A Simplified Diagnostic and Therapeutic Approach to Pulmonary Hypertension

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Abstract: Pulmonary hypertension remains a common but complex disorder that physicians face in their daily practice. Pulmonary hypertension has been classified by the World Health Organization into five major categories according to etiology, pathophysiology, and hemodynamic properties. The clinical course and overall prognosis varies by etiology, therefore making the correct diagnosis is paramount to avoid delay in treatment and improve outcomes. This review aims to provide clinicians with a simplified diagnostic approach to pulmonary hypertension. We also provide a guide to risk stratification and when to refer patient to a pulmonary hypertension expert center. (Curr Probl Cardiol 2022;47:100857.)

Introduction

It is estimated that approximately 1% of all adults worldwide and over half of patients with congestive heart failure are affected by pulmonary hypertension (PH).[1,2] PH has been classified by the World Health Organization (WHO) into 5 major categories according to etiology, pathophysiology, and hemodynamic properties. The clinical course and overall

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prognosis varies by etiology, therefore making the correct diagnosis is paramount to avoid delay in treatment. This review aims to provide clinicians with a stepwise approach to diagnosis and management of PH. We also provide a guide to risk stratification and when to refer patient to a PH expert center.

Definition of PH

WHO Classification

PH has been classified by the WHO into five major groups; WHO group 1: pulmonary arterial hypertension (PAH); WHO group 2: PH due to left heart disease, WHO group 3: PH due to pulmonary disease, WHO group 4: PH due to chronic thromboembolism pulmonary hypertension (CTEPH), and lastly WHO group 5: PH due to unclear and multifactorial mechanisms[3] (Table 1).

Hemodynamic Definition

WHO Group 1 PH or PAH is characterized by a mean pulmonary artery pressure (mPAP) >25 mm Hg, a pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg and a pulmonary vascular resistance (PVR) >3 Wood units (WU) in absence of other causes. At the sixth World Symposium for Pulmonary Hypertension in 2018, it was suggested that PAH should include mPAP >20 mm Hg.[4] Therefore in clinical practice, clinicians should adopt this new definition. WHO Group 2 PH or PH due to left heart disease has been divided into post-capillary PH and combined pre-capillary and post-capillary PH. Post-capillary PH is defined by mPAP > 20 mm Hg, PCWP >15 mm Hg and PVR <3 WU.[4] Combined pre-capillary and post-capillary PH is defined by mPAP > 20 mm Hg, PAWP >15 mm Hg and PVR ≥3.[4]

Group 1 Pulmonary Arterial Hypertension

Pathogenesis

The trademark of PAH is smooth muscle cell proliferation, endothelial cell dysfunction, inflammation and remodeling of the pulmonary vasculature.[5] Overtime, the increase in precapillary vasculature results in rise in pulmonary vascular resistance and progressive right ventricular afterload, dilatation and right ventricular failure.

Table 1. WHO clinical classification of pulmonary hypertension

Group 1	Pulmonary arterial hypertension	Idiopathic Heritable (BMPR2, AKL1, endoglin) Drugs and toxins induced (anorexigens, amphetamines) Associated with connective tissue disease Associated with HIV infection Associated with portal hypertension Associated with congenital heart disease Associated with schistosomiasis Associated with chronic hemolytic anemia Pulmonary veno-occlusive disease and/or pulmonary capillary hemagiomatosis
Group 2	Pulmonary hypertension due to left heart disease	Left ventricular systolic dysfunction Left ventricular diastolic dysfunction Valvular disease Congenital or acquired left heart inflow/outflow tract obstruction and continental cardiomyopathies
Group 3	Pulmonary hypertension due to lung disease and/or hypoxia	Chronic obstructive pulmonary disease Interstitial lung disease Other pulmonary diseases with mixed restrictive and obstructive pattern Sleep disordered breathing Alveolar hypoventilation disorders Chronic exposure to high altitude Developmental lung disease
Group 4	Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions	Chronic thromboembolic pulmonary hypertension Other pulmonary artery obstructions (ex: angiosarcoma, arteritis, congenital pulmonary arteries stenoses, parasites)
Group 5	Pulmonary hypertension with unclear and/or multifactorial mechanisms	Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis Metabolic disorders: glycogen storage disease, gaucher disease, thyroid disorders Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension

ALK1, activin receptor-like kinase 1; BMPR2, bone morphogenic protein receptor type 2; HIV, human immunodeficiency virus.

PAH includes several subtypes; (1) Idiopathic PAH (IPAH) being the most common subtype accounting for 50%-60% of cases, (2) PAH associated with connective tissue disease; (3) PAH associated with congenital heart disease; and (4) PAH associated with portal hypertension.[6] Genetic causes of

PAH include germline mutation in the bone morphogenetic protein receptor type II (BMPR2) in 80% of patients with familial disease and 20% of sporadic PAH.[1] Other mutations of the ALK1, ENG, SMAD9, CAV1 and KCN 3 genes have also been correlated with heritable PAH.[7] These mutations allow proliferation of smooth muscle cells by a variety of mechanisms including loss of apoptosis. In addition, a procoagulant state develops as a result of endothelial dysfunction and amplifies vascular proliferation. Toxins that are definite risk factors for PAH include aminorex, fenfluramine, dexfenfluramine, toxic rapeseed oil while those unlikely for PAH are oral contraceptives, estrogen, and cigarette smoking.[8]

Diagnosis

History and Physical Exam. Patients may present with a variety of symptoms ranging from no symptoms with mild disease to symptoms with exertion such as shortness of breath, fatigue and angina as the disease progresses.[2,3] Less commonly, mechanical complications such as rupture of hypertrophied bronchial arteries or compression of the laryngeal nerve can result in hemoptysis and hoarse voice, respectively. Shortness of breath on exertion can be classified into WHO functional class I - IV as the symptoms progress from moderate exertion to at symptoms at rest in end stage disease.[2,3] Syncope occurs in end stage pulmonary hypertension when right atrial pressures and right ventricular enlargement impacts forward flow and results in low cardiac output. Patients suspected of having pulmonary hypertension or with known disease should be assessed for these symptoms.[2,3]

Physical examination findings may include an elevated jugular venous pressure, hepatomegaly, ascites, lower extremity edema, parasternal lift, an accentuated pulmonary component of the second heart sound, a third heart sound (S3), pansystolic murmur of tricuspid regurgitation and a diastolic murmur of pulmonary regurgitation.[2,3]

Noninvasive Testing. When clinically suspected, PH can be further assessed by electrocardiogram (ECG), chest x-ray (CXR) and echocardiogram (ECHO) (Fig 1). An ECG may have findings of right axis deviation, right ventricular hypertrophy (RVH), right bundle branch block or a prolonged QTc interval. However, the absence of these findings does not rule out PH. RVH on ECG has only a 55% sensitivity and 70% specificity.[9] A chest x-ray may show pulmonary arterial dilatation, right atrial or right ventricular enlargement or pulmonary venous congestion of the PH

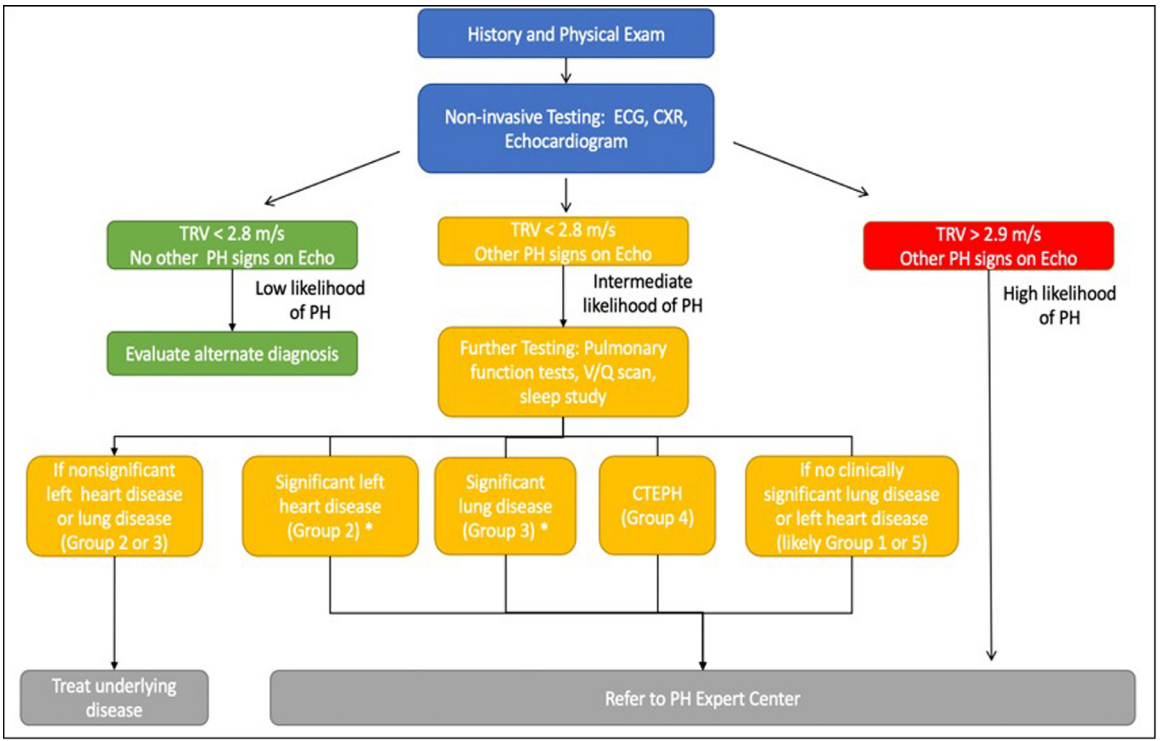

Figure 1. Diagnostic Algorithm for Pulmonary Hypertension. *left heart disease or lung disease with moderate or severe pulmonary hypertension or in the presence of right ventricular dysfunction. CTEPH, chronic thromboemebolic pulmonary hypertension; CXR, chest x-ray; ECG, electrocardiogram; PH, pulmonary hypertension; TRV, tricuspid regurgitation velocity jet; V/Q, ventilation/perfusion.

is due to left heart disease. These findings are non-specific, however, and a normal CXR does not exclude PH.[3]

A transthoracic echocardiogram can give valuable information about the pulmonary arterial pressures, right ventricle (RV) size and function and left ventricle (LV) function (Table 2).[3] In absence of pulmonary stenosis, the modified Bernoulli equation can estimate pulmonary arterial systolic pressures (PASP) by using peak tricuspid regurgitation velocity (TRv^2) and right atrial pressure (RAP) such that $PASP = 4*TRv^2 + RAP$.[3] The right atrial pressure is estimated by measuring diameter of inferior vena cava and percent compression with respiration "sniff test". The pulmonary artery (PA) diameter dilates in response to increased afterload and a PA diameter > 25 mm is considered abnormal.[3] Most importantly, the presence of pericardial effusion is correlated with mortality in numerous studies; patients with small effusions have 94%, 80%, 64% 1-year, 3-year and 5-year survival, respectively while those with moderate effusions have 80%, 20% and 0% 1-year, 3-year and 5-year survival,

Table 2. Echocardiographic parameters suggestive of pulmonary hypertension

Echocardiographic parameters	Features supporting RV dysfunction in the setting of PH
RA pressure	RA pressure > 15 mm Hg
RA area	RA area > 18 cm^2
Right ventricle basal diameter	> 4.2 cm
Peak tricuspid velocity	< 2.8 m/s or non measurable: low probability of PH > 2.8 m/s and additional parameters of PH: intermediate probability > 3.4 m/s: high probability of PH
Pulmonic regurgitation velocity	PR velocity > 2.2 m/sec
PA diameter	PA diameter > 25 mm
RVOT acceleration time	RVOT acceleration time < 105 msec and/or midsystolic notching
TAPSE	TAPSE < 1.6 mm
S'	S' < 10 cm/sec
Myocardial performance index (RIMP)	RIMP > 0.43 by pulsed wave doppler RIMP > 0.54 by continuous wave doppler
Tei index	Tei index < 0.83
RV strain	RV free wall strain < - 20%
RV FAC	RV FAC < 35%
Right ventricular/left ventricle basal diameter ratio	RV/LV basal diameter ratio > 1.0
Eccentricity index	Eccentricity index > 1.1

cm, centimeter; FAC, fractional area change; mm, millimeter; PA, pulmonary artery; PH, pulmonary hypertension; PR, pulmonary regurgitation; TAPSE, tricuspid annular plane systolic excursion; RA, right atrium; RIMP, right ventricular index of myocardial performance; RV, right ventricle; RVOT, right ventricular outflow tract; sec, second.

respectively.[10-12] Cardiac tamponade in the setting of moderate or large effusion is unique because classic features such as right atrial and ventricular collapse, pulsus paradoxus and hypotension may be absent. Instead, when increased pericardial pressure exceeds left ventricular diastolic pressure, there is left atrial and/or ventricular diastolic collapse.[11]

Right Heart Catheterization (RHC). RHC remains the gold standard for diagnosing and assess severity of PH.[3] During RHC, pressures in the right atrium, RV, pulmonary artery and pulmonary capillary wedge pressure are obtained. Additionally, PVR, cardiac output (CO), cardiac index (CI) and pulmonary vascular resistance (PVR) are calculated. A PVR >3 woods units is required for diagnosis of PAH.

In patients with idiopathic PAH, hereditary PAH or drug-induced PAH, pulmonary vasoreactivity testing is recommended. Inhaled nitric oxide (NO) is commonly used for vasoreactivity testing, but intravenous epoprostenol, adenosine, or inhaled iloprost can also be used as alternatives. A positive response is suggested by reduction of mPAP ≥10 mm Hg to reach an absolute value of mPAP ≤ 40 mm Hg without decreasing cardiac output.[3]

The utility of a RHC in management of PH is not only for diagnosis but also for monitoring progression or response to PH therapy. In a precompensated patient, the increase in PVR mirrors the rise in PA pressures without affecting cardiac output. In the decompensating patient, the RV is no longer able to compensate against the high PA pressures and results in symptoms with exertion and progressively decreasing cardiac output. In the decompensated patient with severe pulmonary hypertension, the PA pressures also decrease.[13]

Additional Diagnostic Testing. PH is very common in patients with chronic lung disease (CLD). In this regard, pulmonary function tests can help determine the presence and severity of lung disease.[3,14] For example, a decreased diffusion lung capacity for carbon monoxide (DLCO) with normal lung volumes suggests pulmonary venous occlusive disease such as scleroderma or other parenchymal lung disease. While patients with WHO Group 1 PAH will have FEV1 >60% predicted and FVC >70% predicted, WHO Group 3 PH patients will have FEV1 < 60% or FVC < 70%.[14] Similarly, a sleep study can identify presence of nocturnal hypoxemia and central sleep apnea which can be found in up to 80% of patients with PAH.[3] A ventilation perfusion (V/Q) scan remains the diagnostic test of choice to exclude chronic thromboembolism pulmonary hypertension (CTEPH) or WHO Group 4.

Prognosis

Several risk scores are available to guide clinicians in determining prognosis for their patients with PH. The Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) risk score predicts survival at baseline, 1- year and 5-years.[15-17] Alternative tools include the Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), Swedish PAH Registry (SPAHR) and French Pulmonary Hypertension Network (FPHN).[18-20] Regardless of which tool a clinician chooses, all have comparable efficacy in stratifying patients into low (<5%), intermediate (5%-10%) and high-risk (>10%) mortality at 1 year.[21] Variables with the highest yield in the registry is the 6-minute walk distance, NT-proBNP, or BNP plasma levels, cardiac index, RAP and Svo2.

Medical Management

Patients with more than mild PH or RV dilation or dysfunction, regardless of degree of PH, should be referred to an expert PH center. A variety of therapeutic options exist based on etiology. For instance, treatment of WHO group 2 PH should focus of treating the underlying etiology (eg, blood pressure control, guideline directed medical therapy for heart failure with reduced and preserved function). WHO Group 3 should focus on treating the underlying lung disease (chronic obstructive pulmonary disease, interstitial lung disease, obstructive sleep apnea). This section will focus on available therapeutic options for WHO group 1 PH.

Calcium Channel Blockers

In patients who exhibit a positive vasoreactivity test on RHC, calcium channel blockers (CCB) such as diltiazem or nifedipine can be initiated and uptitrated as tolerated.[3,22] CCB controls intracellular calcium influx in vascular smooth muscle cells. In the initial study by Rich et al, patients given CCB during RHC had an acute decrease in their mPAP and PVR by 39% and 53%, respectively. Responders who achieved at least a 20% decrease in mPAP and PVR had better functional capacity and survival rates at 12 months than non-responders.[22]

Targeted Therapy for PAH

Alternative management of PAH targets smooth muscle cell proliferation by targeting three main pathways: (1) prostacyclins, (2) endothelin and (3) nitric oxide[3] (Table 3).

Table 3. Medical management options for PH

Class	Examples	Side effects
Calcium channel blockers	Amlodipine 20 mg qD (PO)	Peripheral edema, hypotension, dizziness, gastrointestinal distress
	Nifedipine 120 - 240 mg qD (PO)	Peripheral edema, hypotension, dizziness, gastrointestinal distress
	Diltiazem 240 - 720 mg qD (PO)	Peripheral edema, hypotension, bradycardia, cardiac conduction delay, gastrointestinal distress
Phosphodiesterase-5 inhibitor (PDE -5i)	Sildenafil 20 mg TID (PO)	Headache, flushing, hypotension, nauseous, visual disturbances, epistaxis, insomnia
	Tadalafil 40 mg qD (PO)	Headache, flushing, nausea, myalgia, respiratory tract infection, nasopharyngitis
Endothelin receptor antagonist (ERA)	Ambrisentan 10 mg qD (PO)	Peripheral edema, flushing, headache, dyspepsia, anemia, nasal congestion, bronchitis, sinusitis
	Bosentan 62.5 mg BID (< 40 kg) or 125 mg BID (> 40 kg) (PO)	Peripheral edema, headache, increased serum transaminases, respiratory tract infection, hypotension, flushing, sinusitis, anemia, hepatotoxicity
	Macitetan 10 mg qD (PO)	Headache, anemia, nasopharyngitis, bronchitis, urinary tract infections, anemia
Prostacyclin analogues	Epoprostenol 2 ng/kg/min increase 1-2 ng/kg/min every 15 min until dose-limiting side effects (IV)	Flushing, jaw pain, headache, hypotension, hypoxemia, nausea
	Treprostinil 0.125mg TID - 0.25 mg TID (PO)	Flushing, headache, diarrhea, nausea, vomiting, abdominal pain, limb or jaw pain, hypokalemia
	Treprostinil 1.25 ng/kg/min for first 4 weeks to target 40-80 ng/kg/min (IV or subcutaneous)	
	Treprostinil 18 mcg QID (IH)	
	Iloprost 2.5 mcg/dose 6-9 times daily; target 5 mcg/dose 9 times daily (IH)	Flushing, hypotension, headache, trismus, nausea, jaw pain, cough, flu-like symptoms
	Selexipag 1600 mcg BID (PO)	Headache, flushing, diarrhea, nausea, flushing, flu-like symptoms, myalgia, jaw pain, skin rash
cGMP stimulators	Riociguat 2.5 mg TID (PO)	Headache, dyspepsia, dizziness, hypotension, anemia, GI distress

cGMP, cyclic guanosine monophosphate; BID, twice daily; IH, inhaled; IV, intravenous; PO, oral; QID, four times daily; qD, once daily; TID, thrice daily.

Prostacyclin Analogs: Prostaglandin I2 (PGI2) is a potent vasodilator in the vascular endothelium which, when stimulated, leads to increased production of cyclic adenosine monophosphate (cAMP), inhibits platelet aggregation and has antiproliferative properties. In PAH, PGI2 synthesis is suppressed and so PGI2 analogs such as epoprostanol, treprostinil and iloprost help overcome the deficiency. Selexipag is a PGI2 receptor analog.[3]

Endothelin Receptor Antagonists (ERA)

Endothelin-1 (ET) is upregulated in vascular endothelial cells of patients with pulmonary hypertension. It acts on ET_A and ET_B receptors on the pulmonary vasculature to vasoconstrict and promote pulmonary vascular remodeling. ET-receptor antagonists (ERA) include ambrisentan, bosentan and macitentan which compete with endothelin-1 on ET_A and ET_B receptors.[3]

Phosphodiesterase-5 Inhibitor/Cyclic Guanosine Monophosphate Stimulators

Nitric oxide (NO) - Nitric oxide acts as a potent vasodilator in the pulmonary circulation which acts through the increase in cyclic guanosine monophosphate (cGMP) pathway, and is cleared mainly as result of degradation by PDE5. Given that the reduction of NO has been described in patients with PH, PDE5-inhibitors such as sildenafil and tadalafil decrease degradation of NO while cGMP stimulators such riociguat work synergistically with NO to promote further vasorelaxation and inhibit smooth muscle cell proliferation.[3]

Commonly Used Combination Therapies for PAH

In patients who do not respond to a vasodilator during RHC and are at low or intermediate risk (Table 4), initial oral therapy with an ERA or PDE5i can be initiated.[3] Non-responders to vasodilators or patients deemed at high risk should be initiated on combination therapy. Combination therapy with 10 mg tadalafil and ambrisentan 40 mg daily had greater clinical response and improvement in 6-minute walk distance than the monotherapy alone, 39% vs 29% OR 1.56 (95% CI 1.05-2.32, $P= 0.03$) and 48.98 m vs 23.80 m, $P< 0.001$, respectively.[23] Combinations of bostentan + IV epoprostenol have demonstrated improvement in exercise capacity and functional class at week 16.[24]

Patients should be evaluated 3-6 months to assess functional capacity and uptitration of medications to achieve NYHA FC II.[3] A 6-minute walk test with a Borg dyspnea score can provide a quantitative assessment of

Table 4. Risk assessment in pulmonary arterial hypertension

Determinants of prognosis (1-year mortality)	Low risk (<5%)	Intermediate risk (5%-10%)	High risk (>10%)
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope	Repeated syncope
NYHA functional class	I, II	III	IV
6-minute walk distance	> 440 meters	165 - 440 meters	< 165 meters
Cardiopulmonary exercise testing	Peak VO2 > 15 mL/min/kg (> 65% predicted)	Peak VO2 11-15 mL/min/kg (35-65% predicted)	Peak VO2 < 11 mL/min/kg (< 35% predicted)
NT-proBNP plasma levels	BNP < 50 ng/l NT-proBNP < 300 ng/l	BNP 50-300 ng/l NT-proBNP 300 - 1400 ng/l	BNP > 300 ng/l NT-proBNP > 1400 ng/l
Imaging (echocardiography, CMR, imaging)	RA area < 18 cm^2 No pericardial effusion	RA area 18-26 cm^2 No or small pericardial effusion	RA area > 26 ^{cm2} Pericardial effusion
Hemodynamics	RA pressure < 8 mm Hg, CI $\geq$ 2.5 mL/min/m^2, SvO2 > 65%	RA pressure 8-14 mm Hg, CI 2.0-2.4 mL/min/m^2, SvO2 60%-65%	RA pressure > 14 mm Hg, CI < 2.0 mL/min/m^2, SvO2 < 60%

BNP, brain natriuretic peptide; CI, cardiac index; CMR, cardiac magnetic resonance imaging; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; NYHA, New York Heart Association; RA, right atria; SvO2, mixed venous oxygen saturation; VO2, oxygen uptake.

exercise capacity. When the initial treatment approach results in low-risk within 3-6 months, therapy can be continued.[3] When the initial treatment results in an intermediate risk, escalation to triple combination therapy is recommended (ex: macitentan and sildenafil, riociguat and bosentan, selexipag and ERA and/or PDE5i) as well as referral for lung transplantation. When the initial treatment approach results in high risk, maximal medial therapy including IV prostacyclin analogies is recommended as well as referral for lung transplantation.[3]

If the second step results in low-risk status within 3-6 months, therapy can be continued. If the second treatment step results in an intermediate or high-risk status, medical therapy must be escalated to a triple combination therapy including IV or subcutaneous prostacyclin analogue.

If patients with low risk deteriorate to intermediate or high-risk group, medical therapy should be escalated.

Lung Transplantation

As patients are uptitrated to IV prostacyclin or multi-drug combination regimens for PH, they should also be referred for evaluation of lung transplantation. Eligible patients include those with persistent NYHA functional class III or IV symptoms with other clinical, and/or hemodynamic predictors of poor prognosis on best standard of care.[3] Survival post lung transplantation for PAH is 51.7% and 32.4%% at 5-years and 10-years, respectively.[24]

Not everyone is a candidate for transplantation, however, and in these circumstances a goals of care discussion with a Palliative Care team to determine a patient's wishes for further aggressive therapy, comfort care or opinion on the use of mechanical ventilation is essential.

Adjunctive Therapy

In addition to medical therapy, preventative measures such as regular physical activity, influenza vaccine is recommended. Oral anticoagulation may be considered in PAH patients receiving IV prostaglandins in the absence of contraindications due to risk of catheter-associated thrombosis, and in IPAH, HPAH and drug-induced PAH.[3] Reversible etiologies such as iron deficiency anemia, thyroid function and volume status must be assessed and optimized. Supplemental oxygen is indicated for patients with arterial O2 saturation is < 60 mm Hg and ambulatory oxygen may be considered for symptomatic benefit for exertional hypoxia.[3]

Conclusion

PH remains a common and complex disorder. As the prevalence of PH grows, a simplified approach to determining diagnosis and management is essential. A thorough history and physical exam in association with stepwise approach to non-invasive testing can help prevent unnecessary testing and allow for early diagnosis and risk stratification of patients. Echocardiography is the screening test of choice to diagnose PH. Right heart catheterization is necessary is selected cases. Similarly a V/Q scan may be necessary to exclude CTEPH. Prompt referral of patients with suspected WHO group 1 and 3 PH (PAH and CTEPH) to a PH center is paramount to prevent delay of treatment and improve survival

REFERENCES

1. Hoeper MM, Humber M, Souza R, et al. A global view of pulmonary hypertension. *Lancet Resp Med* 2016;4:306–22.
2. Mandras SA, Mehta HS, Vaidya A. Pulmonary hypertension: a brief guide for clinicians. *Mayo Clin Proc* 2020;95:1978–88.
3. Galie N, Humbert M, Vachiery JL, 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 European respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016;37:67–119.
4. Simmoneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019;53:1801913.
5. Mayeux JD, Pan IZ, Dechand J, et al. Management of pulmonary arterial hypertension. *Curr Cardiovasc Risk Resp* 2021;15:2.
6. Badesch DB, Raskob GE, Elliot CG, et al. Pulmonary arterial hypertension: baseline characteristics from REVEAL registry. *Chest* 2010;137:376–87.
7. Fan R, Penny D, Fan Y. Genetics and its associated pathways of pulmonary arterial hypertension. *Int J of Respir Pulm Med* 2015;2:031.
8. Simmoneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;54:543–54.
9. Bonderman D, Wexberg P, Martischnig AM, et al. A noninvasive algorithm to exclude pre-capillary pulmonary hypertension. *Eur Respir J* 2011;37:1096–103.
10. Raymond RJ, Hinderliter AL, Willis PW, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. *J Am Coll Cardiol* 2002;39:1214–9.
11. Sahay S, Tonelli AR. Pericardial effusion in pulmonary arterial hypertension. *Pulm Circ* 2013;3:467–77.

12. Shimony A, Fox BD, Langleben D, et al. Incidence and significance of pericardial effusion in patients with pulmonary arterial hypertension. *Can J Cardiol* 2013;29:678–82.
13. Bhatnagar A, Wiesen J, Dweik R, et al. Evaluating suspected pulmonary hypertension: a structured approach. *Cleve Clin J Med* 2018;85:468–80.
14. Nathan SD, Barbera JA, Gaine SP, et al. Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J* 2019;53:1801814.
15. Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL Registry Risk Score calculator in patients newly diagnosed with pulmonary arterial hypertension. *Chest* 2012;141:354–62. 29.
16. Benza RL, Miller DP, Foreman AJ, et al. Prognostic implications of serial risk score assessments in patients with pulmonary arterial hypertension: a registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL) analysis. *J Heart Lung Transplant* 2015;34:356–61. 30.
17. Farber HW, Miller DP, Poms AD, et al. Five-year outcomes of patients enrolled in the REVEAL registry. *Chest* 2015;148:1043–54.
18. Galie N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J* 2019;53:1801889. 34.
19. Kylhammar D, Kjellstrom B, Hjalmarsson C, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J* 2018;39:4175–81. 35.
20. Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Resp J* 2017;50:1700889.
21. Thomas CA, Anderson RJ, Condon DF, et al. Diagnosis and management of pulmonary hypertension in the modern era: insights from the 6th World Symposium. *Pulm Thera* 2020;6:9–22.
22. Rich S, Kaufmann E, Levy PS. The Effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Eng J Med* 1992;327:76–81.
23. Galie N, Barbera JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Eng J Med* 2015;373:834–44.
24. Humbert M, Barst RJ, Robbins IM, et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Resp J* 2004;24:353–9.