idiopathic” PAP [42, 48]. It was also demonstrated that GM-CSF autoantibodies
3 reproduced the molecular, cellular, and histopathologic features of PAP in healthy primates,
4 demonstrating that GM-CSF autoantibodies directly cause PAP [49, 50]. GM-CSF autoantibody
5 testing in the form of a simple blood test is pathognomonic for the diagnosis of aPAP, which accounts
6 for almost 90% of all cases of PAP. More recently, studies have shown that a combination of GM-
7 CSF antibody testing and genetic testing for hereditary causes can achieve a diagnosis in 95% of
8 patients without a biopsy [43, 51, 52]. In these scenarios, this testing precludes the need for invasive
9 tissue biopsy. As further evidence of GM-CSF autoantibodies being the main mechanism of disease
10 in aPAP, treatments acting on this specific mechanism such as inhaled GM-CSF and rituximab have
11 successfully been used to treat this disease. This supports the testing of GM-CSF autoantibodies in
12 all suspected patients with PAP. This non-invasive test with minimal risk outweighs the risk of not
13 testing for aPAP.

14 Practical considerations

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

21

22 **Question 3 (PICO)**

23 *Should patients with clinical symptoms and/or functional impairment due to PAP undergo whole lung*
24 *lavage?*

25 Recommendation

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

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

6 Justification of recommendations

7 There is a lack of RCT data to define the exact impact of WLL on symptoms or pulmonary function
8 tests in patients with a diagnosis of PAP. However, there is moderate certainty of evidence that WLL
9 improves both symptoms and pulmonary function over time and, reassuringly, minimal serious short
10 term adverse events or mortality issues reported in the post WLL period. Bilateral WLL is suggested
11 as both lungs are affected almost universally.

12 Since WLL was first performed in 1964, it has been the most common treatment for patients with
13 PAP [53]. There are no specific guidelines for the procedure itself and indications to perform a WLL
14 vary between centres [54]. Briefly, WLL is done under general anaesthesia and intubation is
15 performed using a double lumen endotracheal tube to ventilate one lung while washing the other
16 with several litres of saline (See supplementary appendix) [54-56]. The main indications for WLL
17 were decline in lung function and/or resting PaO₂, and an increase in respiratory symptoms or
18 parenchymal abnormalities on CT. The most common complications reported were fever (18%),
19 pneumonia (5%), fluid leakage (4%) and pneumothorax (0.8%).

20 Systematic review identified 26 retrospective case series each describing 5 or more patients who
21 had at least one unilateral or bilateral WLL (See supplementary appendix). The median study
22 population in the 26 selected studies was 14 patients (IQR: 8-21). Twenty series included adults
23 only, five included both children and adults and one study described the experience in children alone.
24 No clear differences were reported in the effects of treatment in children compared to adults.

1 There was low certainty evidence suggesting that WLL improves respiratory symptoms when
2 compared to pre-WLL symptom burden. While we were not able to pool data from all of the included
3 studies due to limitations, six of the ten studies reporting on symptoms showed a moderate or
4 significant symptomatic improvement in all participants [57-62], while the remaining 4 studies
5 reported symptomatic improvement in 68-90% of participants [17, 18, 63, 64]. Two studies
6 measuring exercise capacity reported increases in walking distance of 101m in the 6MWT (95% CI
7 66.35, 136.05) and 417m using a treadmill (95% CI 235, 598). The certainty of evidence was low
8 and very low, respectively. There was low certainty evidence to suggest an improvement in PaO₂
9 within a month of WLL (20.07mmHg [95% CI 9.54, 30.60], I₂=92%) and within months to years of
10 WLL (13.98mmHg [95% CI 10.15, 17.80], I₂= 35%). Moreover, a trend towards improved AaDO₂ was
11 observed post-WLL (-14.87mmHg [-32.44, 2.70], I₂=16%, very low certainty), with a clear
12 improvement at longer follow-up (-21.33 mmHg [-26.99, -15.66], I₂=11%, low certainty). No clear
13 improvement was observed in FVC at short (8.54% [-8.22, 25.29], I₂ = 96%), or longer follow-up
14 (5.43% [-0.67, 11.53]), low certainty of evidence.

15 Practical considerations

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

24

25 **Question 4 (PICO)**

1 *Should patients with confirmed autoimmune PAP be treated with exogenous GM-CSF?*

2 Recommendation

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

5 Justification of recommendations

6 The beneficial outcomes of inhaled GM-CSF treatment reported in all clinical trials regarding
7 physiological, functional, clinical, and radiological outcomes in combination with the safety and non-
8 invasiveness of this treatment modality justify the strong recommendation for inhaled GM-CSF for
9 symptomatic patients with confirmed aPAP. The very low certainty of evidence relates mostly to the
10 limited number of patients related to the rarity of the disease and the very limited number of recently
11 published RCTs, most studies being observational, retrospective studies and case reports/series.
12 Systematic review revealed three RCTs [13, 14, 65], 1 comparative observational study and 7
13 observational, non-comparative studies on exogenous GM-CSF for patients with confirmed aPAP
14 [16, 66-72]. All studies included adult patients with aPAP confirmed by the presence of high GM-
15 CSF autoantibody titres. In the PAGE trial [13], 64 patients with mild to moderate aPAP were
16 randomised to intermittent inhaled GM-CSF [sargramostin 125µg BD every other week] or placebo
17 for 25 weeks. Patients who underwent WLL within the previous six months or those who had severe
18 disease (PaO₂ <50mmHg) were excluded. In the IMPALA trial [14], 138 patients were randomised
19 to continuous inhaled GM-CSF [molgramostin 300µg OD], or intermittent GM-CSF [300µg OD every
20 other week] or placebo for 24 weeks. The 24-week intervention period was followed by an open-
21 label treatment-extension period with intermittent treatment. Patients who underwent WLL within the
22 previous month were excluded. In an open-label RCT [65], 36 patients were randomised to
23 intermittent inhaled GM-CSF [sargramostin 150µg BD every other week for 3 months, then 150µg
24 OD every other week for 3 months] or placebo for 26 weeks. Patients who had undergone a WLL in
25 the 3 months prior were excluded. The above mentioned RCTs were the main source of evidence,
26 and data were pooled for intermittent, inhaled GM-CSF at approximately 6 months after treatment

1 initiation. Evidence suggests that compared to placebo, intermittent, inhaled GM-CSF reduces
2 AaDO₂ with a mean difference (MD) of -4.36 mmHg (95% [95%CI] -7.71; 1.01), improves the PaO₂
3 with a MD of 4.47 mmHg (95%CI 1.16; 7.78) and the DLCO with an absolute change (MD) of 4.05%
4 (95%CI 0.23; 7.88). Further evidence is provided for either beneficial or no beneficial effects
5 regarding 6MWT distance in metres (MD 14.53 m (95%CI -17.5; +46.6)), VC or FVC (MD 2.08%
6 (95%CI -0.6; +4.8)), lung density in HRCT (MD -22.82 HU (95%CI -48.7; +7.0)), and symptoms when
7 measured by SGRQ symptoms domain (MD -6.94 points (95%CI -19.2; +5.3)). The PAGE trial also
8 assessed symptoms by measuring CAT and mMRC [16]. CAT was estimated to be higher in those
9 treated with GM-CSF (MD 3.91 points, 95% CI 0.44; 7.38) and mMRC was estimated to be lower
10 (MD -0.4 points, 95% CI -0.7; -0.2). Trivial, transient side effects were reported [13, 14, 65]. No
11 mortality events were observed in any of the trials.

12

13 Eight observational studies with a total of 156 included patients evaluating either inhaled [16, 67, 69,
14 71, 72] or subcutaneous GM-CSF were included [66, 68, 70]. In 2010, the first prospective,
15 multicentre, phase II trial was published, examining 39 aPAP patients with a PaO₂ of <75mmHg.
16 The patients sequentially received a 12-week high-dose therapy with inhaled GM-CSF (sargramostin
17 250µg for 8 days, no treatment for 5 days), followed by a 12-week low-dose therapy (125µg for 4
18 days, no treatment for 10 days), and a follow-up period of 52 weeks [16]. Individuals were excluded
19 if they had undergone WLL within 6 months prior to enrolment. The study demonstrated that the
20 overall response rate was 62% at 6 months, response being defined as reduction in AaDO₂ by at
21 least 10mmHg at the end of the low-dose period; the response was maintained in 83% of patients
22 for 1 year without the need for additional therapy and treatment was safe [16]. Four years later, the
23 long-term effects of intermittent inhaled GM-CSF during a 30-month observation period were
24 reported in the same population [16, 72], There was sustained remission of PAP in >50% of cases
25 [72]. In 2014, a case series of six patients with PAP also showed promising long-term results by the
26 application of the “as far as it takes protocol”, minimizing both disease burden and treatment costs
27 in safety [69]. Finally, an observational study compared WLL alone with a combination of WLL

1 followed by inhaled GM-CSF for 3 months in a total of 33 patients with severe aPAP [71]. The GM-
2 CSF/WLL group had significantly faster functional, exercise capacity and radiological improvement
3 as well as reduction in the need for WLL compared with the WLL alone group [71]. Additional studies
4 include two case series in adult patients [73, 74] as well as four case series in children and young
5 adolescents with documented aPAP [75-78] (See supplementary appendix). Paediatric studies
6 reported beneficial effects in 5/7 children and young adolescents treated with inhaled GM-CSF either
7 alone (n=1) or in combination with WLL (n=4).

8

9 Practical considerations

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

18

19 **Question 5 (PICO)**

20 *Should patients with confirmed autoimmune PAP be treated with rituximab?*

21 Recommendation

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

25 Justification of recommendation

1 A systematic review revealed a single arm interventional study involving ten patients [79], a
2 retrospective case series of 13 patients [80] and seven case reports. [81-87]. All studies and case
3 reports evaluated adults with aPAP. Most patients included in the studies had undergone WLL and/or
4 GM-CSF treatment prior to recruitment. Studies by both Kavuru and Soyez compared the clinical
5 status of patients 6-12 months after rituximab treatment to baseline [79, 80], hence, the data were
6 pooled together. Participants in both studies received two doses of rituximab 1,000 mg, administered
7 15 days apart. One patient in the observational study only received a single dose, while three
8 received an additional, maintenance dose. There was very low certainty evidence suggesting that
9 rituximab may reduce the AaDO₂ by a mean of -15.59 mmHg (95% CI 12.15 to 19.03 mmHg) and
10 improve the partial concentration of oxygen measured on room air (MD 19.6 [8.39, 30.81] mmHg).
11 In addition, very low certainty evidence suggests no substantial impact of rituximab on DLCO, (MD:
12 15.72% [9.05%, 22.4%] predicted, I² =0%), FVC (MD: 2.7% [-22.47%, 27.87%] predicted) or 6MWT
13 (MD: 19 [-93.47, 131.47] meters) [91][92]. Kavuru *et al* reported that 4/7 patients that were observed
14 for a mean of 32 (±6) months did not require WLL [79]. The remaining three patients required one
15 WLL each during follow-up. Soyez *et al* 2018 reports 4/11 patients exerted significant improvement
16 at 12 months [80], compared to baseline. Improvement was defined as a decrease in the AaDO₂ by
17 at least 10mmHg. Kavuru *et al* also reported a significant improvement in the HRCT scores (p =
18 0.027) [79], which was, however, not observed by Soyez[80]. No deaths or serious adverse events
19 were observed in these studies. However, the results should be interpreted carefully, as the sample
20 size of the included studies was limited, and they were not controlled. Five of seven case reports
21 documented a clinically relevant improvement at various timepoints after rituximab initiation (3-12
22 months). Benefits included better oxygenation, improved exercise capacity, reduction in frequency
23 of WLL, and/or improvement in pulmonary function. Only one of the case reports addressed safety
24 and it did not report any serious adverse events. Two of seven cases (28.6%) did not gain any
25 benefits from rituximab. The certainty of the available evidence is very low (for all comparisons).
26 There are serious concerns around the methodological limitations of these small single-arm
27 uncontrolled studies.

1

2 Practical considerations

3 While the safety of rituximab has not been adequately assessed in patients with aPAP, ample data
4 are available from other disease areas. More specifically, the safety profile of rituximab at a similar
5 dose (two doses of 1,000 mg) in adults has been evaluated in more detail in a Cochrane review
6 evaluating rituximab in rheumatoid arthritis [88]. (See supplementary appendix for details of dosing)
7 The addition of rituximab was not associated with increased risk of serious adverse events, at 48-56
8 weeks follow-up, or at 104 weeks follow-up. Rituximab was associated with a trend of increased
9 discontinuation due to adverse events during the first six months, this trend disappeared at 1 year
10 follow-up and was reverted at longer follow-up. In children, the safety of rituximab at a dose of 1-4
11 infusions of 375mg/m² has been assessed in more detail in a meta-analysis evaluating rituximab for
12 childhood steroid-dependent nephrotic syndrome. This meta-analysis did not reveal any increase in
13 the risk of infections, or cardiovascular disease events, but found a trend over increased risk of
14 infusion reactions. The authors reported that the rate of severe allergic reactions in children was very
15 low [89].

16

17 **Question 6 (PICO)**

18 *Should patients with confirmed autoimmune PAP be treated with plasmapheresis?*

19 Recommendation

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

24 Justification of recommendation

1 The quality of evidence is very low and evidence arises from case reports only. Spontaneous
2 remission is observed in some patients with PAP and therefore, a treatment effect cannot confidently
3 be established based on the available case reports. In addition, the reported benefits were mostly
4 subjective and not based on a validated measurement instrument. The systematic review revealed
5 only nine case reports [77, 85, 86, 90-95] and no RCTs or observational studies on the role of
6 plasmapheresis in aPAP. Only one case report described the use of plasmapheresis in an
7 adolescent with aPAP, while all other cases were adults. The duration of the disease was variable;
8 from 4 to 120 months (median 12 months). One of the patients was not tested for GM-CSF
9 autoantibodies [94]. Patients all presented with severe disease: all but one was receiving
10 supplemental oxygen therapy up to 8L/minute, and one patient was intubated receiving 60-75%
11 FiO₂. All had persisting symptoms and had undergone several WLL prior to treatment with
12 plasmapheresis. Four of nine patients had WLL and exogenous GM-CSF and one had WLL,
13 exogenous GM-CSF and Rituximab prior to plasmapheresis. Thus, plasmapheresis was used in
14 patients with severe PAP, refractory to other treatments. No significant clinical benefits were
15 observed in three of the reported cases [85, 91, 95]. Yu *et al* [94] reported improved clinical
16 symptoms and radiological findings, which were however short-lived, as relapse was observed five
17 months later. Luisetti *et al* [93] reported a reduced frequency of WLL after plasmapheresis, but no
18 clear improvement in the symptoms after plasmapheresis. Finally, four cases reported significant
19 improvement in the symptoms [77, 86, 90, 92], oxygenation, radiological findings and/or pulmonary
20 function [77, 91]. A significant reduction in the GM-CSF antibody titres was reported in 5/9 cases
21 [79, 86, 90, 93]. Rituximab was also administered after completion of plasmapheresis in two case
22 reports, that only reported outcomes after both treatments were administered [77, 86]. It appears
23 that higher intensity plasmapheresis regimens successfully suppress GM-CSF autoantibodies and
24 may offer clinical benefit.

25

26 Practical considerations

1 The safety of plasmapheresis was evaluated in detail in a Cochrane meta-analysis of the safety and
2 efficacy of plasmapheresis for Guillain-Barre disease [96]. Based on data from three trials totalling
3 556 participants, plasmapheresis did not increase the risk of infection (RR 0.91 [0.73, 1.13]), of blood
4 pressure instability (RR 0.88 [0.64, 1.22]), cardiac arrhythmias (RR 0.75 [0.56, 1.00]), or pulmonary
5 embolism (RR 1.01 [0.26, 4.00]). However, it should be noted that the included studies employed 2-
6 6 sessions of plasmapheresis, a lower number compared to those proposed for aPAP. The mortality
7 associated with plasmapheresis has been estimated to be 0.05%, based on a systematic review
8 meta-analysis of >15,500 patients, mainly adults [97]. The complications of >4,500 sessions of
9 plasmapheresis in 593 children with neurological disease have been summarised in a narrative
10 review [98], that concluded that the intervention is well-tolerated and associated with adverse events
11 that can be anticipated and avoided. Complications were reported in 15% of plasmapheresis
12 sessions and 70% of children. However, life-threatening complications were limited to 0.4% of
13 treatment sessions and 2.4% of children. The patient representatives consider that potential
14 prevention of WLL and improvement in the hypoxia may be considered important by patients with
15 aPAP that is refractory to treatment and associated with a significant disease burden.

16

17 **Question 7 (PICO)**

18 *Should patients with PAP progressing despite whole lung lavage or pharmacological treatment be*
19 *considered for lung transplantation?*

20 Recommendation

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

25 Justification of recommendation

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

4 Data regarding lung transplantation in patients with PAP is derived from 14 individual case reports,
5 9 adults and 5 children. Causes of PAP included graft vs host disease (GVHD) (2 cases [99, 100]),
6 aPAP (4 cases [101-104]), hereditary PAP (2 cases [105, 106]) and lysinuric protein intolerance
7 (*SLC7A7* mutation, 1 case [107]). Cause was not reported in 5 cases [108-111]. Median duration of
8 follow-up was 3 years [range 0.2 to 7]. Two patients died, one 4 years after lung transplantation in
9 the context of recurrence of PAP, fungal infection and bronchiolitis obliterans syndrome (BOS) [106],
10 and one 2 years after lung transplantation in the context of recurrence of PAP [107]. For the
11 remaining patients with outcome data (n=11), the desirable effects of lung transplantation were
12 quantified based on durable wean from oxygen, lung function and quality of life (QoL) at last follow-
13 up. Nine patients were weaned from oxygen after transplantation, 1 was still on home oxygen and
14 data was missing for one. Lung function among patients alive at last follow-up was reported to be
15 improved in 5, stable in 1, and not available in 5. The reported QoL among alive patients was good
16 in 10/11. Among the 13 patients with post-lung transplantation data available, adverse events were
17 mainly infections (9/13), post-transplant lymphoproliferative disease (PTLD) was observed in 2
18 cases [103, 110] and BOS in 2 cases [106, 109]. Graft rejection was not reported. Recurrence of
19 PAP on the transplant was reported in 3 cases. In these patients, the cause of the PAP was *CSF2RB*
20 mutation in 1, *SLC7A7* mutations in 1 and unknown in the last case. Twelve additional paediatric
21 cases were recorded in a report on the outcome of 190 children after lung transplantation; no causes
22 of PAP and individual patient data were available. Survival and complications were not different from
23 transplant for other diseases [112]. A query was made at the registry of the ISHLT. Of 101 patients
24 reported by ISHLT with different forms of PAP and lung transplant, 43 had died at the end of the
25 observation period. In none of the patients the diagnosis “Graft Failure: Recurrent Disease” was
26 noted. Thus, no relapses of PAP in the transplanted patients were noted leading to graft failure.

1 Practical considerations

2 In treatment-refractory PAP, with or without pulmonary fibrosis and likely death within a few years,
3 lung transplant, associated with life-long medication and medical treatment/surveillance is an
4 alternative that can improve QoL [113]. Indeed, many patients consider lung transplantation for
5 palliation of symptoms and improvement of QoL even when extended survival is not assured [113].
6 However, there are always few people who reject an offer of transplantation and wish palliative care
7 [114]. A scoping review identified 28 studies in adults and made cost-utility estimates of lung
8 transplantation versus waitlist, from the healthcare payer perspective. For a time-horizon of at least
9 10-years costs ranged between \$42,459 and \$154,051 per quality-adjusted life year [115]. The costs
10 of care for patients with end-stage lung disease and chronic respiratory insufficiency should be
11 balanced with the costs of care of hospitalisation for lung transplantation including stays in surgery
12 and ICU and lifelong costs for medications and care [115].

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

1 CSF2RB genes and progressive PAP progressing despite all treatments, another theoretical
2 possibility would be to consider the combination of lung transplantation and BMT.

3

4 **Treatment Hierarchy**

5 Treatment is indicated in patients with active or worsening disease, as defined earlier. The
6 appropriateness of treatment should be based on the degree of impairment of lung function, CT
7 imaging changes, blood oxygenation and QoL. If no respiratory failure or life-threatening
8 complications are present, and the patient still has an acceptable QoL, a *wait and see* strategy can
9 be justified. In a survey of 20 PAP centres practising WLL, indications for WLL varied among centres
10 [54]. Specific indications included an unspecified decline in lung function, a decline in resting PaO₂,
11 worsening of lung disease severity based on a comparison of serial chest imaging, decline in DLco,
12 decline in FVC, decline in resting oxygen saturation on pulse oximetry (SpO₂) or an increase in
13 respiratory symptoms. The inclusion criteria in the RCTs of inhaled GM-CSF for aPAP were variable
14 in terms of disease activity. In the PAGE trial, patients were eligible to receive treatment if PaO₂ was
15 <70 mm Hg after 5 minutes in the supine position while breathing ambient air, or <75 mm Hg, and
16 at least one symptom (cough, sputum production, or exertional dyspnea) was present [13]. In the
17 IMPALA trial, inclusion criteria were stable or progressive aPAP during a minimum period of two
18 months prior to the baseline visit, PaO₂ <75 mmHg at rest, or desaturation of >4% in a 6MWT, and
19 an AaDO₂ of ≥25 mmHg [14]. The TF panel recognises the need for more research in this field and
20 of an international consensus on treatment indication criteria. The proposed hierarchy of treatment
21 in aPAP is illustrated in **Figure 3**.

22

23 Treatment response

24 There are no standard criteria defining treatment response. Treatment goals in PAP are to achieve
25 either disease regression or long-term disease stabilisation, without the need for repeat WLL. In the
26 reports on the efficacy of WLL, changes in blood gas parameters and radiological improvement have

1 been used to assess response [54, 117]. In RCTs of GM-CSF, AaDO₂ while breathing room air was
2 chosen as the primary endpoint, whereas improvements in DLco and HRCT infiltrates were
3 secondary outcomes [13, 14] The magnitude of improvement in these, and other, RCT endpoints
4 has been reviewed by our TF and is outlined in the summary of evidence in PICO 2 above. Changes
5 in QoL and/or symptoms of patients with a diagnosis of PAP have been anecdotally reported in
6 retrospective studies and RCTs of inhaled GM-CSF [13, 14], although these studies rely on
7 respiratory questionnaires which are nonspecific for PAP. Although several circulating biomarkers,
8 like KL-6, SP-D, LDH, YKL-40, tumor tissue antigens [44, 66, 118-123], seem to be promising for
9 assessing treatment response, validation studies are needed. The TF panel recognises the
10 usefulness of lung function tests and blood gas parameters to define treatment response but does
11 not indicate specific thresholds of decline or improvement. Beside functional assessment, a careful
12 evaluation of symptoms and radiological changes over an appropriate follow-up (at least 6 months)
13 is suggested.

14 Refractory disease

15 Refractory PAP can be defined by persistence or worsening of respiratory symptoms, lung function
16 or gas exchange impairment, and HRCT infiltrates despite adequate treatment and after appropriate
17 follow-up (~6 months). Post interventional complications should be excluded as a reason of
18 treatment failure. The need of repeated WLL over time and the reduction of the time interval between
19 two consecutive WLLs has been used as indicators of unresponsiveness to treatment [14, 124], but
20 the studies are too heterogeneous to draw conclusions. The same is true for circulating and genetic
21 biomarkers [125]. The TF panel suggests a careful and close evaluation of the patients after
22 treatment, aimed at assessing disease activity, and to exclude immediate or long-term treatment
23 complications or concomitant diseases as causes of treatment failure.

1 **Discussion**

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

13 In terms of disease outcome, ~7% of patients diagnosed with PAP have spontaneous remission and
14 never require treatment[1]. In this guideline, we propose that patients are treated in cases of
15 respiratory failure, lung function impairment or symptoms leading to disrupted QoL. Despite
16 increasing evidence for DLco, HRCT infiltrates and blood gas parameters as treatment indicators,
17 the authors strongly suggest considering multiple aspects at once, including patient needs. This
18 concept has become readily accepted in clinical practice of expert centres [125]. For most PAP
19 patients, treatment with WLL translates into rapid improvement of symptoms, gas exchange and
20 radiology[126]. However, the paucity of data does not allow conclusions to be drawn regarding the
21 long term effects of WLL [127]. Similarly, the evidence for effectiveness of treatment, especially in
22 relation to QoL is weak, since no validated instruments for PAP patients exist [125]. The authors
23 were able to provide a positive recommendation for WLL in adult patients with aPAP, since most
24 studies have focused on adult disease [54, 128, 129]. Nonetheless, the authors included special
25 considerations for the management of PAP in children, based on small and mostly single centre
26 observational studies, or case series.

1 Inhaled exogenous GM-CSF, the only treatment investigated in RCTs of adult patients aPAP,
2 received a strong recommendation, whereas the certainty of evidence was graded as very low. Due
3 to the heterogeneous endpoints and trial design, a *head to head* comparison of molgramostim and
4 sargramostim is currently not feasible[13, 14]. Beside the need of further confirmatory data on
5 efficacy of inhaled GM-CSF, the authors underscore the unmet need of PAP-specific endpoints and
6 more standardized administration protocols for the clinical routine and future clinical trials. Despite
7 the results of a recent trial [128] examining whether WLL and inhaled GM-CSF should be combined
8 into specific protocols with *add on* or sequential administration, this remains a question relevant to
9 futures studies.

10 This guideline has several limitations. Firstly, the diagnostic recommendations provided by this
11 guideline refer to an ideal situation in which all procedures or tests are available. Few centres offer
12 GM-CSF antibody measurement, GM-CSF signalling assessment or genetic testing, and early
13 referral to a PAP expertise centre or network is mandatory. Secondly, despite the authors' efforts to
14 provide definitions of disease severity and progression, as well as treatment indications, they mostly
15 remain based on a case-by-case approach and expert opinion. Thirdly, measurements of response
16 to treatments are still too heterogeneous across observational studies and RCTs, so that a
17 consensus on clinically meaningful outcomes and best endpoints is urgently needed. Fourthly, the
18 hierarchy of treatments provided in this guideline (**Figure 3**) is mainly based on the experts clinical
19 practice and has a low quality of evidence, hence should be considered as orientative only. In fact,
20 treatment decision depends on several factors, including local availability and reimbursement
21 policies. Finally, this guideline does not make specific recommendations regarding supportive
22 treatments such as oxygen supplementation or pulmonary rehabilitation. In conclusion, the
23 committee identified areas where there is sufficient information to make informed recommendations
24 based on current evidence and clinical experience. While great progress has been made in
25 understanding the pathogenesis and clinical progression of PAP syndrome, many questions remain
26 unanswered, several recommendations for future research were proposed by the TF(**Table 3**).

1 Obviously, many of the research topics require international collaboration such as consensus reports
2 and international registries.

3 The guidelines published by the ERS incorporate data obtained from a comprehensive and
4 systematic literature review of the most recent studies available at the time. Health professionals are
5 encouraged to take the guideline into account in their clinical practice. However, the
6 recommendations issued by this guideline may not be appropriate for use in all situations. It is the
7 individual responsibility of health professionals to consult other sources of relevant information, to
8 make appropriate and accurate decisions in consideration of each patient's health condition and in
9 consultation with the patient and the patient's caregiver where appropriate and/or necessary, and to
10 verify rules and regulations applicable to drugs and devices at the time of prescription. This
11 document was endorsed by the ERS Executive Committee on XX January 2024, ERN-LUNG on XX
12 January 2024.

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1 **Tables**

2 **Table 1: Classification of PAP Causing Diseases**

Disorders of Surfactant Clearance	
Primary PAP (GM-CSF signalling disruption)	
Autoimmune PAP	Mediated by autoantibodies to GM-CSF
Hereditary PAP	GM-CSF signalling disruption due to GM-CSF receptor mutations (CSF2RA or CSF2RB)
Secondary PAP (Reduced alveolar macrophage function or number)	
Haematological Conditions	Acute lymphocytic leukaemia, acute myeloid leukaemia, aplastic anaemia, chronic lymphocytic leukaemia, chronic myeloid leukaemia, myelodysplastic syndromes, multiple myeloma, lymphoma, Waldenstrom's macroglobulinaemia, GATA2 deficiency
Non-Haematological Malignancies	Adenocarcinoma, glioblastoma, melanoma
Immune Deficiency and Chronic Inflammatory Conditions	Acquired immunodeficiency syndrome, amyloidosis, Fanconi's syndrome, agammaglobulinaemia, juvenile dermatomyositis, renal tubular acidosis, severe combined immunodeficiency disease
Occupational and Environmental Exposures	aluminium, cement, silica, titanium, indium, flour, fertilizer, sawdust, chlorine fumes, cleaning products, gasoline/petroleum fume, nitrogen dioxide, paint fumes, synthetic plastic fumes, varnish
Chronic Infections	Cytomegalovirus, mycobacterium tuberculosis, nocardia, pneumocystis jirovecii
Others including mutations affecting mononuclear phagocytes	Lysinuric protein intolerance, mutations in methionyl-tRNA synthetase (MARS)
Disorders of Surfactant Production	
Pulmonary Surfactant Metabolic Dysfunction Disorders	
Mutations in SFTPB, SFTPC, ABCA3, NKX2.1	Surfactant homeostasis affected due to mutations causing surfactant protein deficiency, lipid transporter deficiency or mutations that affecting lung development

1 **Table 2: PICO Questions and Recommendations**

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

<p>PICO 6. Should patients with confirmed autoimmune PAP be treated with plasmapheresis?</p>	<p>We suggest the use of plasmapheresis for patients with confirmed autoimmune PAP who remain significantly symptomatic, requiring high flow of supplemental oxygen ($\geq 4L/min$) or two or more WLL over a period of a year, despite receiving exogenous GM-CSF and rituximab, or having previously failed these treatments (conditional recommendation, very low certainty).</p>
<p>PICO 7. Should patients with PAP progressing despite whole lung lavage or pharmacological treatment be considered for lung transplantation?</p>	<p>We suggest lung transplantation for patients with PAP progressing despite whole lung lavage and/or pharmacological treatment, who fulfil the International Society for Heart and Lung Transplantation (ISHLT) criteria for patients with interstitial lung disease (conditional recommendation, very low certainty).</p>

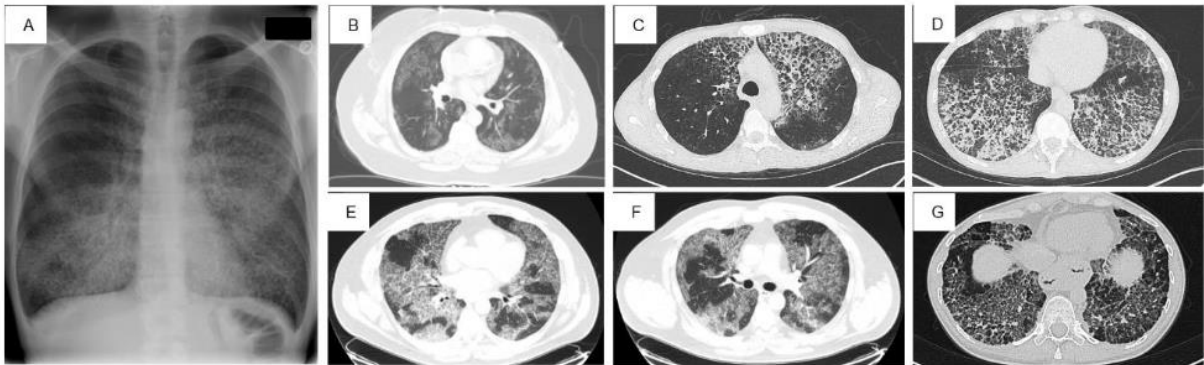
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1 **Table 3: Future Research Needs**

<ul style="list-style-type: none"> • Biomarkers (molecular, inflammatory, cytokines) in BAL and serum for disease progression, treatment response and prognosis
<ul style="list-style-type: none"> • Definition of core outcome set
<ul style="list-style-type: none"> • Development of PAP disease specific patient reported outcome measures
<ul style="list-style-type: none"> • Establish minimum clinically important differences (MCID) in current and new outcomes
<ul style="list-style-type: none"> • Establishment of criteria to categorize the severity of disease (mild, moderate, severe)
<ul style="list-style-type: none"> • Definition and diagnostic criteria of fibrotic PAP
<ul style="list-style-type: none"> • Clarify the role of opportunistic infections as an indicator of disease severity or a complication
<ul style="list-style-type: none"> • Explore/use new trial designs that consider the severity of disease of the patients (mild, moderate, severe)
<ul style="list-style-type: none"> • Compare WLL procedures (technique, concomitant physiotherapy etc.)
<ul style="list-style-type: none"> • Homogenisation of WLL standard protocol to allow better comparison across populations and therapies
<ul style="list-style-type: none"> • Definition on WLL indications, contraindications, and parameters to define treatment responsiveness
<ul style="list-style-type: none"> • Comparison of sequential or combination therapy with WLL and inhaled GM-CSF
<ul style="list-style-type: none"> • Comparison of continuous vs. intermittent GM-CSF treatment regimens
<ul style="list-style-type: none"> • Evaluate individualised dose and treatment duration of GM-CSF therapy
<ul style="list-style-type: none"> • Evaluate the role of GM-CSF therapy as rescue therapy
<ul style="list-style-type: none"> • Evaluate the role of inhaled GM-CSF in children with aPAP
<ul style="list-style-type: none"> • Evaluate safety and clinical effectiveness of combination therapy with GM-CSF substitution and rituximab
<ul style="list-style-type: none"> • Systematic evaluation of the effectiveness rituximab therapy for GM-CSF
<ul style="list-style-type: none"> • Evaluate of the effectiveness of plasmapheresis and standardisation of technique
<ul style="list-style-type: none"> • Outcome of lung transplantation in patients with different types of PAP
<ul style="list-style-type: none"> • Development of a specific registry for patients with PAP who undergo lung transplantation
<ul style="list-style-type: none"> • Development of a registry for patients with PAP

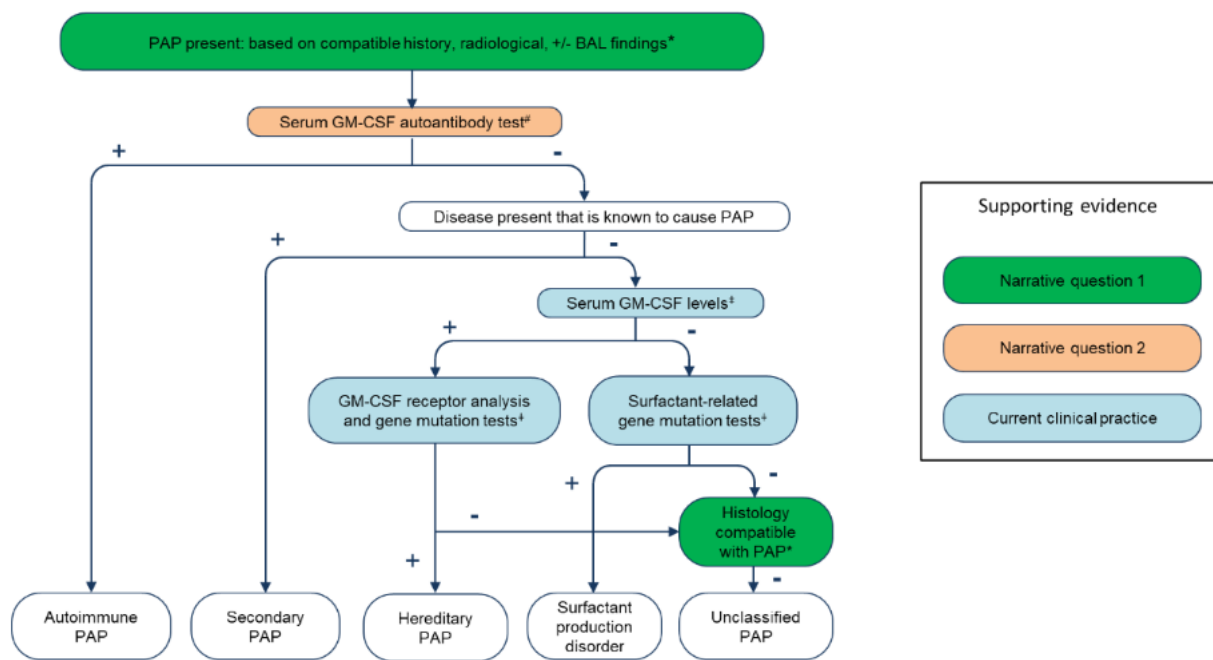
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1 **Figure Legends.**



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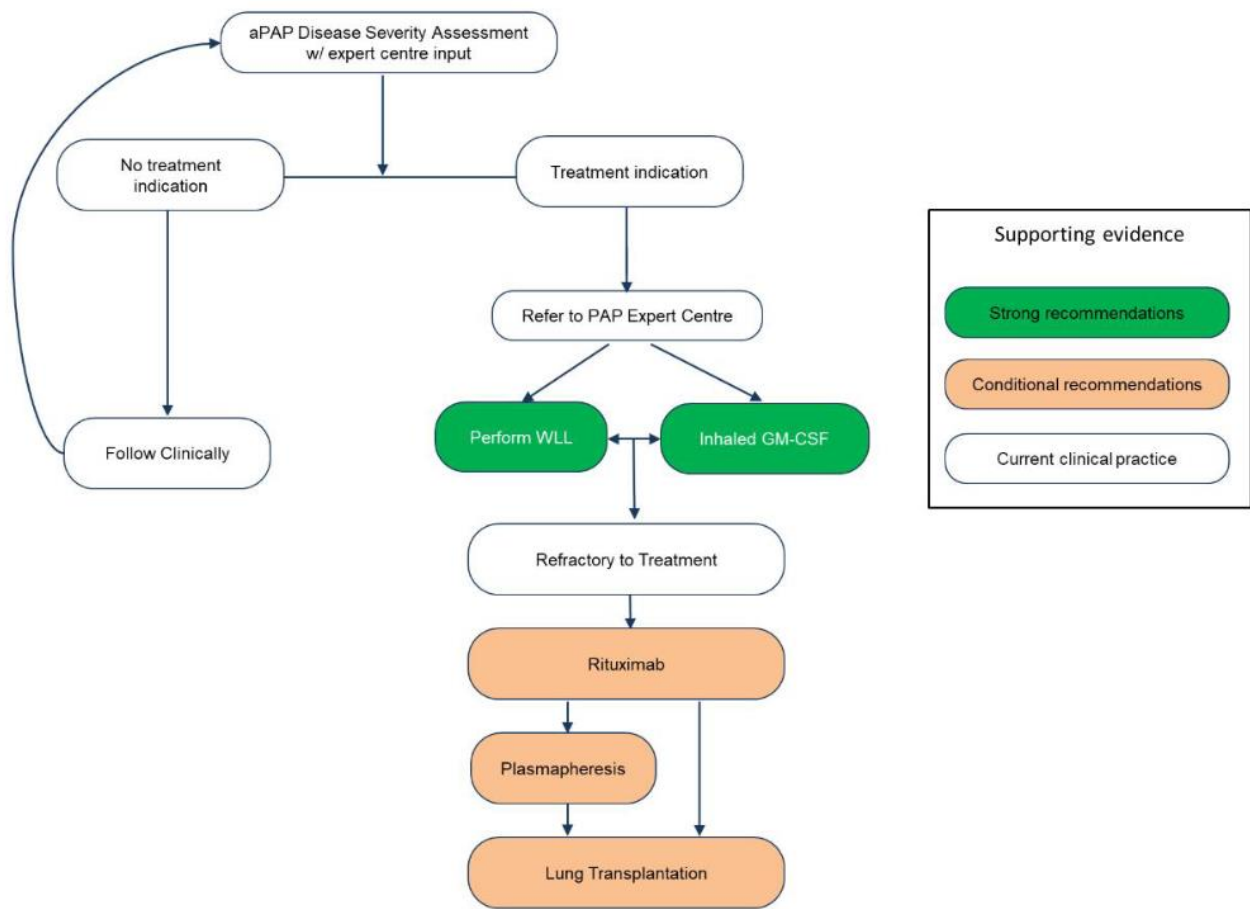
3 **Figure 1: Radiological findings in PAP.** Representative images from chest radiograph (A) and CT
4 of the thorax demonstrating the diversity of radiographic findings in PAP (B-G). (B) Ground-glass
5 infiltrates in a mild case of aPAP without interlobular septal thickening. (C-F) CT images
6 demonstrating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



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2

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



1

2 **Figure 3: Hierarchy of Treatments in autoimmune PAP.** Treatment is indicated in patients with
 3 active or worsening disease. The appropriateness of treatment should be based on the degree of
 4 impairment of lung function, CT imaging changes, blood oxygenation and symptoms. Depending on
 5 immediacy of treatment need either WLL or exogenous GM-CSF should be offered as first line
 6 therapy. If these fail to show sustained benefit or in life threatening respiratory failure, rituximab or
 7 plasmapheresis may be considered. Lung transportation remains an option for refractory cases.

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