Pulmonary Hypertension Associated with ILD: Diagnosis and Management

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Conflicts of Interest

No relevant conflicts of interest to report

Objectives

- Summarize the impact of pulmonary hypertension on patients with interstitial lung disease
- Highlight important mechanisms of disease in PH-ILD
- Discuss a diagnostic algorithm for PH-ILD, including screening and confirmatory testing
- Understand management options for PH in the ILD patient, including recent therapeutic advances (e.g. – inhaled treprostinil)

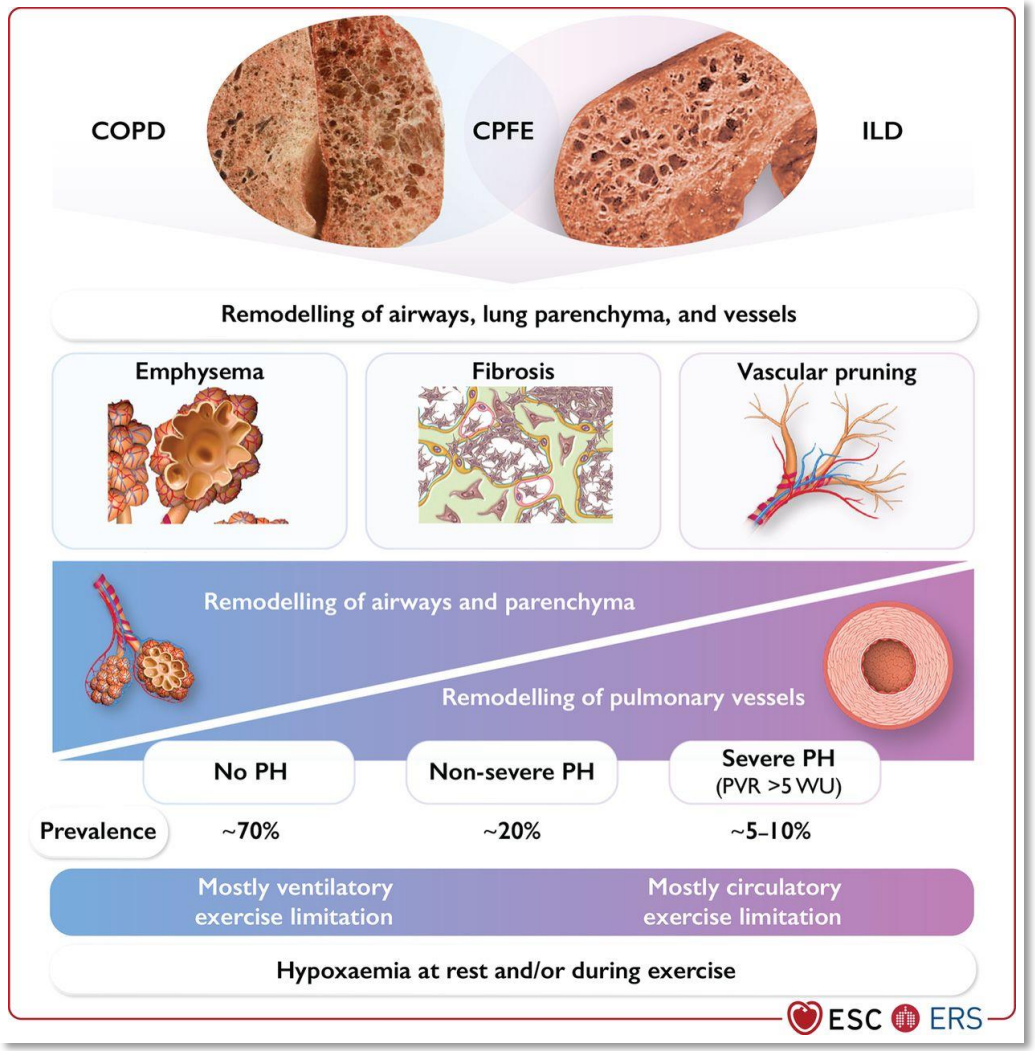
Understanding the Impact of PH in ILD

Prevalence

- Estimates vary widely = 3% - 90% depending on population chosen and timing of PH diagnosis
- Generalized cohorts estimate prevalence ~ 30%

Clinical Features:

- Exertional dyspnea
- Fatigue
- Lower extremity edema / volume overload



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Understanding the Impact of PH in ILD

Contributing Factors

Local vascular compression/perivascular fibrosis

Vascular destruction/pruning

Chronic *irreversible* hypoxic vasoconstriction

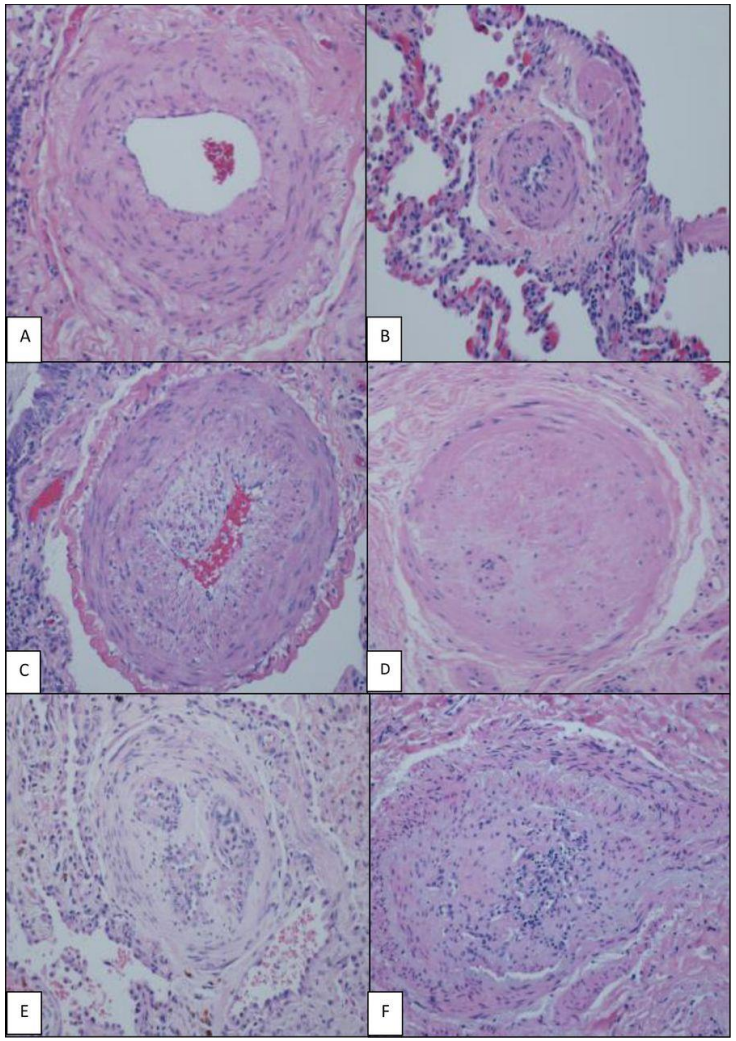
Vascular inflammation

Biochemical pathways implicated include nitric oxide, prostacyclin, thromboxane, C-reactive protein, tumor necrosis factor alpha, transforming growth factor-beta, and vascular endothelial growth factor

Pathologic Findings

Vascular remodeling including:

- Intimal thickening
- Medial hypertrophy
- Distal muscularization of arterioles



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Definition of PH-ILD and Severity

Recent updates in definition of PH

- mPAP > 20 mmHg
- Precapillary PH PVR threshold reduced to PVR > 2 Woods units (decreased from ≥ 3 WU)

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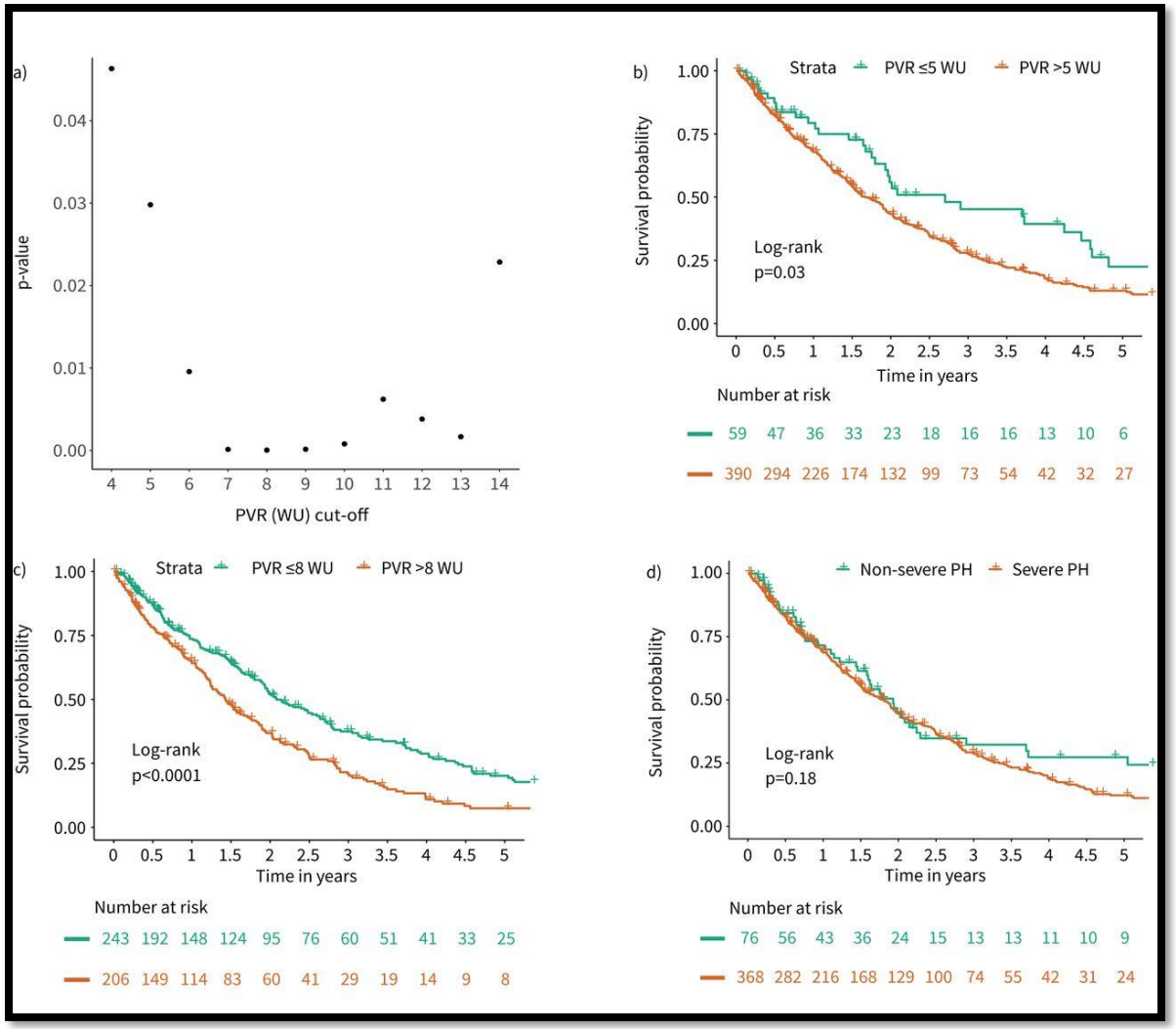
Severe PH in Chronic Lung Disease

- Traditionally mPAP ≥ 35 mmHg (or ≥ 25 mmHg + cardiac index < 2.0 L/s/m^2)
- However, data suggestive of worse survival in PVR > 5 WU in the ILD population



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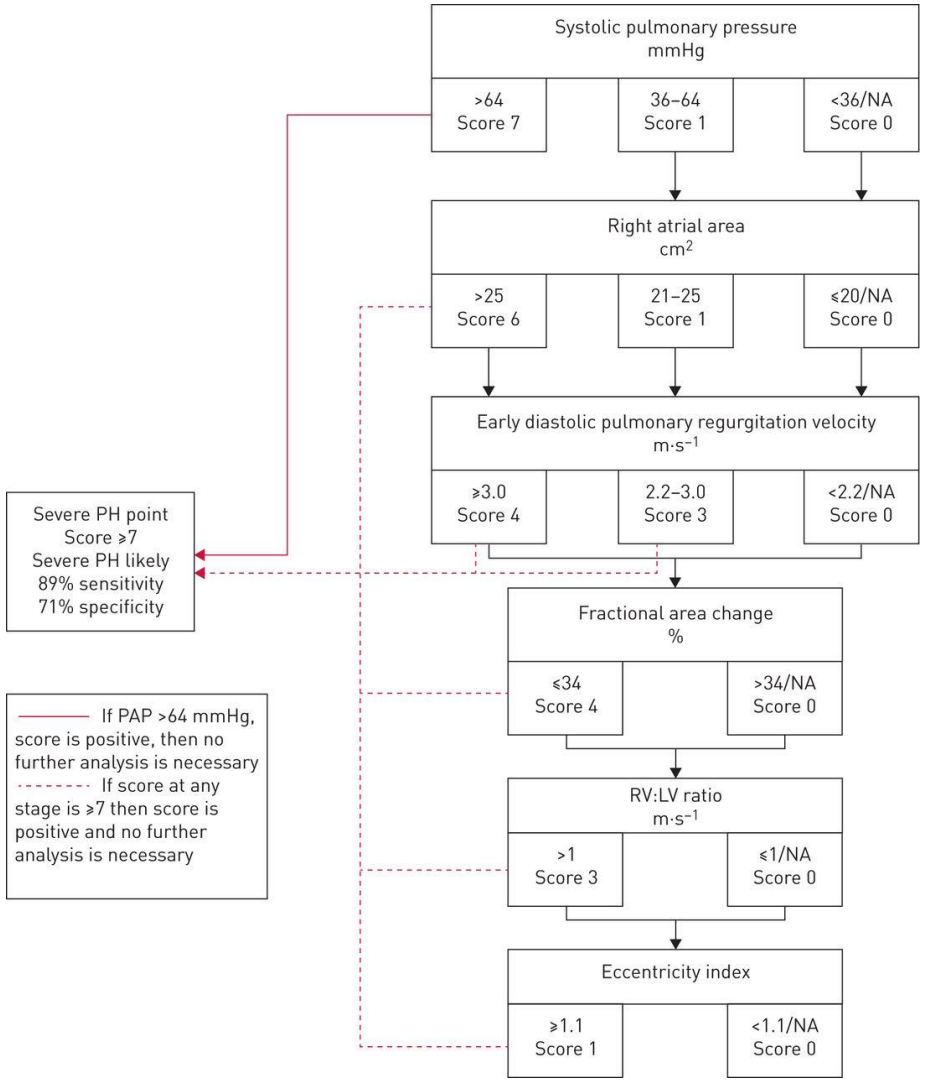
Non-Invasive Diagnostics

Transthoracic Echocardiography

- Traditionally moderate PH defined by estimated PASP ≥ 40 mmHg
- However, underestimation or overestimation of PASP by at least 10mmHg in around 50% of cases
- ePASP not obtained in many studies due to lack of adequate TR jet
- Move toward multimodal echo risk determination:
  1) RV pressure domain
  2) RV morphology domain
  3) RV functional domain

CT Imaging

- PA enlargement
- RV outflow hypertrophy
- Increased RV:LV ratio



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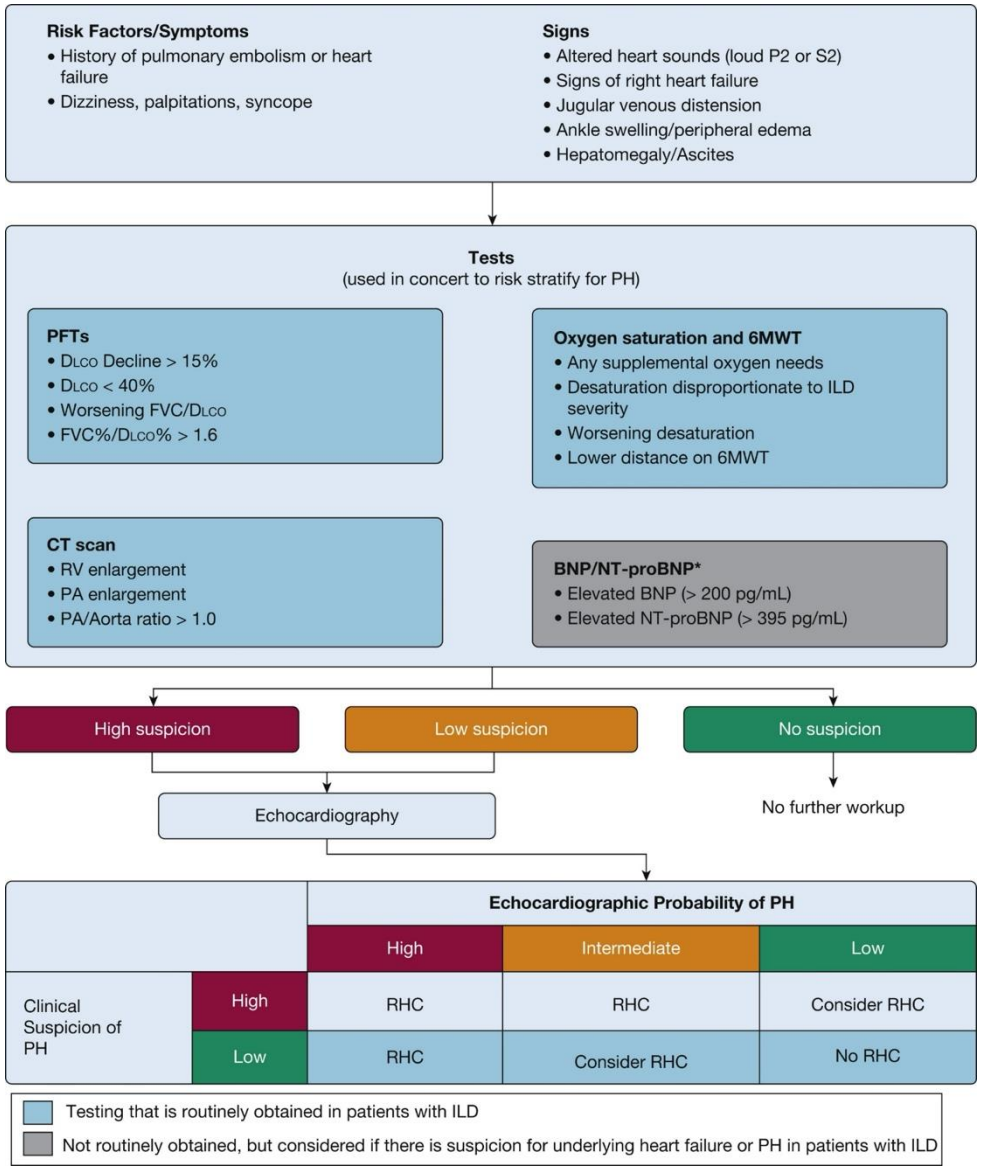
Right Heart Catheterization

Remains the gold standard for confirmatory testing in pulmonary hypertension, including PH-ILD

Indications:

- Needed for surgical planning (lung transplant, volume reduction surgery)
- Suspected severe PH-ILD and will aid in management in decisions
- Concern for alternate PH process



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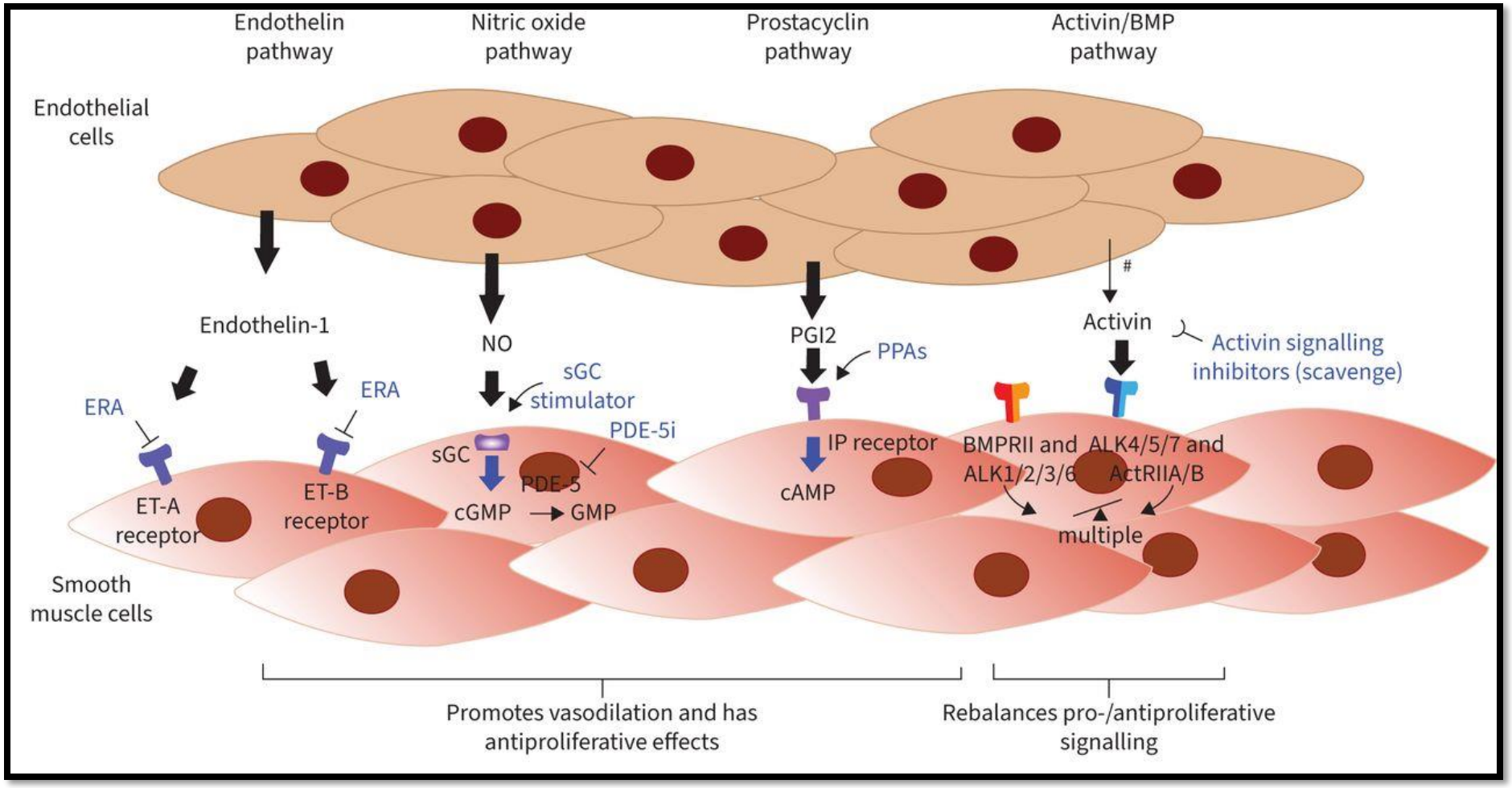
Basics of Management

Treatment Concepts:

- Treatment of underlying lung disease
- Address chronic hypoxemia or hypercarbia with respiratory support (supplemental oxygen or NIPPV)
- Preventative care – immunizations, PJP prophylaxis

PAH Treatment



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PAH Therapy is Not Generalizable to PH-ILD

Trials studying oral pulmonary vasodilator therapy in PH-ILD have consistently not reached their primary end-point, some demonstrating unacceptable risk profiles

- Ambrisentan
  - ARTEMIS-IPF = terminated early for lack of benefit; treatment group more likely to have disease progression and respiratory hospitalizations
- Riociguat
  - RISE-IIP = terminated early for increased serious adverse events in treatment group; lack of signal for benefit, increased serious adverse events, and increased incidence of death
- Sildenafil
  - STEP-IPF = did not demonstrate improvement in 6MWD in advanced IPF; however, possible benefit (post-hoc subgroup analysis) in patients with RV dysfunction

INCREASE Trial

Phase 3 RCT evaluating inhaled treprostinil vs placebo in PH-ILD

- Enrolled 326 patients

Cause of lung disease — no. (%)			
Idiopathic interstitial pneumonia	65 (39.9)	81 (49.7)	146 (44.8)
Chronic hypersensitivity pneumonitis	10 (6.1)	9 (5.5)	19 (5.8)
Occupational lung disease	5 (3.1)	1 (0.6)	6 (1.8)
Combined pulmonary fibrosis and emphysema	42 (25.8)	40 (24.5)	82 (25.2)
Connective tissue disease	40 (24.5)	32 (19.6)	72 (22.1)
Other	1 (0.6)	0	1 (0.3)
Idiopathic interstitial pneumonia subcategory — no. (%)			
Idiopathic pulmonary fibrosis	37 (22.7)	55 (33.7)	92 (28.2)
Idiopathic nonspecific interstitial pneumonia	21 (12.9)	16 (9.8)	37 (11.3)
Respiratory bronchiolitis associated with interstitial lung disease	2 (1.2)	0	2 (0.6)
Desquamative interstitial pneumonia	0	1 (0.6)	1 (0.3)
Acute interstitial pneumonia	0	1 (0.6)	1 (0.3)
Unclassified idiopathic interstitial pneumonia	5 (3.1)	8 (4.9)	13 (4.0)

Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. *N Engl J Med*. 2021;384(4):325-334

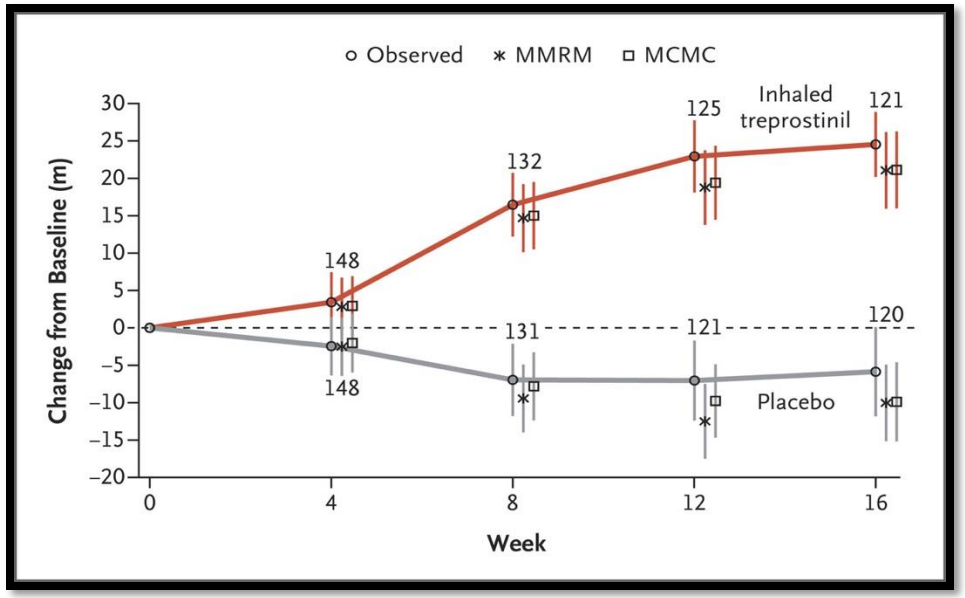
INCREASE Trial

Phase 3 RCT evaluating inhaled treprostinil vs placebo in PH-ILD

- Met primary end-point of change in peak 6MWD at 16 weeks
- Adverse effects included headache, cough, dyspnea, dizziness, nausea, fatigue, diarrhea, and throat irritation; no serious adverse events reported more frequently in treatment group vs placebo

Table 2. Summary of Primary and Secondary End Points.*

End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
Primary end point				
Change in peak 6-minute walk distance from baseline to wk 16 — m†	21.08±5.12	−10.04±5.12	31.12±7.25 (16.85 to 45.39)‡	<0.001
Secondary end points§				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change — pg/ml	−396.35±1904.90	1453.95±7296.20		
Median — pg/ml	−22.65	20.65		
Range — pg/ml	−11,433.0 to 5373.1	−5483.3 to 87,148.3		
Ratio to baseline	0.85±0.06	1.46±0.11	0.58±0.06 (0.47 to 0.72)‖	<0.001
Occurrence of clinical worsening — no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6-minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		
Least-squares mean change in peak 6-minute walk distance from baseline to wk 12 — m†	18.77±4.99	−12.52±5.01	31.29±7.07 (17.37 to 45.21)‡	<0.001
Least-squares mean change in trough 6-minute walk distance from baseline to wk 15 — m	9.3±5.5	−12.7±5.5	21.99±7.7 (6.85 to 37.14)‡	0.005††



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INCREASE Trial

Phase 3 RCT evaluating inhaled treprostinil vs placebo in PH-ILD

- Also noted that there was a significant increase in FVC (% predicted) in the treatment group vs placebo group
- Post-hoc subgroup analysis suggests greatest improvement in patients with idiopathic interstitial pneumonia, particularly those with idiopathic pulmonary fibrosis

Now → Awaiting results of TETON-1 (US) and TETON-2 (outside US)

- Phase 3 RCTs comparing change in absolute FVC at 52 weeks in patients with IPF on inhaled treprostinil vs placebo, enrollment complete as of early 2025
- Results for TETON-2 expected late 2025, TETON-1 early 2026

Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. *N Engl J Med*. 2021;384(4):325-334

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Sotatercept in PH-ILD?

Not a well-studied indication for a new PAH drug

- Single small cohort study of 7 patients with CTD-PAH with ILD

Table 3. Summary of paired *t*-test results for clinical parameters after 24 weeks of treatment.

Parameter	Baseline Mean	Mean After 24 Weeks	Difference	Percentage Change (%)	*T* Score	*p* Value
PVR (WU)	7.77	4.53	3.24	41.7	10.308	0.000049
6MWD (m)	211.57	347.57	136	64.28	8.459	0.00015
NT-proBNP (pg/mL)	3056.86	1404.29	1652.57	54.06	3.013	0.02362
eRVSP (mmHg)	79.43	54.14	25.29	31.84	8.262	0.00017
Supplemental O_2 (L/min)	3	1.14	1.86	62	5.461	0.00157

PVR: pulmonary vascular resistance; WU: Wood units; 6MWD: six-minute walk distance; m: meters; NT-proBNP: N-terminal pro-brain natriuretic peptide; pg/mL: picograms per milliliter; eRVSP: estimated right ventricular systolic pressure; mmHg: millimeters of mercury; O_2 Therapy: supplemental oxygen therapy; L/min: liters per minute.

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Lung Transplant in PH-ILD

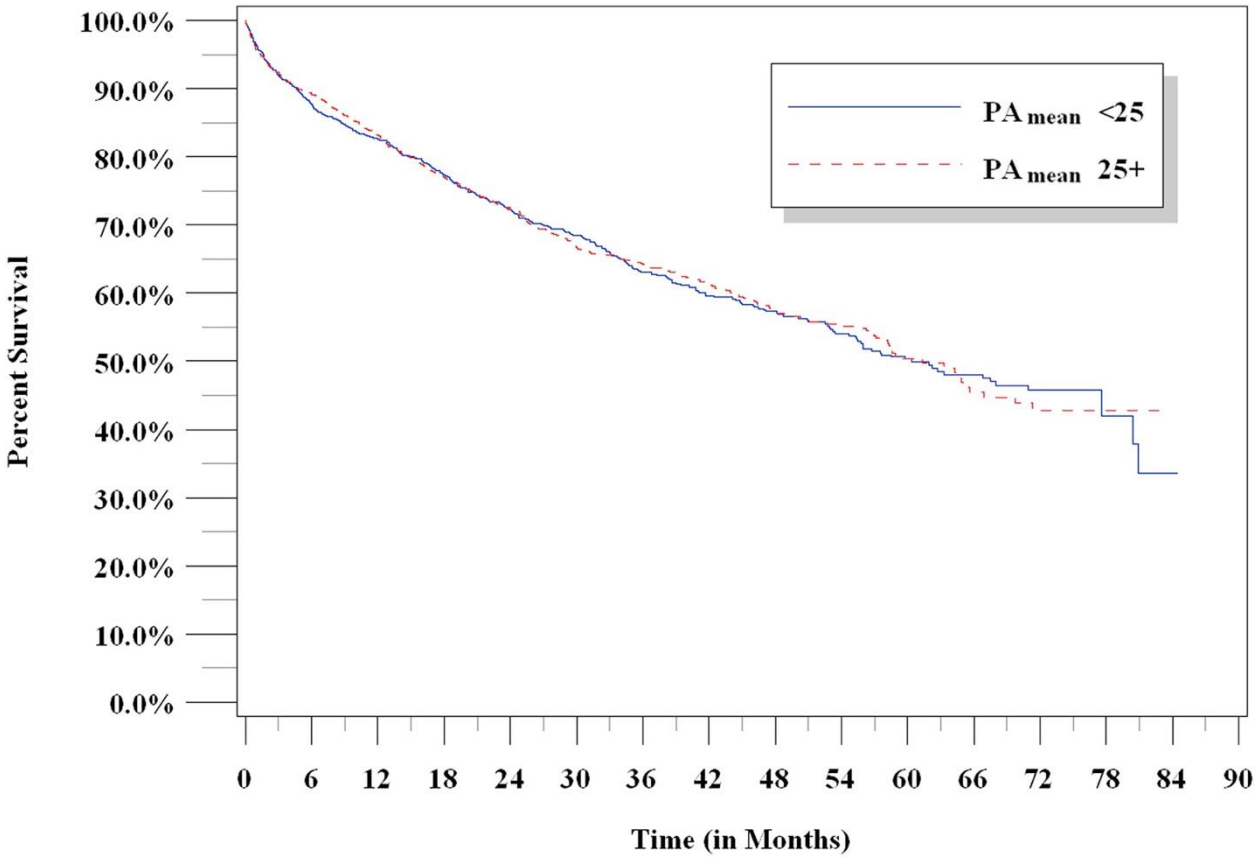
No significant impact on long-term outcomes, though short-term metrics impacted – not an exclusion criteria

2015 analysis of UNOS registry data

- 2542 IPF patients undergoing lung transplant
- No increased risk of death in PH group

Other studies suggest:

- Increased ischemic time, increased incidence of primary graft dysfunction



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Summary

- PH-ILD affects approximately 30% of patients with ILD and shares some pathophysiologic mechanisms with PAH
- Diagnosis of PH-ILD involves screening by echocardiography and confirmation by right heart catheterization
- Pharmacologic treatment options for PH-ILD have been limited given many negative therapeutic trials, though now recent data shows benefit with inhaled treprostinil (at least on short term outcomes)
- PH-ILD is not in and of itself a contraindication to lung transplant