Current Pulmonology Reports (2023) 12:105–112
https://doi.org/10.1007/s13665-023-00311-2

REVIEW

Pulmonary Hypertension in Interstitial Lung Disease: Management Options to Move Beyond Supportive Care

Kimberly D. Fabyan[1] · Abhimanyu Chandel[1] · Christopher S. King[2]

Accepted: 8 May 2023 / Published online: 22 May 2023

Abstract

Purpose of Review This review delineates current diagnostic and management strategies for pulmonary hypertension due to interstitial lung disease (PH-ILD).

Recent Findings The INCREASE trial, a phase III multicenter, randomized, placebo-controlled trial demonstrated both improved 6-min walk distance and decreased disease progression with inhaled treprostinil. This pivotal trial led to inhaled treprostinil becoming the first FDA approved medication for treatment of PH-ILD. The availability of this treatment has generated subsequent recommendations for the screening for PH in patients with ILD. As a result, it is becoming increasingly important for clinicians to gain awareness and familiarity with the evolving management options for PH-ILD.

Summary The management of PH-ILD has its roots in goal-directed treatment of the underlying lung disease. However, recent medication advances and ongoing clinical studies are opening opportunities for more disease-specific treatment.

Keywords Pulmonary hypertension · Interstitial lung disease

Introduction

The World Health Organization (WHO) divides pulmonary hypertension (PH) into five groups based on underlying etiology and therapeutic options [1••]. PH due to lung disease or hypoxia is assigned to Group 3 (Table 1). Group 3 is the second most common group of PH and the prevalence of this category of PH is increasing. Compared to other causes of PH, Group 3 PH is associated with the highest morbidity and the lowest survivability [2, 3].

PH is a common complication of interstitial lung diseases (ILD) including idiopathic pulmonary fibrosis, chronic hypersensitivity pneumonitis, and non-specific interstitial pneumonia. In patients with ILD, the development of PH is associated with increased mortality, more frequent ILD exacerbations, decreased quality of life, decreased exercise capacity, and an increased need for supplemental oxygen [4–8].

Prior to the recent INCREASE trial, studies of pulmonary vasodilators in pulmonary hypertension due to ILD (PH-ILD) were largely negative. As evidence was lacking regarding the benefits of pulmonary vasodilators in this population, clinical practice guidelines related to the care of patients with PH-ILD emphasized optimization of the underlying lung disease [9]. However, recently emerging evidence, including the results from the INCREASE trial, suggest the potential for benefit from pulmonary vasodilators in patients with PH-ILD. This changing paradigm and the important prognostic impact of PH in patients with ILD have led to an increased emphasis on screening for PH in these patients [10•].

Relatedly, the 6th World Symposium on Pulmonary Hypertension re-defined case criteria for pulmonary hypertension, establishing a mean pulmonary artery pressure (mPAP) greater than 20 mmHg, compared to the previous cut-off of 25 mmHg, as the diagnostic threshold [11]. Subsequently, the European Society of Cardiology and the European Respiratory Society have further refined the requisite

✉ Abhimanyu Chandel
Abhimanyu.chandel.mil@health.mil

Kimberly D. Fabyan
Kimberly.d.fabyan.mil@health.mil

Christopher S. King
Christopher.king@inova.org

[1] Department of Pulmonary and Critical Care, Walter Reed National Military Medical Center, 8901, Rockville Pike, Bethesda, MD 20889, USA

[2] Advanced Lung Disease and Transplant Program, Inova Heart and Vascular Institute, Inova Fairfax Hospital, 3330 Gallows Road, Falls Church, VA 22003, USA

Table 1 Causes of Group 3 PH

Obstructive lung disease or emphysema
Interstitial lung disease (ILD)
Combined pulmonary fibrosis and emphysema (CPFE)
Hypoventilation syndromes & sleep-disordered breathing
Hypoxia without lung disease (e.g., high altitude)
Developmental lung disorders

hemodynamic thresholds, establishing a lower pulmonary vascular resistance (PVR) threshold (greater than 2 Wood units) in their diagnostic definition of pre-capillary PH [12]. Given these more inclusive criteria and the increasing emphasis on screening, it is reasonable to expect an increased rate of PH-ILD diagnoses [1••, 13]. With this assumption in mind, we describe currently established diagnostic and management strategies for PH-ILD. We focus on exploring opportunities to move beyond the long-standing advice to "treat the underlying lung disease" and conclude with a discussion of the approach we utilize to diagnose and manage these complex patients.

Establishing a Diagnosis of PH-ILD

Symptoms of PH often overlap with those of ILD, making the detection of PH in these patients a clinical challenge. No standard method for screening for PH has been established, and a combination of laboratory data, non-invasive functional and exercise testing, and cross-sectional imaging is often utilized to estimate the probability of PH coexisting with ILD [14]. A recently published multidisciplinary Delphi study examined commonly utilized PH-ILD screening techniques and provided a clear framework for how clinicians may incorporate this data into the decision for recommending invasive testing. Some recommended triggers for screening for PH in these patients included symptoms out of proportion with ILD severity, severely reduced DLCO, changes in symptoms not explained by ILD progression, the requirement for supplemental oxygen, and impaired heart rate recovery or markedly reduced distance on 6-min walk testing [10•].

A series of tests evaluated in combination in patients suspected of having PH-ILD can provide the highest diagnostic accuracy. For example, utilization of transthoracic echocardiography to evaluate right ventricular function combined with thoracic contrast-enhanced CT examining pulmonary artery diameter and RV outflow tract hypertrophy is likely to improve the diagnostic accuracy of PH-ILD prior to invasive testing [10•, 12]. Ultimately, right heart catheterization (RHC) remains the only way to diagnose and risk-stratify the severity of PH-ILD and should be considered in patients with ILD where symptoms are out of proportion to the degree of ILD, suspicious for PH-ILD, and who might make appropriate candidates for pulmonary vasodilator therapies and in patients undergoing lung transplantation evaluation [12]. It should be noted that TTE is an imperfect screening tool for PH-ILD, so RHC should be pursued in patients with a high clinical suspicion of the diagnosis based on other clinical parameters.

The Basics: Treating the Underlying Disease

Management of PH-ILD and other causes of Group 3 PH starts with optimizing the treatment of the underlying lung disease [1••]. Recommendations for conservative management of PH-ILD including supplemental oxygen and smoking cessation are largely extrapolated from data from other chronic pulmonary conditions and other causes of pulmonary hypertension.

Supplemental Oxygen and Sleep Disordered Breathing

The recommendation for supplemental oxygen is extrapolated from data from patients with COPD [1••, 15]. In this population, supplemental oxygen has been shown to decrease pulmonary vascular resistance, improve exercise tolerance, and improve survival [15–17]. Continuous supplemental oxygen for at least 18 h per day is recommended for patients with resting hypoxemia, PaO2 < 60 mmHg, or oxygen saturation < 92%. Ambulatory oxygen is recommended for patients with exertional symptoms and oxygen desaturations that improve with supplemental oxygen. Additionally, nocturnal oxygen therapy is recommended for patients with sleep-related oxygen desaturations [18]. Furthermore, sleep-disordered breathing and alveolar hypoventilation should be screened for and optimized if found [12].

Exercise and Pulmonary Rehabilitation

The general recommendation in patients with PH is that they remain as active as tolerated [12, 19]. However, patients should avoid exertion with severe breathlessness, dizziness, or chest pain. Because of the high frequency of deconditioning and oxygen desaturations seen in patients with PH-ILD, a formal exercise program or pulmonary rehabilitation is often recommended [12]. Pulmonary rehabilitation has been shown to improve exercise tolerance and quality of life in patients with PH. In patients with Group 3 PH, a similar improvement in 6-min walk distance has been observed [20].

Smoking Cessation

A retrospective study of patients with PH found that those who had ever smoked had decreased time to hospitalization and diminished survival [21]. Additionally, animal studies of the effect of inhaled nicotine on the pulmonary vasculature have demonstrated substantial increases in PVR and progression of PH [22]. Thus, smoking cessation remains a cornerstone, not only in the management of chronic lung disease but also in PH-ILD.

Vaccinations

A metanalysis of multiple randomized controlled trials has established that in COPD, the influenza vaccine reduces exacerbations, hospitalizations, and deaths [23]. The data in ILD is not as robust, with one epidemiologic study published in 2022 demonstrating reduced mortality only in years that the influenza vaccine was effective [24]. Despite the lack of data, respiratory failure, frequently related to infectious pneumonia, is the leading cause of death in Group 3 PH [25, 26]. Relatedly, patients with pulmonary arterial hypertension have been found to be more likely to die from COVID-19 compared to the broader population [26]. As a result, standard influenza, pneumococcal pneumonia, and COVID-19 vaccinations are recommended in this at-risk population [12, 27].

PH-Directed Therapies: Beyond the Underlying ILD

According to the most recent clinical practice guidelines, patients with severe PH-ILD may benefit from PH-directed therapies and/or enrollment in a clinical trial [1••]. For context, though prior guidelines defined severe PH by mPAP > 35 mmHg or mPAP ≥ 25 with CI < 2.5 L/min/m^2, recently, severe PH in ILD has been redefined by a PVR greater than 5 WU [1••]. This new threshold has been found to be better predictive of worse prognosis [28, 29].

Several small, open-label, retrospective studies suggested that pulmonary vasodilator therapy may improve 6-min walk distance and right-ventricular function [30–37]. However, for the most part, randomized controlled trials evaluating vasodilator therapy in patients with PH-ILD have had negative outcomes (Table 2) [38–44]. While most of these trials demonstrated no difference, there was an increase in disease progression or serious adverse events including mortality leading to the early termination of two trials: Artemis-IPF and RISE-IIP [43, 44]. These resulted in recommendations against the usage of both ambrisentan and riociguat in PH-ILD [1••].

The use of prostanoids had previously been limited as IV therapy can potentially cause systemic hypotension and oxygen desaturation [33]. These adverse effects were minimized when the therapy was aerosolized and administered via inhalation. In 2021, results from the INCREASE study were published [45••]. The INCREASE study was a phase III, randomized, blinded, placebo-controlled clinical trial with 326 patients. After 16 weeks, patients treated with inhaled treprostinil demonstrated improved distance on the 6-min walk test (6MWT). Patients in the treatment group were also noted to have decreased disease progression and biomarker levels (NT-proBNP). The results of the INCREASE study led to the FDA approval of inhaled treprostinil for PH-ILD in April 2021. This step made it the first FDA-approved medication specifically for PH-ILD[46].

Practically, inhaled treprostinil is administered four times daily and is titrated to a maximum tolerated dose up to 72 mcg or 12 breaths per dose [46]. Flushing, headache, diarrhea, and cough are the most common dose-limiting symptoms. Additionally, important adverse effects related to inhaled treprostinil include symptomatic hypotension, increased bleeding risk secondary to inhibition of platelet aggregation, and bronchospasm [46]. Additionally, treprostinil is metabolized by the liver via CYP2C8, and significant drug-drug interactions are possible.

Another inhaled therapeutic option being actively explored is inhaled nitric oxide [47]. Recently, a small phase IIb trial reported increased moderately to vigorous activity as measured by actigraphy and a trend towards improved measures of dyspnea and quality of life in patients receiving pulsed inhaled nitric oxide in addition to their supplemental oxygen therapy. While the actigraphy based measure is a novel primary endpoint, the outcome is patient-centered and could suggest that patients with PH-ILD feel better and are able to better tolerate physical activity. A phase III clinical trial further investigating inhaled nitric oxide using that same primary endpoint has completed recruitment (ClinicalTrials.gov: NCT03267108).

Lung Transplantation

A lung transplant is a treatment option available for both advanced ILD and PH-ILD that progresses despite therapy [48]. However, the presence of PH in patient undergoing lung transplant for ILD is associated with increased risk of primary graft dysfunction and greater mortality [49, 50].

The consensus is that bilateral lung transplant is the procedure of choice for primary PH not secondary to lung disease [51]. However, there is less certainty in PH-ILD whether bilateral or single lung transplant should be recommended given how frequently elevated pulmonary

Table 2 Randomized controlled trials of pulmonary vasodilator therapy in ILD

	Trial	Drug	Patient *N* =	Duration	Primary EP	Results
PDE-5 inhibitors	STEP-IPF (2010) [38]	Sildenafil	180	12 weeks	Δ 6MWT ≥ 20%	Negative 10% sildenafil vs 7% placebo ($p=0.39$)[a]
	INSTAGE (2018) [39]	Nintedanib + / − sildenafil	273	12 weeks	Δ SGRQ	Negative − 1.28 pts vs − 0.77 pts ($p=0.72$)
	SP-IPF (2021) [40]	Pirfenidone + / − sildenafil	177	52 weeks	Disease progression	Negative 73% vs 70% ($p=0.65$)
Endothelin receptor antagonists	CORTE (2014) [41]	Bosentan	60	16 weeks	Δ PVRI	Negative 28.0% vs 28.6% ($p=0.97$)
	MUSIC (2013) [42]	Macitentan	178	52 weeks	Δ FVC	Negative − 0.2 L vs − 0.2 L ($p=1.00$)
	Artemis IPF (2013) [43]	Ambrisentan	494	52 weeks	Disease progression	Harm Terminated early due to increased disease progression
Soluble guanylate cyclase stimulators	RISE-IIP (2019) [44]	Riociguat	147	26 weeks	Δ 6MWT	Harm Terminated early due to increased adverse events
Inhaled prostanoids	INCREASE (2021) [45••]	Inhaled treprostinil	326	16 weeks	Δ 6MWT	Positive Improved 6MWT and decreased disease progression in the treatment group
Inhaled nitric oxide	Pulsed iNO–phase IIb (2020) [47]	Pulsed inhaled nitric oxide	41	8 weeks	Activity monitoring by actigraphy	Positive Improved moderate and vigorous activity in the treatment group

[a]Notably, STEP-IPF did demonstrate significant improvements in dyspnea, quality of life, and oxygenation (secondary endpoints) among patients randomized to sildenafil compared to placebo

artery pressures complicate ILD and the scarcity of transplant resources. As a result, recommendations have been to perform bilateral lung transplant when mPAP is greater than 40 mmHg. Two observational studies have found that a single lung transplant is as effective as a double lung transplant in PH-ILD [50, 52]. Given superior overall survival for bilateral lung transplantation, this is the preferred strategy for the majority of lung transplant recipients; however, single lung transplantation remains a viable option for patients with mild or moderate PH-ILD.

When to Refer to Expert Center

Centers of excellence in pulmonary hypertension and advanced lung disease provide patients access to experts in the field and advanced therapies, enrollment in clinical trials, and a dedicated multidisciplinary care team [1••]. Despite the benefits of early referral, patients are often referred to expert centers late [53].

Specific indications for referral to PH expert centers include (1) severe disease (PVR > 5 WU) and (2) decompensated right-heart failure [1••, 53, 54]. Additionally, due to the significant impact of PH-ILD on quality of life and exercise capacity, even patients with the non-severe disease (PVR < 5 WU) who are transplant candidates should also be considered for referral for treatment optimization and lung transplant evaluation [1].

Our Approach to Diagnosis and Treatment

When evaluating a patient with ILD, we collate symptoms and physical exam findings with results from multiple routine static and functional tests towards identifying a clinical probability of PH in patients with ILD. A particular emphasis is placed on the 6MWT, where a decrement in distant ambulated or new exertional hypoxia, especially if this occurs despite stable PFTs, heightens suspicion for coexisting PH. Typically, we acquire a transthoracic echocardiogram on a yearly basis, especially in patients

with a significant burden of ILD, progressive symptoms out of proportion to their burden of ILD, or in patients with functional or radiographic testing indicative of a high probability of PH. Echocardiographic signs of PH such as right ventricular systolic pressure > 45 mmHg, tricuspid annular plane systolic excursion (TAPSE) < 18 mm, right ventricular fractional area change < 35%, or right ventricular dilation are all echocardiographic criteria that may prompt invasive testing. In some patients, if clinical suspicion is high, we will proceed with RHC even in the absence of suspicious echocardiographic findings. During the RHC, provocative maneuvers to unmask WHO Group 2 PH are performed if there is clinical suspicion of this condition, either via fluid challenge or exercise.

When RHC is indicative of PH, we perform a comprehensive serologic and imaging evaluation to determine the etiology of PH. Critically, we rule out a contribution from chronic thromboembolic disease and consider carefully that some patients with ILD may be more appropriately classified and managed as WHO Group 1 disease (for example, a patient with minimal ILD related to connective tissue disease who presents with pre-capillary PH and a markedly elevated PVR). Once PH-ILD is identified, we first address supportive measures to optimize preload and afterload in the affected right heart. Supplemental oxygen and sleep-disordered breathing are provided and optimized where appropriate. Diuretics are prescribed to optimize fluid balance. Supportive measures including pulmonary rehabilitation, smoking cessation, and vaccinations (including against COVID-19) are also emphasized. Importantly, all patients diagnosed with PH-ILD are screened for clinical trial eligibility.

Typically, we monitor patients with mild PH-ILD closely with more frequent functional and echocardiographic evaluation. If signs or symptoms progress, we consider obtaining serial RHC data and institute treatment if PH appears progressive. Finally, in select patients with severe PH-ILD, we consider treatment generally in accordance with the most recent clinical practice guidelines [1••]. Our practice is perhaps a bit more aggressive, with the initiation of pulmonary vasodilator therapy in line with the enrollment criteria for the INCREASE study (mPAP ≥ 25 mmHg, PCWP ≤ 15 mmHg, and PVR > 3 Wood units). Given that INCREASE is the only compelling favorable clinical trial data to date, we use inhaled treprostinil as first-line therapy. We encourage patients to titrate their dose up as tolerated, as the most benefit in the trial was seen in those achieving higher doses [55]. Close monitoring of these patients is paramount for side effects or unanticipated clinical changes. We avoid the use of ambrisentan or riociguat in these patients

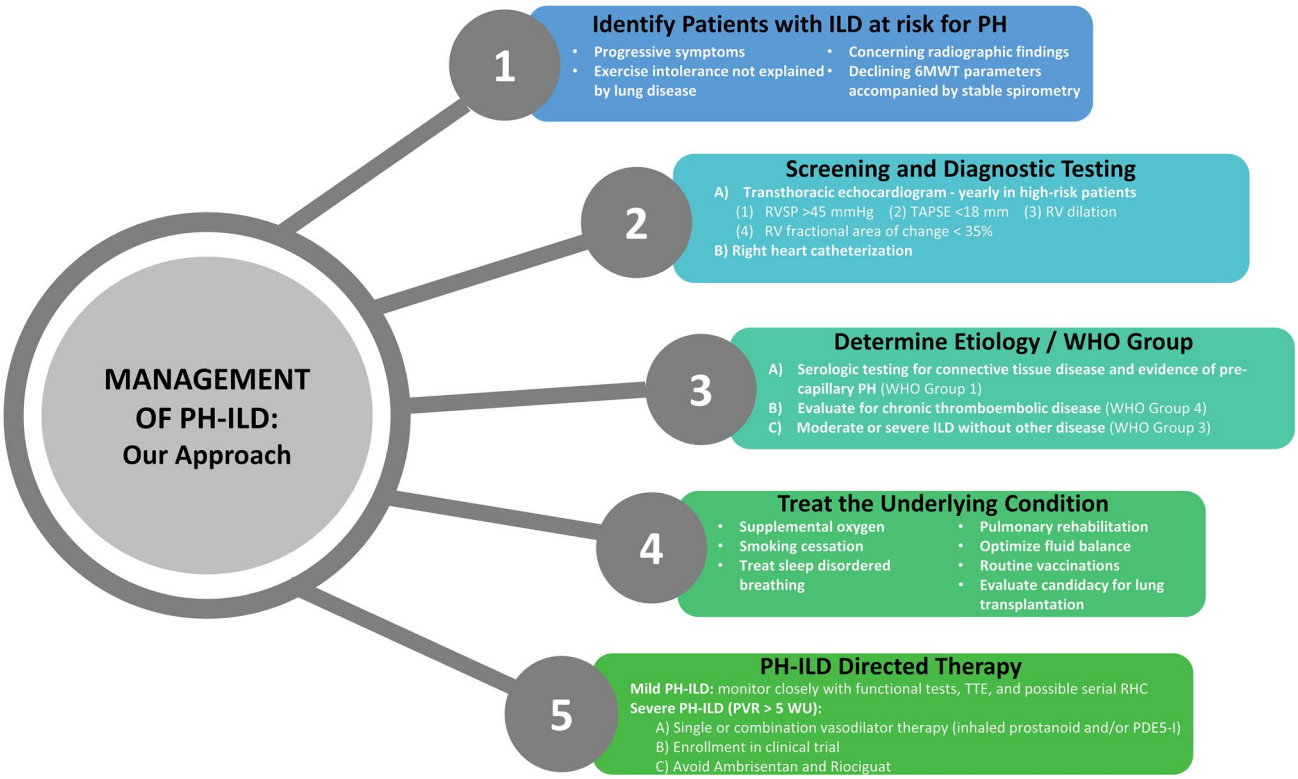

Fig. 1 A summary of our diagnostic and therapeutic approach to PH-ILD. ILD, interstitial lung disease; PH, pulmonary hypertension; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; PH-ILD, pulmonary hypertension due to interstitial lung disease; PVR, pulmonary vascular resistance; PDE5-I, phosphodiesterase-5 inhibitors

for the reasons outlined above. In patients with ongoing PH despite optimization of inhaled treprostinil, we consider the addition of sildenafil as well, again while carefully monitoring for side effects. Sildenafil can also be considered in patients who cannot tolerate inhaled treprostinil due to side effects. In patients with very severe pre-capillary PH-ILD ($CI < 2$ L/min/m^2), we consider initiation of parenteral prostanoids, although there is a paucity of literature supporting this practice. These patients must be carefully selected and monitored very closely for decompensation. This approach should only be employed by experienced PAH centers with close follow-up. All patients with PH-ILD should be considered for lung transplantation referral and listing, as even with pulmonary vasodilator therapy, outcomes remain poor. A summary of our diagnostic and therapeutic approach is provided in Fig. 1.

Conclusion

PH frequently complicates the course of ILD and the development of PH has important prognostic implications for these patients. Recent updates to the hemodynamic definition of PH and the availability of effective treatments have resulted in a more inclusive case definition and increased screening for this condition, both of which will likely increase the prevalence of this condition. Recent medication advances and ongoing clinical studies are opening opportunities for more disease-specific treatment.

Compliance with Ethical Standards

Conflict of Interest KDF and AC have no conflict of interest to report. CSK is a consultant for United Therapeutics, Actelion, Altavant, and Boehringer Ingelheim and serves on the advisory board for Actelion, United Therapeutics, Merck, and Boehringer Ingelheim.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/national research committee standards, and international/national/international guidelines).

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618–731. https://doi.org/10.1093/eurheartj/ehac237.
2. Wijeratne DT, Lajkosz K, Brogly SB, Lougheed MD, Jiang L, Housin A, et al. Increasing incidence and prevalence of world health organization groups 1 to 4 pulmonary hypertension: a population-based cohort study in Ontario, Canada. Circ Cardiovasc Qual Outcomes. 2018;11(2):e003973. https://doi.org/10.1161/circoutcomes.117.003973.
3. Prins KW, Rose L, Archer SL, Pritzker M, Weir EK, Kazmirczak F, et al. Disproportionate right ventricular dysfunction and poor survival in group 3 pulmonary hypertension. Am J Respir Crit Care Med. 2018;197(11):1496–9. https://doi.org/10.1164/rccm.201712-2405LE.
4. Mejía M, Carrillo G, Rojas-Serrano J, Estrada A, Suárez T, Alonso D, et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest. 2009;136(1):10–5. https://doi.org/10.1378/chest.08-2306.
5. Takahashi K, Taniguchi H, Ando M, Sakamoto K, Kondoh Y, Watanabe N, et al. Mean pulmonary arterial pressure as a prognostic indicator in connective tissue disease associated with interstitial lung disease: a retrospective cohort study. BMC Pulm Med. 2016;16(1):55. https://doi.org/10.1186/s12890-016-0207-3.
6. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest. 2006;129(3):746–52. https://doi.org/10.1378/chest.129.3.746.
7. DuBrock HM, Nathan SD, Reeve BB, Kolaitis NA, Mathai SC, Classi PM, et al. Pulmonary hypertension due to interstitial lung disease or chronic obstructive pulmonary disease: a patient experience study of symptoms and their impact on quality of life. Pulmonary circulation. 2021;11(2):20458940211005640. https://doi.org/10.1177/20458940211005641.
8. Judge EP, Fabre A, Adamali HI, Egan JJ. Acute exacerbations and pulmonary hypertension in advanced idiopathic pulmonary fibrosis. Eur Respir J. 2012;40(1):93–100. https://doi.org/10.1183/09031936.00115511.
9. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, et al. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Res J. 2019;53(1). https://doi.org/10.1183/13993003.01914-2018.
10.• Rahaghi FF, Kolaitis NA, Adegunsoye A, de Andrade JA, Flaherty KR, Lancaster LH, et al. Screening strategies for pulmonary hypertension in patients with interstitial lung disease: a multidisciplinary Delphi study. Chest. 2022;162(1):145–55. https://doi.org/10.1016/j.chest.2022.02.012.
11. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D42–50. https://doi.org/10.1016/j.jacc.2013.10.032.
12. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2009;34(6):1219–63. https://doi.org/10.1183/09031936.00139009.
13. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Res J. 2019;53(1). https://doi.org/10.1183/13993003.01913-2018.
14. King CS, Shlobin OA. The trouble with group 3 pulmonary hypertension in interstitial lung disease: dilemmas in diagnosis and the conundrum of treatment. Chest. 2020;158(4):1651–64. https://doi.org/10.1016/j.chest.2020.04.046.
15. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med. 1980;93(3):391–8. https://doi.org/10.7326/0003-4819-93-3-391.

16. Sugarman J, Weatherald J. Management of pulmonary hypertension due to chronic lung disease. Methodist Debakey Cardiovasc J. 2021;17(2):124–33. https://doi.org/10.14797/zkut3813.
17. Farber HW, Badesch DB, Benza RL, Elliott CG, Frantz RP, McGoon MD, et al. Use of supplemental oxygen in patients with pulmonary arterial hypertension in REVEAL. J Heart Lung Transplant. 2018;37(8):948–55. https://doi.org/10.1016/j.healun.2018.03.010.
18. Adir Y, Humbert M, Chaouat A. Sleep-related breathing disorders and pulmonary hypertension. Eur Respir J. 2021;57(1). https://doi.org/10.1183/13993003.02258-2020.
19. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, 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;46(4):903–75. https://doi.org/10.1183/13993003.01032-2015.
20. Moth L, Fitzgerald C, Marino P, Osman L, Mcdonnell L, Hogg L, et al. Pulmonary rehabilitation in patients with group 3 pulmonary hypertension: evaluation of clinical outcomes, adherence and safety. Eur Res J. 2019;54(suppl 63):PA522. https://doi.org/10.1183/13993003.congress-2019.PA522.
21. Frost AE, Zhao C, Farber HW, Benza R, Yen J, Selej M, et al. Smoking history and pulmonary arterial hypertension: demographics, onset, and outcomes. J Heart Lung Transplant. 2023;42(3):377–89. https://doi.org/10.1016/j.healun.2022.10.007.
22. Oakes JM, Xu J, Morris TM, Fried ND, Pearson CS, Lobell TD, et al. Effects of chronic nicotine inhalation on systemic and pulmonary blood pressure and right ventricular remodeling in mice. Hypertension (Dallas, Tex : 1979). 2020;75(5):1305–14. https://doi.org/10.1161/hypertensionaha.119.14608.
23. Kopsaftis Z, Wood-Baker R, Poole P. Influenza vaccine for chronic obstructive pulmonary disease (COPD). The Cochrane database of systematic reviews. 2018;6(6):Cd002733. https://doi.org/10.1002/14651858.CD002733.pub3.
24. Marijic P, Schwarzkopf L, Maier W, Trudzinski F, Schwettmann L, Kreuter M. Effects of influenza vaccination in patients with interstitial lung diseases: an epidemiological claims data analysis. Ann Am Thorac Soc. 2022;19(9):1479–88. https://doi.org/10.1513/AnnalsATS.202112-1359OC.
25. Tonelli AR, Arelli V, Minai OA, Newman J, Bair N, Heresi GA, et al. Causes and circumstances of death in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2013;188(3):365–9. https://doi.org/10.1164/rccm.201209-1640OC.
26. Nakamura J, Tsujino I, Ohira H, Nakaya T, Sugimoto A, Sato T, et al. Various factors contribute to death in patients with different types of pulmonary hypertension: a retrospective pilot study from a single tertiary center. Respir Investig. 2022;60(5):647–57. https://doi.org/10.1016/j.resinv.2022.05.001.
27. Wieteska-Miłek M, Szmit S, Florczyk M, Kuśmierczyk-Droszcz B, Ryczek R, Kurzyna M. COVID-19 vaccination in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: safety profile and reasons for opting against vaccination. Vaccines. 2021;9(12). https://doi.org/10.3390/vaccines9121395.
28. Zeder K, Avian A, Bachmaier G, Douschan P, Foris V, Sassmann T, et al. Elevated pulmonary vascular resistance predicts mortality in COPD patients. Eur Respir J. 2021;58(2). https://doi.org/10.1183/13993003.00944-2021.
29. Olsson KM, Hoeper MM, Pausch C, Grünig E, Huscher D, Pittrow D, et al. Pulmonary vascular resistance predicts mortality in patients with pulmonary hypertension associated with interstitial lung disease: results from the COMPERA registry. Eur Respir J. 2021;58(2). https://doi.org/10.1183/13993003.01483-2021.
30. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. Chest. 2007;131(3):897–9. https://doi.org/10.1378/chest.06-2101.
31. Günther A, Enke B, Markart P, Hammerl P, Morr H, Behr J, et al. Safety and tolerability of bosentan in idiopathic pulmonary fibrosis: an open label study. Eur Respir J. 2007;29(4):713–9. https://doi.org/10.1183/09031936.00149205.
32. Mittoo S, Jacob T, Craig A, Bshouty Z. Treatment of pulmonary hypertension in patients with connective tissue disease and interstitial lung disease. Can Respir J. 2010;17(6):282–6. https://doi.org/10.1155/2010/686098.
33. Olschewski H, Ghofrani HA, Walmrath D, Schermuly R, Temmesfeld-Wollbruck B, Grimminger F, et al. Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. Am J Respir Crit Care Med. 1999;160(2):600–7. https://doi.org/10.1164/ajrccm.160.2.9810008.
34. Ghofrani HA, Wiedemann R, Rose F, Schermuly RT, Olschewski H, Weissmann N, et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet (London, England). 2002;360(9337):895–900. https://doi.org/10.1016/s0140-6736(02)11024-5.
35. Chapman TH, Wilde M, Sheth A, Madden BP. Sildenafil therapy in secondary pulmonary hypertension: is there benefit in prolonged use? Vascul Pharmacol. 2009;51(2–3):90–5. https://doi.org/10.1016/j.vph.2009.04.002.
36. Corte TJ, Gatzoulis MA, Parfitt L, Harries C, Wells AU, Wort SJ. The use of sildenafil to treat pulmonary hypertension associated with interstitial lung disease. Respirology (Carlton, Vic). 2010;15(8):1226–32. https://doi.org/10.1111/j.1440-1843.2010.01860.x.
37. Zimmermann GS, von Wulffen W, Huppmann P, Meis T, Ihle F, Geiseler J, et al. Haemodynamic changes in pulmonary hypertension in patients with interstitial lung disease treated with PDE-5 inhibitors. Respirology (Carlton, Vic). 2014;19(5):700–6. https://doi.org/10.1111/resp.12294.
38. Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med. 2010;363(7):620–8. https://doi.org/10.1056/NEJMoa1002110.
39. Kolb M, Raghu G, Wells AU, Behr J, Richeldi L, Schinzel B, et al. Nintedanib plus sildenafil in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2018;379(18):1722–31. https://doi.org/10.1056/NEJMoa1811737.
40. Gessler N, Gunawardene MA, Wohlmuth P, Arnold D, Behr J, Gloeckner C, et al. Clinical outcome, risk assessment, and seasonal variation in hospitalized COVID-19 patients-results from the CORONA Germany study. PLoS One. 2021;16(6):e0252867. https://doi.org/10.1371/journal.pone.0252867.
41. Corte TJ, Keir GJ, Dimopoulos K, Howard L, Corris PA, Parfitt L, et al. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. Am J Respir Crit Care Med. 2014;190(2):208–17. https://doi.org/10.1164/rccm.201403-0446OC.
42. Raghu G, Million-Rousseau R, Morganti A, Perchenet L, Behr J. Macitentan for the treatment of idiopathic pulmonary fibrosis: the randomised controlled MUSIC trial. Eur Respir J. 2013;42(6):1622–32. https://doi.org/10.1183/09031936.00104612.
43. Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med. 2013;158(9):641–9. https://doi.org/10.7326/0003-4819-158-9-201305070-00003.
44. Nathan SD, Behr J, Collard HR, Cottin V, Hoeper MM, Martinez FJ, et al. Riociguat for idiopathic interstitial pneumonia-associated

pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study. Lancet Respir Med. 2019;7(9):780–90. https://doi.org/10.1016/s2213-2600(19)30250-4.

45.•• Waxman A, Restrepo-Jaramillo R, Thenappan T, Ravichandran A, Engel P, Bajwa A, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. N Engl J Med. 2021;384(4):325–34. https://doi.org/10.1056/NEJMoa2008470.

46. El-Hamshari Y, Hamarshi M, Nazzal Z, Akkawi A, Saleh D, Abdullah I, et al. The outcomes of severe COVID-19 pneumonia managed with supportive care in Palestine: an experience from a developing country. J Infect Dev Ctries. 2021;15(8):1094–103. https://doi.org/10.3855/jidc.14709.

47. Nathan SD, Flaherty KR, Glassberg MK, Raghu G, Swigris J, Alvarez R, 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;158(2):637–45. https://doi.org/10.1016/j.chest.2020.02.016.

48. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, 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;34(1):1–15. https://doi.org/10.1016/j.healun.2014.06.014.

49. Diamond JM, Lee JC, Kawut SM, Shah RJ, Localio AR, Bellamy SL, et al. Clinical risk factors for primary graft dysfunction after lung transplantation. Am J Respir Crit Care Med. 2013;187(5):527–34. https://doi.org/10.1164/rccm.201210-1865OC.

50. Huerd SS, Hodges TN, Grover FL, Mault JR, Mitchell MB, Campbell DN, et al. Secondary pulmonary hypertension does not adversely affect outcome after single lung transplantation. J Thorac Cardiovasc Surg. 2000;119(3):458–65. https://doi.org/10.1016/s0022-5223(00)70124-3.

51. Conte JV, Borja MJ, Patel CB, Yang SC, Jhaveri RM, Orens JB. Lung transplantation for primary and secondary pulmonary hypertension. Ann Thorac Surg. 2001;72(5):1673–9; discussion 9–80. https://doi.org/10.1016/s0003-4975(01)03081-8.

52. Julliard WA, Meyer KC, De Oliveira NC, Osaki S, Cornwell RC, Sonetti DA, et al. The presence or severity of pulmonary hypertension does not affect outcomes for single-lung transplantation. Thorax. 2016;71(5):478–80. https://doi.org/10.1136/thoraxjnl-2015-207354.

53. Deaño RC, Glassner-Kolmin C, Rubenfire M, Frost A, Visovatti S, McLaughlin VV, et al. Referral of patients with pulmonary hypertension diagnoses to tertiary pulmonary hypertension centers: the multicenter RePHerral study. JAMA Intern Med. 2013;173(10):887–93. https://doi.org/10.1001/jamainternmed.2013.319.

54. Hwalek A, Rosenheck JP, Whitson BA. Lung transplantation for pulmonary hypertension. J Thorac Dis. 2021;13(11):6708–16. https://doi.org/10.21037/jtd-2021-20.

55. Nathan SD, Deng C, King CS, DuBrock HM, Elwing J, Rajagopal S, et al. Inhaled treprostinil dosage in pulmonary hypertension associated with interstitial lung disease and its effects on clinical outcomes. Chest. 2023;163(2):398–406. https://doi.org/10.1016/j.chest.2022.09.007.