Management of Pulmonary Hypertension Due to Chronic Lung Disease [CME]

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ABSTRACT: Pulmonary hypertension (PH) is a known complication of chronic parenchymal lung diseases, including chronic obstructive lung disease, interstitial lung diseases, and more rare parenchymal lung diseases. Together, these diseases encompass two of the five clinical classifications of PH: group 3 (chronic lung disease [CLD] and/or hypoxia) and group 5 (unclear and/or multifactorial mechanisms). The principal management strategy in PH associated with CLD is optimization of the underlying lung disease. There has been increasing interest in therapies that treat pulmonary arterial hypertension (group 1, PAH), and although some studies have explored the use of these oral PAH-targeted therapies to treat PH associated with CLD , there is currently no evidence to support their routine use; in fact, some studies suggest harm. Inhaled therapies that target the pulmonary vasculature may avoid certain problems observed with oral PAH therapies. Recent studies suggest a promising role for inhaled PAH therapies in group 3 PH, but this requires further study. The objective of this article is to review the current treatment strategies for group 3 and group 5 PH.

INTRODUCTION

Pulmonary hypertension (PH) is a notable complication of chronic parenchymal lung disease. Chronic lung disease (CLD)-related PH is most commonly caused by chronic obstructive pulmonary disease and interstitial lung diseases. Other rarer parenchymal lung diseases can also cause PH, including combined pulmonary fibrosis and emphysema (CPFE), lymphangioleiomyomatosis, sarcoidosis, and pulmonary Langerhans cell histiocytosis. Lung diseases fall under group 3 (due to CLD and/or chronic hypoxia) and group 5 (unclear and/or multifactorial mechanisms) within the most recent PH clinical classification system (see PH clinical classifications in the manuscript by Beshay et al. on page 9 of this issue).[1,2]

Based on the 2019 update of the 6th World Symposium on Pulmonary Hypertension, PH is defined as having a mean pulmonary artery pressure (mPAP) ≥ 20 mm Hg in the supine position at rest as measured on right heart catheterization (RHC).[2] Similar to those with group 1 PH due to pulmonary arterial hypertension (PAH), patients with lung-disease−related PH have a precapillary hemodynamic profile that includes an elevated pulmonary vascular resistance (PVR) > 3 Wood units (WU) and a normal pulmonary arterial wedge pressure (PAWP) or left ventricular end-diastolic pressure ≤ 15 mm Hg.[3] When present, PH causes more severe symptoms and exercise intolerance and portends a worse prognosis in patients with CLD.[4]

It can be clinically challenging to differentiate patients with PH due to lung disease from those with PAH and comorbid mild lung disease (Figure 1). The principle of managing PH due to CLD is primarily to optimize treatment of the underlying disorder and to identify and manage other potential contributing factors such as concurrent left heart dysfunction, sleep-disordered breathing, and chronic thromboembolic disease.[3] However, histopathologic evidence of pulmonary vascular remodeling and similar precapillary hemodynamics in patients with CLD-associated PH and those with PAH[5,6] has spurred interest in the use of PAH therapies in group 3 PH. It is important to note that oral therapies for PAH have not been approved for use in PH due to CLD, and there is a lack of evidence to support their efficacy. Furthermore, there is concern that by inducing vasodilation in poorly ventilated areas of the lung, PAH therapies can worsen ventilation-perfusion matching and further exacerbate arterial hypoxemia.[7] Therefore, caution must be exercised in the use of PAH therapies in patients with CLD-associated PH. Treatment decisions should be carefully considered solely in specialized PH referral centers with extensive experience in the use of these therapies or in the context of clinical trials. This article reviews the current evidence pertaining to specific therapies for PH associated with CLD.

PULMONARY HYPERTENSION ASSOCIATED WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

According to international guidelines, optimization of underlying chronic obstructive pulmonary disease (COPD) is the primary

approach for managing COPD-associated PH.[8] The pathophysiologic mechanisms of PH in COPD include airflow limitation, hyperinflation and compression of alveolar capillary vessels, alveolar hypoxia, vasoconstriction, and destruction or remodeling in the pulmonary vascular bed, which can all be present in varying degrees, ultimately leading to elevated PVR and mPAP.[9-11] Supplemental oxygen therapy remains a key component of COPD management in patients with resting hypoxemia (PaO_2 < 60 mm Hg or < 55 mm Hg in the presence of PH) because continuously administered oxygen for at least 18 hours per day has been shown to increase survival, improve PVR and cardiac function, and possibly slow the progressive increase in mPAP.[12] Patients with right heart failure and edema may be managed with diuretics and sodium restriction. Due to the poor associated prognosis, moderate-to-severe PH in the setting of COPD is considered a criterion for lung transplantation in otherwise eligible patients.[13]

There is significant interest in the use of PAH therapies for PH in COPD, particularly in patients with severe PH, defined as mPAP ≥ 35 mm Hg or mPAP ≥ 25 mm Hg with a cardiac index < 2.0 L/min/m²·[3,8] Severe PH is rare in COPD and often caused by concomitant left ventricular dysfunction or other pulmonary diseases; however, approximately 1% of cases have severe PH in the absence of another confounding factor. These patients may potentially have a "pulmonary vascular phenotype" of COPD and exhibit severe PH and a cardiovascular limitation to exercise without severe airflow obstruction.[14,15] Therefore, pulmonary vasodilator therapies could be of interest in this subgroup population with severe hemodynamic impairment and lower concern for ventilation-perfusion mismatch and hypoxemia, although evidence to support the use of PAH therapies in this context is limited.[14-16]
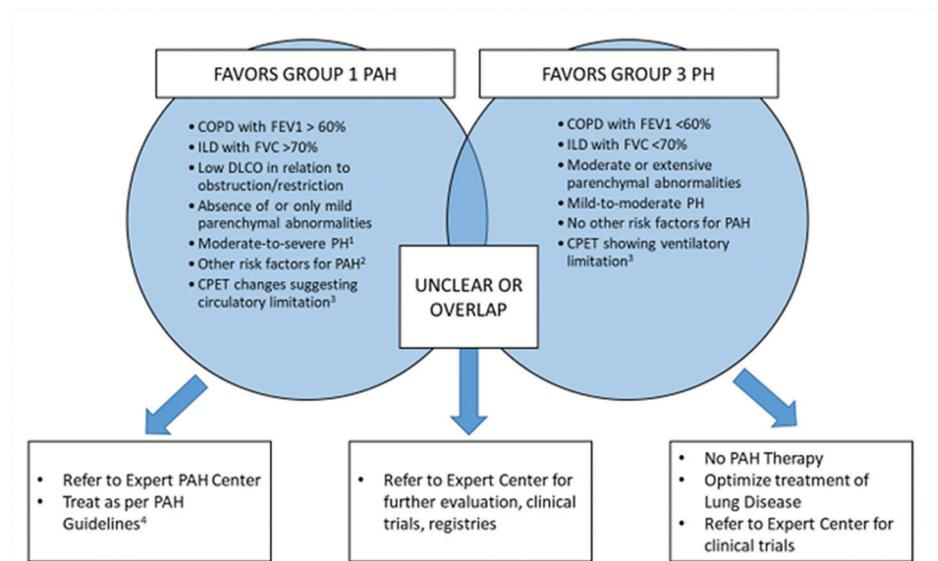

Figure 1.

Differentiation between group 1 pulmonary hypertension (PH) and group 3 PH.[1] Figure courtesy of authors. COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; DLCO: carbon monoxide diffusing capacity test; CPET: cardiopulmonary exercise test

[1] Moderate-to-severe PH defined as mean pulmonary arterial pressure ≥ 35 mm Hg, or ≥ 25 mm Hg with a cardiac index < 2.0 L/min/m²

[2] Other risk factors include connective tissue disease, portal hypertension, human immunodeficiency virus infection, exposure to definite or probable medications that cause group 1 PH, genetic mutations, congenital heart disease

[3] Features of circulatory limitation include preserved breathing reserve, low oxygen pulse, low cardiac output/VO_2 slope, no change or decrease in $PaCO_2$ during exercise. Features of ventilatory limitation include low breathing reserve, normal oxygen pulse, normal cardiac output/VO_2 slope, increase in $PaCO_2$ during exercise, dynamic hyperinflation.

Most randomized controlled trials (RCTs) evaluating PAH therapies in COPD-associated PH have tested phosphodiesterase-5 inhibitors (PDE5i), which have mostly demonstrated equivocal results, with no mortality or consistent functional benefit (Table 1).[17-23] An RCT conducted by Vitulo et al. compared sildenafil with placebo to determine the long-term hemodynamic effects of sildenafil in COPD patients with severe PH. They demonstrated a significant reduction in PVR as well as significant improvements in dyspnea and quality of life scores, both of which were secondary outcomes. However,

there was no change in PaO_2 or 6-minute walk distance (6MWD).[21] A recent meta-analysis by Hao et al. noted modest improvements in 6MWD in patients treated with sildenafil but no change in reported dyspnea or functional symptoms.[22] Further studies of sildenafil or other PDE5i would be of interest in the specific subgroups of patients with mild COPD and severe PH.

Treatment with endothelin receptor antagonists such as bosentan, ambrisentan, or macitentan is not supported by existing evidence.[23,24] Similarly, while studies have been

AUTHOR	REF	N	DRUG	SEVERITY OF PH	FOLLOW-UP PERIOD	END POINT(S)
PDE5 INHIBITORS						
Rao et al., 2011	17	33	Sildenafil 20 mg TID vs placebo	sPAP > 40 mm Hg on echo	12 weeks	6MWD: +190 m vs placebo sPAP: decreased
Lederer et al., 2012	18	10	Sildenafil 25 mg TID vs placebo	No PH	4 weeks	6MWD: no effect VO_2: no effect QoL: worsened
Blanco et al., 2013	19	60	Sildenafil 20 mg TID vs placebo in patients under-going pulmonary rehabilitation	mPAP 31 ± 5 mm Hg	12 weeks	Cycle endurance time: no effect 6MWD: no effect VO_2: no effect
Goudie et al., 2014	20	120	Tadalafil 120 mg daily vs placebo	sPAP 42 ± 10 mm Hg (as estimated on echocardiogram)	12 weeks	sPAP: decreased -12.3 mm Hg 6MWD: no effect QoL: no effect BNP: no effect
Vitulo et al., 2017	21	28	Sildenafil 20 mg TID vs placebo	mPAP 25 mm Hg in 68% mPAP 39 ± 8 mm Hg PVR 7 ± 2.6 WU	16 weeks	PVR: -1.38 WU CI: +0.42 L/min/m² BODE: improved 6MWD: no effect SF-36: +9.85 units
ENDOTHELIN RECEPTOR ANTAGONISTS						
Stoltz et al., 2008	23	30	Bosentan 62.5 mg BID for 2 weeks followed by 125 mg BID vs placebo	mPAP at rest ≥ 30 mm Hg	12 weeks	6MWD: +10 m vs placebo
Valerio et al., 2009	24	32	Bosentan 125 mg BID vs placebo	mPAP 37 ± 5 mm Hg	18 months	6MWD: +65 m mPAP: - 6 mm Hg PVR: -50 dynes·sec·cm⁻⁵ BODE index: improved

Table 1.
Randomized trials of therapies proposed in the management of chronic obstructive pulmonary disease (COPD)-associated pulmonary hypertension (PH). Table courtesy of authors. PDE5: phosphodiesterase type-5; TID: three times a day; sPAP: systolic pulmonary artery pressure; 6MWD: 6-minute walk distance; VO_2: oxygen uptake; QoL: quality of life; mPAP: mean pulmonary artery pressure; BNP: brain natriuretic peptide; PVR: pulmonary vascular resistance; WU: Wood units; BODE: body mass index, obstruction, dyspnea, exercise capacity index; CI: cardiac index; SF-36: Short Form 36; BID: twice daily

conducted on calcium channel blockers, inhaled nitrous oxide, inhaled and intravenous prostacyclins, and guanylate cyclase stimulators in the context of COPD-associated PH, no studies support their routine use in these patients and they are not approved by regulatory bodies for this indication.[3]

Inhaled vasodilators have theoretical advantages in terms of avoiding worsening ventilation-perfusion mismatch, but the data are mixed. In patients with COPD and severe PH, inhaled nitric oxide (NO) may actually worsen gas exchange by inhibiting hypoxic vasoconstriction.[25,26]

Conversely, more recent studies suggest some benefit of NO inhalation on pulmonary vascular function in mild COPD without PH and in patients with PH.[27,28] In nonrandomized studies of COPD patients with PH, inhaled iloprost (a prostacyclin analogue) improved hemodynamics and ventilatory efficiency without a detrimental effect on gas exchange.[29,30]

PULMONARY HYPERTENSION ASSOCIATED WITH INTERSTITIAL LUNG DISEASES

As with COPD, the treatment of PH associated with interstitial lung diseases (ILD) consists of optimizing the underlying condition.[3] ILD-related PH is most frequently seen in patients with idiopathic pulmonary fibrosis (IPF). The main mechanism of PH in ILD is due to parenchymal fibrosis and vascular bed destruction, although other concomitant factors can exist, including venous thromboembolism, sleep-disordered breathing, and left heart dysfunction with postcapillary PH.[31-34] The only approved pharmacologic therapies for treating IPF are the antifibrotic agents pirfenidone and nintedanib, which slow the rate of disease progression but have shown no effect on the development or progression of pulmonary vascular disease.

There has been much effort in testing PAH-targeted therapies for patients with IPF and other ILDs (Table 2). Unfortunately, multiple RCTs have demonstrated no benefit of endothelin receptor antagonists.[35-38] Rather, there have been major safety concerns, as one trial using ambrisentan was terminated early due to increased risk of harm in the treatment group.[37] The recent RISE-IIP study (riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension) was a phase 2b placebo-controlled RCT examining the effectiveness of riociguat (a soluble guanylate cyclase stimulator) in patients with ILD-related PH. This study was also terminated early because it demonstrated serious adverse events and increased mortality in the treatment group (11 deaths with riociguat and 3 with placebo)[39]; therefore, riociguat is not recommended for ILD-related PH.

The STEP-IPF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis) RCT evaluated sildenafil in IPF patients but was not specifically designed to enroll patients with IPF and PH.[40] Although the STEP-IPF primary end point was not achieved, there was a signal for improved exercise tolerance and quality of life in the subgroup with baseline RV dysfunction.[41] In contrast, a recent RCT demonstrated no benefit in the addition of sildenafil to pirfenidone in IPF patients with no firm diagnosis of PH.[42] As with COPD patients, there is concern that pulmonary vasodilation with PDE5i may aggravate hypoxemia in patients with ILD. Finally, a recent phase 2b/3 RCT demonstrated a modest improvement in moderate/vigorous physical activity in patients with fibrotic ILD who are at risk for PH and who were treated with pulsed inhaled NO at 30 μg/kg ideal body weight/h over an 8-week period.[43] Although the clinical implications of this remain unclear, inhaled vasodilators may have particular advantages and may mitigate concerns over worsening ventilation-perfusion matching.

Research on the management of ILD-associated PH has targeted patients with systemic sclerosis (SSc) due to its association with group 1 PAH. SSc causes PH through multiple mechanisms, including PAH (group 1), postcapillary PH secondary to left ventricular fibrosis and diastolic dysfunction (group 2), precapillary PH secondary to ILD (group 3), and pulmonary veno-occlusive disease.[44] Although PAH therapies are effective in SSc-induced PAH, several observational studies have shown no benefit from PAH-targeted therapies when significant ILD is present. No improvements were seen in functional class or 6MWD, and even the presence of ILD is known to portend a worse prognosis.[44,45] A recent observational study demonstrated modest hemodynamic improvements in SSc ILD-associated PH when treated with PAH therapies, but no significant improvement was seen in 6MWD, and only 13% of patients experienced improved symptoms.[46] This dissociation between hemodynamic benefits, symptoms, and exercise capacity indicates that PH may not be the key mechanism of limitation in ILD patients because

symptoms and exercise limitation are frequently multifactorial and related to restrictive lung physiology, impaired gas exchange, and peripheral factors (eg, deconditioning, myopathy, arthritis). Therefore, there is no clear evidence that patients with SSc and moderate-to-severe ILD with PH benefit from PAH therapies.

Research on inhaled PAH-targeted therapies may yield more promising results for improved exercise tolerance in patients with ILD-associated PH, and the therapeutic landscape may change in the coming years. The INCREASE (Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE) RCT tested the effect of inhaled treprostinil (a prostacyclin analogue) in patients with ILD. There were 326 participants with ILD of various etiologies randomized to inhaled treprostinil or a placebo four times daily. After 16 weeks of treatment, inhaled treprostinil improved placebo-corrected 6MWD (+31.12 m, 95% CI, 16.85-45.39) while also offering statistically significant improvements in secondary outcomes including N-terminal pro-brain natriuretic peptide and a 39% reduction in time to clinical worsening. Importantly, the effect of inhaled treprostinil on 6MWD was consistent across age groups, between men and women, and between patients with idiopathic interstitial pneumonias and connective tissue disease. There were some important insights from subgroup analyses that may help with patient selection. First, the effect of inhaled treprostinil was a 40.8 m (95% CI 24.1-57.6) improvement in 6MWD in patients with a PVR ≥ 4 WU but tended to be null in patients with a PVR < 4 WU. Additionally, there was a less impressive effect in those with 6MWD > 350 m at baseline and in patients with CPFE. The most frequent adverse events in the inhaled treprostinil group were cough (43.6%), headache (27.6%), and dyspnea (25.2%), which were similar to placebo. Throat irritation (12.3%) and oropharyngeal pain (11%) were more common with inhaled treprostinil, however. Serious adverse events, such as respiratory failure, pneumonia, or death, occurred in 23.3% of patients with inhaled treprostinil and 25.8% of patients with placebo.[47]

While there is now evidence supporting inhaled PAH therapies, data are still insufficient to recommend oral PAH therapies in ILD-associated PH, and they are not approved by regulatory bodies for this indication. Inhaled vasoactive therapies present a promising new strategy for ILD patients with PH since they may avoid the potentially detrimental effects of oral therapies on ventilation-perfusion matching and hypoxemia and could minimize systemic toxicities or side effects such as hypotension. Optimization of medical therapy should be the goal for ILD patients, including supplemental oxygen and antifibrotic agents such as nintedanib or pirfenidone, where appropriate.[48] As with COPD, a diagnosis of PH in a patient with ILD should prompt consideration of lung transplantation.[13]

AUTHOR	REF	N	LUNG DISEASE	DRUG	PH PATIENTS INCLUDED?	FOLLOW-UP PERIOD	END POINT(S)
ENDOTHELIN RECEPTOR ANTAGONISTS							
King et al., 2008	35	158	IPF	Bosentan 62.5 mg BID for 4 weeks followed by 125 mg BID vs placebo	Yes: mild PH on echo (RVSP < 50 mm Hg) included	12 months	6MWD: no difference Disease progression: favors bosentan Lung function: no difference Dyspnea and QoL: favors bosentan
King et al., 2011	36	616	IPF	Bosentan 62.5 mg BID for 4 weeks followed by 125 mg BID vs placebo	Yes	20 months	Time to IPF worsening or death: no difference QoL: no difference Dyspnea: no difference Change in FVC: no difference
Raghu et al., 2013	37	494	IPF	Ambrisentan 10 mg daily vs placebo	Yes, but excluded patients on other long-term PH therapies	34 weeks	Time to IPF progression: terminated early due to higher disease progression in ambrisentan group Hospitalizations: increased in ambrisentan group 6MWD: no difference Lung function decline: no difference
Raghu et al., 2013	38	494	IPF	Macitentan 10 mg vs placebo	Yes	12 months	Change in FVC: no difference Time to IPF worsening or death: no difference Dyspnea: no difference Adverse events: no difference
SOLUBLE GUANYLATE CYCLASE STIMULATORS							
Nathan et al., 2019	39	147	IIP	Riociguat, up to 2.5 mg TID vs placebo	Yes	26 weeks	6MWD: no difference Time to clinical worsening: no difference
PDE5 INHIBITORS							
Zisman et al., 2010	40	180	IPF	Sildenafil 20 mg TID vs placebo	Yes	12 weeks	6MWD improvement of > 20%: no significant difference
Han et al., 2013	41	119	IPF	Sildenafil 20 mg TID vs placebo	Yes	12 weeks	6MWD improvement of > 20%: no significant difference QoL improvement: no significant difference
Behr et al., 2020	42	177	IPF	Sildenafil 20 mg TID with pirfenidone vs placebo with pirfenidone	Yes	52 weeks	Progression-free survival: no significant difference 6MWD decline < 15%: no significant difference
INHALED MEDICATIONS							
Nathan et al., 2020	43	41	Fibrosing ILD	Inhaled NO 30-45 µg/kg IBW/h vs. placebo	Subjects stratified as low-, intermediate- and high-probability of PH. Subjects included if PH proven on RHC.	8 weeks	Moderate/ vigorous physical activity: statistically significant improvement
Waxman et al., 2020	47	326	Any ILD	Treprostinil 60-72 µg inhaled vs. placebo	Yes	16 weeks	Mean change from baseline in peak 6MWD through week 16: +31.12 m (95% CI, 16.85-45.39) NT-proBNP: improved Time to clinical worsening: 39% reduction

Table 2.

Randomized trials of therapies proposed in the management of interstitial lung disease–associated pulmonary hypertension (PH). Table courtesy of authors. IPF: idiopathic pulmonary fibrosis; BID: twice daily; RVSP: right ventricular systolic pressure; 6MWD: 6-minute walk distance; QoL: quality of life; FVC: forced vital capacity; TID: three times daily; ILD: interstitial lung disease; IIP: idiopathic interstitial pneumonia; IBW: ideal body weight

PULMONARY HYPERTENSION DUE TO OTHER RARE PARENCHYMAL LUNG DISEASES

Pulmonary Hypertension in Patients with Sarcoidosis

The management of PH in individuals with sarcoidosis is complex because the mechanisms of PH in these patients can be multifactorial, heterogeneous, and often combined. If precapillary PH is established in a patient with sarcoidosis, there are three primary mechanisms that may contribute, each with different treatment strategies: (1) granulomatous pulmonary vasculopathy; (2) vascular bed destruction from lung parenchymal disease; and (3) vascular remodeling due to chronic hypoxia (also in the case of severe lung parenchymal involvement).[49] Postcapillary PH can be due to left ventricular involvement or progressive massive fibrosis, which can cause compression of the mediastinal vascular structures among other potential mechanisms.[50] The presence of PH in patients with sarcoidosis is associated with worse functional capacity and survival.[49,51,52]

Overall, there is no evidence supporting the use of PAH-specific therapies in patients with sarcoidosis-associated PH.[53] There has been only one RCT, which demonstrated that bosentan was effective at lowering mPAP and PVR at 16 weeks but had no significant effect on any functional parameters.[54] Other observational studies have similarly reported improvements in hemodynamics with no improvement in functional parameters with oral or parenteral PAH therapies.[52,55,56] Use of PAH therapies is not associated with better survival in observational studies,[52,57] although this could be subject to confounding by indication since more severely impaired patients tend to be treated with off-label PAH drugs. Disease-specific immunosuppressive therapies can be considered in patients with sarcoidosis-associated PH caused by mechanical compression of pulmonary vasculature by large mediastinal lymph nodes, fibrosing mediastinitis, or proven pulmonary vascular granulomatous inflammation, though the specific role of these medications is not well established.[53]

Pulmonary artery angioplasty, with or without stenting of focal stenoses, can be a useful therapy in selected patients.[58] A recent systematic review and meta-analysis found that angioplasty with or without stenting may lead to improvements in 6MWD,[59] and this remains an option in some patients.

Pulmonary Hypertension in Patients with Pulmonary Langerhans Cell Histiocytosis

Pulmonary Langerhans cell histiocytosis (PLCH) is a rare lung disease caused by smoking and is characterized by the presence of Langerhans-like cells with stellate scar formation, interstitial fibrosis, parenchymal nodules, and lung cysts as well as airflow obstruction on pulmonary function testing. A process resembling pulmonary veno-occlusive disease caused by diffuse vasculopathy and fibrotic obliteration of the pulmonary veins can also occur and contribute to PH.[60] Management of PH in PLCH focuses on treating the underlying lung disease, including smoking cessation and potentially cladribine as a chemotherapeutic agent.[61] PAH-specific therapies have not been robustly studied in this rare condition. A small retrospective observational study demonstrated improvements in both functional and hemodynamic parameters in patients with PLCH-associated PH receiving PAH-specific therapies,[62] but PAH

SUGGESTED INTERVENTIONS FOR PATIENTS WITH GROUP 3 AND GROUP 5 PH[1]	
All patients	Optimization of the underlying pulmonary condition, including smoking cessation and relevant disease-specific therapies
	Supplemental O_2 therapy in patients with resting hypoxemia
	Referral for lung transplantation, if eligible
INTERVENTIONS THAT MAY BE CONSIDERED FOR PATIENTS WITH GROUP 3 AND GROUP 5 PH[1]	
All patients	Referral to a PH expert center for consideration of invasive diagnostic testing and individualized therapy or enrollment in clinical trials
INTERVENTIONS THAT SHOULD NOT BE ROUTINELY CONSIDERED FOR PATIENTS WITH WHO GROUP 3 AND GROUP 5 PH[1]	
All patients	Phosphodiesterase type-5 (PDE5) inhibitors, endothelin receptor antagonists (ERAs); calcium channel blockers; inhaled nitric oxide; inhaled and intravenous prostacyclins; guanylate cyclase stimulators
INTERVENTIONS THAT ARE CURRENTLY UNDER INVESTIGATION OR CONSIDERATION ON AN INDIVIDUALIZED OR EXPERIMENTAL BASIS FOR PATIENTS WITH GROUP 3 AND GROUP 5 PH	
COPD-associated PH	PDE5-inhibitors (sildenafil)[21,22]; inhaled treprostinil (NCT03496623); inhaled soluble guanate cyclase modulator (NCT04370873)
ILD-associated PH	Inhaled pulmonary vasodilators, including inhaled treprostinil[47]
Sarcoidosis-associated PH	Bosentan[52,53,55,56]; pulmonary artery angioplasty, with or without stenting of focal stenoses[58,59]

Table 3.

Approach to management of lung disease-associated pulmonary hypertension (PH). Table courtesy of authors. COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; WHO: World Health Organization

therapies must be considered with caution given the risk of inducing pulmonary edema if pulmonary veno-occlusive changes are prominent.

Pulmonary Hypertension in Patients with Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare condition that almost exclusively affects women and is characterized by diffuse cystic lung disease, chylous pleural effusions, ascites, renal angiomyolipomas, and lymphangioleiomyomas.[63] The mechanism of PH largely lies in pulmonary vascular infiltration of LAM cells leading to elevated pulmonary arterial pressure. This occurs in 8% of all patients with LAM and 45% of patients with LAM who are referred for lung transplantation.[64] LAM-associated PH has not been well studied, and the evidence for PAH therapies in these patients is primarily limited to case reports. One small study of 20 patients with LAM-associated PH, six of whom were treated with bosentan or sildenafil, demonstrated hemodynamic improvements but no improvement in functional parameters.[65] Therefore, therapy should be directed at treating the underlying condition, with no specific recommendation for treatment of PH in these patients.[63] Table 3 shows management approaches for PH associated with lung disease.

CONCLUSION

PH is a known complication of CLDs, adversely affecting survival and contributing to impaired functional capacity. Despite promising results from observational studies and some signals of benefit in RCTs, the existing evidence does not support the use of PAH therapies in patients with CLD-related PH. Furthermore, some PAH therapies may be harmful in certain lung diseases, such as the experience with ambrisentan in IPF. Therefore, the core treatment strategy for PH is directed at medical optimization of the underlying lung disease, provision of supplemental oxygen to patients with hypoxemia, and lung transplantation referral in eligible patients. Attention should also be paid to diagnosing and treating other potential causes and aggravating factors for PH in this group, including left heart disease, sleep-disordered breathing, and thromboembolic disease. There is a need for well-designed and adequately powered clinical trials to investigate the use of PAH therapies, particularly inhaled agents, in patients with severe PH in the context of mild-to-moderate lung disease. Patients with PH due to CLD should be evaluated in specialized expert referral centers for consideration in clinical trials or for PAH-targeted therapies on an individualized basis with close follow-up.

KEY POINTS

- Pulmonary hypertension (PH) is an important complication of many lung diseases and is associated with worse outcomes.
- Management of PH due to lung disease consists of optimizing treatment of the underlying pulmonary condition and contributing comorbidities—such as left heart disease, thromboembolic disease, and sleep disordered breathing—as well as supplemental oxygen and lung transplantation for suitable candidates.
- There is little evidence to support the use of medications that treat pulmonary arterial hypertension (PAH) in patients with PH due to lung disease. In some cases, PAH therapies can be harmful, but there is emerging interest in using inhaled pulmonary vasodilator therapies in PH due to lung disease.

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REFERENCES

1. Galiè N, Humbert M, Vachiery J-L, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J. 2015 Oct;46(4):903-75. doi: 10.1183/13993003.01032-2015.

2. Simmoneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019 Jan 24;53(1):1801913. doi: 10.1183/13993003.01913-2018.

3. Nathan SD, Barbera JA, Gaine SP, et al. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J. 2019 Jan 24;53(1):1801914. doi: 10.1183/13993003.01914-2018.

4. Seeger W, Adir Y, Barberà JA, Champion H, et al. Pulmonary hypertension in chronic lung diseases. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl):D109-16. doi: 10.1016/j.jacc.2013.10.036.

5.   Sakao S, Voelkel NF, Tatsumi K. The vascular bed in COPD: pulmonary hypertension and pulmonary vascular alterations. Eur Respir Rev. 2014 Sep;23(133):350-5. doi: 10.1183/09059180.00007913.

6.   Ruffenach G, Hong J, Vaillancourt M, Medzikovic L, Eghbali M. Pulmonary hypertension secondary to pulmonary fibrosis: clinical data, histopathology and molecular insights. Respir Res. 2020 Nov 18;21(1):303. doi: 10.1186/s12931-020-01570-2.

7.   Prins KW, Duval S, Markowitz J, Pritzker M, Thenappan T. Chronic use of PAH-specific therapy in World Health Organization Group III Pulmonary Hypertension: a systematic review and meta-analysis. Pulm Circ. 2017 Mar 24;7(1):145-155. doi: 10.1086/690017.

8.   Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med. 2017 Mar 1;195(5):557-582. doi: 10.1164/rccm.201701-0218PP.

9.   Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. Eur Respir J. 2008 Nov;32(5):1371-85. doi: 10.1183/09031936.00015608.

10. Wells MJ, Iyer AS, Rahaghi FN, et al. Pulmonary artery enlargement is associated with right ventricular dysfunction and loss of blood volume in small pulmonary vessels in chronic obstructive pulmonary disease. Circ Cardiovasc Imaging. 2015 Apr; 8(4): 10.1161/CIRCIMAGING.114.002546 e002546. doi: 10.1161/CIRCIMAGING.114.002546.

11. Poor HD, Kawut SM, Chia-Ying Liu, et al. Pulmonary hyperinflation due to gas trapping and pulmonary artery size: The MESA COPD Study. PLoS One. 2017 May 2;12(5):e0176812.

12. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med. 1980 Sep;93(3):391-8. doi: 10.7326/0003-4819-93-3-391.

13. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015 Jan;34(1):1-15. doi: 10.1016/j.healun.2014.06.014.

14. Kovacs G, Agusti A, Barberà JA, et al. Pulmonary Vascular Involvement in Chronic Obstructive Pulmonary Disease. Is There a Pulmonary Vascular Phenotype? Am J Respir Crit Care Med. 2018 Oct 15;198(8):1000-1011. doi: 10.1164/rccm.201801-0095PP.

15. Weatherald J, Montani D, Humbert M. Seeing the Forest for the (Arterial) Tree: Vascular Pruning and the Chronic Obstructive Pulmonary Disease Pulmonary Vascular Phenotype. Am J Respir Crit Care Med. 2019 Aug 15;200(4):406-408. doi: 10.1164/rccm.201901-0248ED.

16. Boerrigter BG, Bogaard HJ, Trip P, et al. Ventilatory and cardiocirculatory exercise profiles in COPD: the role of pulmonary hypertension. Chest. 2012 Nov;142(5):1166-74. doi: 10.1378/chest.11-2798.

17. Rao RS, Singh S, Sharma BB, Agarwal VV, Singh V. Sildenafil improves six-minute walk distance in chronic obstructive pulmonary disease: a randomised, double-blind, placebo-controlled trial. Indian J Chest Dis Allied Sci. Apr-Jun 2011;53(2):81-5.

18. Lederer DJ, Bartels MN, Schluger NW, et al. Sildenafil for chronic obstructive pulmonary disease: a randomized crossover trial. COPD. 2012 Jun;9(3):268-75. doi: 10.3109/15412555.2011.651180.

19. Blanco I, Santos S, Gea J, et al. Sildenafil to improve respiratory rehabilitation outcomes in COPD: a controlled trial. Eur Respir J. 2013 Oct;42(4):982-92. doi: 10.1183/09031936.00176312.

20. Goudie AR, Lipworth BJ, Hopkinson PJ, Wei L, Struthers AD. Tadalafil in patients with chronic obstructive pulmonary disease: a randomised, double-blind, parallel-group, placebo-controlled trial. Lancet Respir Med. 2014 Apr;2(4):293-300. doi: 10.1016/S2213-2600(14)70013-X.

21. Vitulo P, Stanziola A, Confalonieri M, et al. Sildenafil in severe pulmonary hypertension associated with chronic obstructive pulmonary disease: A randomized controlled multicenter clinical trial. J Heart Lung Transplant. 2017 Feb;36(2):166-174. doi: 10.1016/j.healun.2016.04.010.

22. Hao Y, Zhu Y, Mao Y, et al. Efficacy and safety of Sildenafil treatment in pulmonary hypertension caused by chronic obstructive pulmonary disease: A meta-analysis. Life Sci. 2020 Sep 15;257:118001. doi: 10.1016/j.lfs.2020.118001.

23. Stolz D, Rasch H, Linka A, et al. A randomised, controlled trial of bosentan in severe COPD. Eur Respir J. 2008 Sep;32(3):619-28. doi: 10.1183/09031936.00011308.

24. Valerio G, Bracciale P, Grazia D'Agostino A. Effect of bosentan upon pulmonary hypertension in chronic obstructive pulmonary disease. Ther Adv Respir Dis. 2009 Feb;3(1):15-21. doi: 10.1177/1753465808103499.

25. Katayama Y, Higenbottam TW, Diaz de Atauri MJ, et al. Inhaled nitric oxide and arterial oxygen tension in patients with chronic obstructive pulmonary disease and severe pulmonary hypertension. Thorax. 1997 Feb;52(2):120-4. doi: 10.1136/thx.52.2.120.

26. Barberà JA, Roger N, Roca J, Rovira I, Higenbottam TW, Rodriguez-Roisin R. Worsening of pulmonary gas exchange with nitric oxide inhalation in chronic obstructive pulmonary disease. Lancet. 1996 Feb 17;347(8999):436-40. doi: 10.1016/s0140-6736(96)90011-2.

27. Phillips DB, Brotto AR, Ross BA, et al.; Canadian Respiratory Research Network. Inhaled nitric oxide improves ventilatory efficiency and exercise capacity in patients with mild COPD: A randomized-control cross-over trial. J Physiol. 2021 Mar;599(5):1665-1683. doi: 10.1113/JP280913.

28. Hajian B, De Backer J, Vos W, et al. Pulmonary vascular effects of pulsed inhaled nitric oxide in COPD patients with pulmonary hypertension. Int J Chron Obstruct Pulmon Dis. 2016 Jul 5;11:1533-41. doi: 10.2147/COPD.S106480.

29. Wang L, Jin YZ, Zhao QH, et al. Hemodynamic and gas exchange effects of inhaled iloprost in patients with COPD and pulmonary hypertension. Int J Chron Obstruct Pulmon Dis. 2017 Nov 22;12:3353-3360. doi: 10.2147/COPD.S141798.

30. Dernaika TA, Beavin M, Kinasewitz GT. Iloprost improves gas exchange and exercise tolerance in patients with pulmonary hypertension and chronic obstructive pulmonary disease. Respiration. 2010;79(5):377-82. doi: 10.1159/000242498.

31. Sprunger DB, Olson AL, Huie TJ, et al. Pulmonary fibrosis is associated with an elevated risk of thromboembolic disease. Eur Respir J. 2012 Jan;39(1):125-32. doi: 10.1183/09031936.00041411.

32. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest. 2006 Mar;129(3):746-52. doi: 10.1378/chest.129.3.746.

33. Lancaster LH, Mason WR, Parnell JA, et al. Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. Chest. 2009 Sep;136(3):772-8. doi: 10.1378/chest.08-2776.

34. Ghigna MR, Mooi WJ, Grünberg K. Pulmonary hypertensive vasculopathy in parenchymal lung diseases and/or hypoxia: Number 1 in the Series "Pathology for the clinician" Edited by Peter Dorfmüller and Alberto Cavazza. Eur Respir Rev. 2017 Jun 28;26(144):170003. doi: 10.1183/16000617.0003-2017.

35. King TE, Behr J, Brown KK, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2008 Jan 1;177(1):75-81. doi: 10.1164/rccm.200705-732OC.

36. King TE, Brown KK, Raghu G, et al. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011 Jul 1;184(1):92-9. doi: 10.1164/rccm.201011-1874OC.

37. Raghu G, Behr J, Brown KK, et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med. 2013 May 7;158(9):641-9. doi: 10.7326/0003-4819-158-9-201305070-00003.

38. Raghu G, Million-Rousseau R, Morganti A, Perchenet L, Behr J, MUSIC Study Group. Macitentan for the treatment of idiopathic pulmonary fibrosis: the randomised controlled MUSIC trial. Eur Respir J. 2013 Dec;42(6):1622-32. doi: 10.1183/09031936.00104612.

39. Nathan SD, Behr J, Collard HR, et al. Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study. Lancet Respir Med. 2019 Sep;7(9):780-790. doi: 10.1016/S2213-2600(19)30250-4.

40. Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR. Idiopathic Pulmonary Fibrosis Clinical Research Network. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med 2010 Aug 12;363(7):620-8. doi: 10.1056/NEJMoa1002110.

41. Han MK, Bach DS, Hagan PG, et al. Sildenafil preserves exercise capacity in patients with idiopathic pulmonary fibrosis and right-sided ventricular dysfunction. Chest. 2013 Jun; 143(6):1699-1708. doi: 10.1378/chest.12-1594.

42. Behr J, Nathan SD, Wuyts WA, et al. Efficacy and safety of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension: a double-blind, randomised, placebo-controlled, phase 2b trial. Lancet Respir Med. 2021 Jan;9(1):85-95. doi: 10.1016/S2213-2600(20)30356-8.

43. Nathan SD, Flaherty KR, Glassberg MK, et al. A Randomized, Double-Blind, Placebo-Controlled Study of Pulsed, Inhaled Nitric Oxide in Subjects at Risk of Pulmonary Hypertension Associated With Pulmonary Fibrosis. Chest. 2020 Aug;158(2):637-645. doi: 10.1016/j.chest.2020.02.016.

44. Lefèvre G, Dauchet L, Hachulla E, et al. Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: a systematic review and meta-analysis. Arthritis Rheum. 2013 Sep;65(9):2412-23. doi: 10.1002/art.38029.

45. Le Pavec J, Girgis RE, Lechtzin N, et al. Systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease: impact of pulmonary arterial hypertension therapies. Arthritis Rheum. 2011 Aug;63(8):2456-64. doi: 10.1002/art.30423.

46. Chauvelot L, Gamondes D, Berthiller J, et al. Hemodynamic Response to Treatment and Outcomes in Pulmonary Hypertension Associated With Interstitial Lung Disease Versus Pulmonary Arterial Hypertension in Systemic Sclerosis: Data From a Study Identifying Prognostic Factors in Pulmonary Hypertension Associated With Interstitial Lung Disease. Arthritis Rheum. 2021 Feb;73(2):295-304. doi: 10.1002/art.41512.

47. Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease. N Engl J Med. 2021 Jan 28;384(4):325-334. doi: 10.1056/NEJMoa2008470.

48. Raghu G, Rochwerg B, Zhang Y, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med. 2015 Jul 15;192(2):e3-19. doi: 10.1164/rccm.201506-1063ST.

49. Vis D, Boucly A, Humbert M, Weatherald J. Which patients are SaPHe in sarcoidosis-associated pulmonary hypertension? Eur Respir J. 2020 May 14;55(5):2000700. doi: 10.1183/13993003.00700-2020.

50. Nunes H, Humbert M, Capron F, et al. Pulmonary hypertension associated with sarcoidosis: mechanisms, haemodynamics and prognosis. Thorax. 2006 Jan;61(1):68-74. doi: 10.1136/thx.2005.042838.

51. Baughman RP, Engel PJ, Taylor L, Lower EE. Survival in sarcoidosis-associated pulmonary hypertension: the importance of hemodynamic evaluation. Chest. 2010 Nov;138(5):1078-85. doi: 10.1378/chest.09-2002.

52. Boucly A, Cottin V, Nunes H, et al. Management and long-term outcomes of sarcoidosis-associated pulmonary hypertension. Eur Respir J. 2017 Oct 19;50(4):1700465. doi: 10.1183/13993003.00465-2017.

53. Bandyopadhyay D, Humbert M. An update on sarcoidosis-associated pulmonary hypertension. Curr Opin Pulm Med. 2020 Sep;26(5):582-590. doi: 10.1097/MCP.0000000000000701.

54. Baughman RP, Culver DA, Cordova FC, et al. Bosentan for sarcoidosis-associated pulmonary hypertension: a double-blind placebo controlled randomized trial. Chest. 2014 Apr;145(4):810-817. doi: 10.1378/chest.13-1766.

55. Barnett CF, Bonura EJ, Nathan SD, et al. Treatment of sarcoidosis-associated pulmonary hypertension. A two-center experience. Chest. 2009 Jun;135(6):1455-1461. doi: 10.1378/chest.08-1881.

56. Bonham CA, Oldham JM, Gomberg-Maitland M, Vij R. Prostacyclin and oral vasodilator therapy in sarcoidosis-associated pulmonary hypertension: a retrospective case series. Chest. 2015 Oct;148(4):1055-62. doi: 10.1378/chest.14-2546.

57. Shlobin OA, Kouranos V, Barnett SD, et al. Physiological predictors of survival in patients with sarcoidosis-associated pulmonary hypertension: results from an international registry. Eur Respir J. 2020;55(5):1901747.

58. Condado JF, Babaliaros V, Henry TS, Kaebnick B, Kim D, Staton GW Jr. Pulmonary stenting for the treatment of sarcoid induced pulmonary vascular stenosis. Sarcoidosis Vasc Diffuse Lung Dis. 2016 Oct 7;33(3):281-7.

59. DaSilva-deAbreu A, Bracamonte-Baran W, Condado JF, Babaliaros V, Tafur-Soto J, Mandras SA. Characteristics and outcomes of pulmonary angioplasty with or without stenting for sarcoidosis-associated pulmonary hypertension: systematic review and individual participant data meta-analysis. Curr Probl Cardiol. 2020; doi: 10.1016/j.cpcardiol.2020.100616.

60. Fartoukh M, Humbert M, Capron F, et al. Severe pulmonary hypertension in histiocytosis X. Am J Respir Crit Care Med. 2000 Jan;161(1):216-23. doi: 10.1164/ajrccm.161.1.9807024.

61. Lorillon G, Bergeron A, Detourmignies L, et al. Cladribine is effective against cystic pulmonary Langerhans cell histiocytosis. Am J Respir Crit Care Med. 2012 Nov 1;186(9):930-2. doi: 10.1164/ajrccm.186.9.930.

62. Le Pavec J, Lorillon G, Jaïs X, et al. Pulmonary Langerhans cell histiocytosis-associated pulmonary hypertension: clinical characteristics and impact of pulmonary arterial hypertension therapies. Chest. 2012 Nov;142(5):1150-1157. doi: 10.1378/chest.11-2490.

63. McCormack FX, Gupta N, Finlay GR, et al. Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guidelines: Lymphangioleiomyomatosis Diagnosis and Management. Am J Respir Crit Care Med. 2016 Sep 15;194(6):748-61. doi: 10.1164/rccm.201607-1384ST.

64. Reynaud-Gaubert M, Mornex J-F, Mal H, et al. Lung transplantation for lymphangioleiomyomatosis: the French experience. Transplantation. 2008 Aug 27;86(4):515-20. doi: 10.1097/TP.0b013e31817c15df.

65. Cottin V, Harari S, Humbert M, et al. Pulmonary hypertension in lymphangioleiomyomatosis: characteristics in 20 patients. Eur Respir J. 2012 Sep;40(3):630-40. doi: 10.1183/09031936.00093111.