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Pulmonary hypertension: An update of Dx and Tx guidelines

Here is how to reduce risk factors that can lead to pulmonary hypertension; play a pivotal role in diagnosis; and know when disease requires a referral.

PRACTICE RECOMMENDATIONS

› *Employ echocardiography as the first-line diagnostic test when pulmonary hypertension (PH) is suspected.* (C)

› *Order a ventilation–perfusion scan in patients with unexplained PH to exclude chronic thromboembolic PH.* (C)

› *Order lung function testing with diffusion capacity for carbon monoxide as part of the initial evaluation of PH.* (C)

› *Use right heart catheterization to confirm the diagnosis of pulmonary arterial hypertension.* (C)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

New guidelines that redefine pulmonary hypertension (PH) by a lower mean pulmonary artery pressure (mPAP) have led to a reported increase in the number of patients given a diagnosis of PH. Although the evaluation and treatment of PH relies on the specialist, as we explain here, family physicians play a pivotal role in the diagnosis, reduction or elimination of risk factors for PH, and timely referral to a pulmonologist or cardiologist who has expertise in managing the disease. We also address the important finding that adult patients who have been evaluated, treated, and followed based on guidelines—updated just last year—have a longer life expectancy than patients who have not been treated properly or not treated at all.

Last, we summarize the etiology, evaluation, and management of PH in the pediatric population.

What is pulmonary hypertension?

A revised definition

Prior to 2018, PH was defined as mPAP (measured by right heart catheterization [RHC]) ≥ 25 mm Hg at rest. Now, based on guidelines developed at the 6th World Symposium on Pulmonary Hypertension (WSPH) in 2018, PH is defined as mPAP > 20 mm Hg.[1,2] That change was based on studies in which researchers noted higher mortality in adults who had mPAP below the traditional threshold.[3,4] There is no evidence, however, of increased mortality in the pediatric population in this lower mPAP range.[5]

PH is estimated to be present in approximately 1% of the population.[6] PH due to other diseases—eg, cardiac disease, lung disease, or a chronic thromboembolic condition—reflects the prevalence of the causative disease.[7]

How is pulmonary hypertension classified?

Based on the work of a Task Force of the 6th WSPH, PH is classified by underlying pathophysiology, hemodynamics, and

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functional status. Clinical classification comprises 5 categories, or "groups," based on underlying pathophysiology (**TABLE 1**[6]).

Clinical classification

Group 1 PH includes patients with primary pulmonary hypertension, also referred to (including in this article) as *pulmonary arterial hypertension* (PAH). Hemodynamic criteria that define PAH include pulmonary vascular resistance (PVR) > 2 Woods units[a] and pulmonary capillary wedge pressure > 15 mm Hg. Idiopathic PAH is the most common diagnosis in this group.

The incidence of PAH is approximately 6 cases for every 1 million adults; prevalence is 48 to 55 cases for every 1 million adults. PAH is more common in women.[6]

Less common causes in Group 1 include connective tissue disorders and exposure to toxins. Drugs and toxins that have a well-defined association with PAH include aminorex, fenfluramine, dexfenfluramine, benfluorex, methamphetamines, dasatinib, and toxic rapeseed oil.

Group 2 PH comprises patients whose disease results from left heart dysfunction, the most common cause of PH. This subgroup has an elevated pulmonary artery wedge pressure > 15 mm Hg.[8] Patients have either isolated postcapillary PH or combined pre-capillary and postcapillary PH.

Group 3 PH comprises patients whose PH is secondary to chronic and hypoxic lung disease. Patients in this group have pre-capillary PH; even a modest elevation in mPAP (20-29 mm Hg) is associated with a poor prognosis. Group 3 patients have elevated PVR, even with mild PH.[2] Exertional dyspnea disproportionate to the results of pulmonary function testing, low carbon monoxide diffusion capacity, and rapid decline of arterial oxygenation with exercise all point to severe PH in these patients.[9]

Group 4 PH encompasses patients with pulmonary artery obstruction, the most common cause of which is related to chronic thromboembolism. Other causes include obstruction of the pulmonary artery from an extrinsic source. Patients with chronic thromboembolic pulmonary hypertension (CTEPH) also have pre-capillary PH, resulting from elevated pulmonary pressures secondary to thromboembolic burden, as well as pulmonary remodeling in unobstructed small arterioles.

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[a] PVR in Woods units is calculated as mPAP – pulmonary artery systolic pressure/cardiac output.

IMAGE: © STEVE OH

TABLE 1

Updated (2022) clinical classification of PH[6]

GROUP 1 PAH
1.1 Idiopathic
1.1.1 Nonresponders at vasoreactivity testing
1.1.2 Acute responders at vasoreactivity testing
1.2 Heritable
1.3 Associated with drugs and toxins
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH with features of venous (pulmonary veno-occlusive disease) or capillary (pulmonary capillary hemangiomatosis) involvement
1.6 Persistent PH of the newborn
GROUP 2 PH associated with left heart disease
2.1 Heart failure
2.1.1 With preserved ejection fraction
2.1.2 With reduced or mildly reduced ejection fraction
2.2 Valvular heart disease
2.3 Congenital or acquired cardiovascular conditions leading to postcapillary PH
GROUP 3 PH associated with lung disease or hypoxia, or both
3.1 Obstructive lung disease or emphysema
3.2 Restrictive lung disease
3.3 Lung disease with a mixed restrictive or obstructive pattern
3.4 Hypoventilation disorders
3.5 Hypoxia without lung disease (eg, high altitude)
3.6 Developmental lung disorders
GROUP 4 PH associated with pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
GROUP 5 PH with an unclear or multifactorial mechanism, or both
5.1 Hematologic disorders
5.2 Systemic disorders
5.3 Metabolic disorders
5.4 Chronic renal failure with or without hemodialysis
5.5 Pulmonary tumor thrombotic microangiopathy
5.6 Fibrosing mediastinitis

PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

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Group 5 PH is a miscellaneous group secondary to unclear or multiple causes, including chronic hematologic anemia (eg, sickle cell disease), systemic disorders (eg, sarcoidosis), and metabolic disorders (eg, glycogen storage disease). Patients in Group 5 can have both precapillary and postcapillary hypertension.

Classification by functional status

The World Health Organization (WHO) Functional Classification of Patients with Pulmonary Hypertension is divided into 4 classes.[10] This system is used to guide treatment and for prognostic purposes:

Class I. Patients have no limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near-syncope.

Class II. Patients have slight limitation of physical activity. They are comfortable at rest but daily physical activity causes dyspnea, fatigue, chest pain, or near-syncope.

Class III. These patients have marked limitation of physical activity. They are comfortable at rest, but less-than-ordinary activity causes dyspnea, fatigue, chest pain, or near-syncope.

Class IV. Patients are unable to carry out any physical activity without symptoms. They manifest signs of right heart failure. Dyspnea or fatigue, or both, might be present even at rest.

How is the pathophysiology of PH described?

The term *pulmonary hypertension* refers to an elevation in PAP that can result from any number of causes. *Pulmonary arterial hypertension* is a subcategory of PH in which a rise in PAP is due to primary pathology in the arteries proper.

As noted, PH results from a variety of pathophysiologic mechanisms, reflected in the classification in **TABLE 1**.[6]

WSPH Group 1 patients are considered to have PAH; for most, disease is idiopathic. In small-caliber pulmonary arteries, hypertrophy of smooth muscle, endothelial cells, and adventitia leads to increased resistance. Production of nitric oxide and prostacyclins is also impaired in endothe-

lial cells. Genetic mutation, environmental factors such as exposure to stimulant use, and collagen vascular disease have a role in different subtypes of PAH. Portopulmonary hypertension is a subtype of PAH in patients with portal hypertension.

WSPH Groups 2-5. Increased PVR can result from pulmonary vascular congestion due to left heart dysfunction; destruction of the alveolar capillary bed; chronic hypoxic vasoconstriction; and vascular occlusion from thromboembolism.

Once approximately 30% of the pulmonary vasculature is involved, pressure in the pulmonary circulation starts to rise. In all WSPH groups, this increase in PVR results in increased right ventricular afterload that, over time, leads to right ventricular dysfunction.[7,11,12]

How does PH manifest?

Patients who have PH usually present with dyspnea, fatigue, chest pain, near-syncope, syncope, or lower-extremity edema, or any combination of these symptoms. The nonspecificity of presenting symptoms can lead to a delay in diagnosis.

In addition, suspicion of PH should be raised when a patient:

- presents with skin discoloration (light or dark) or a telangiectatic rash
- presents with difficulty swallowing
- has a history of connective tissue disease or hemolytic anemia
- has risk factors for HIV infection or liver disease
- takes an appetite suppressant
- has been exposed to other toxins known to increase the risk of PH.

A detailed medical history—looking for chronic lung or heart disease, thromboembolism, sleep-disordered breathing, a thyroid disorder, chronic renal failure, or a metabolic disorder—should be obtained.

Common findings on the physical exam in PH include:

- an increased P2 heart sound (pulmonic closure)
- high-pitched holosystolic murmur from tricuspid regurgitation
- pulmonic insufficiency murmur
- jugular venous distension
- hepatojugular reflux
- peripheral edema.

These findings are *not* specific to PH but, again, their presence warrants consideration of PH.

How best to approach evaluation and diagnosis?

The work-up for PH is broad; **FIGURE 1**[13,14] provides an outline of how to proceed when there is a concern for PH. For the work-up of symptoms and signs listed earlier, chest radiography and electrocardiography are recommended.

Radiographic findings that suggest PH include enlargement of central pulmonary arteries and the right ventricle and dilation of the right atrium. Pulmonary vascular congestion might also be seen, secondary to left heart disease.[7]

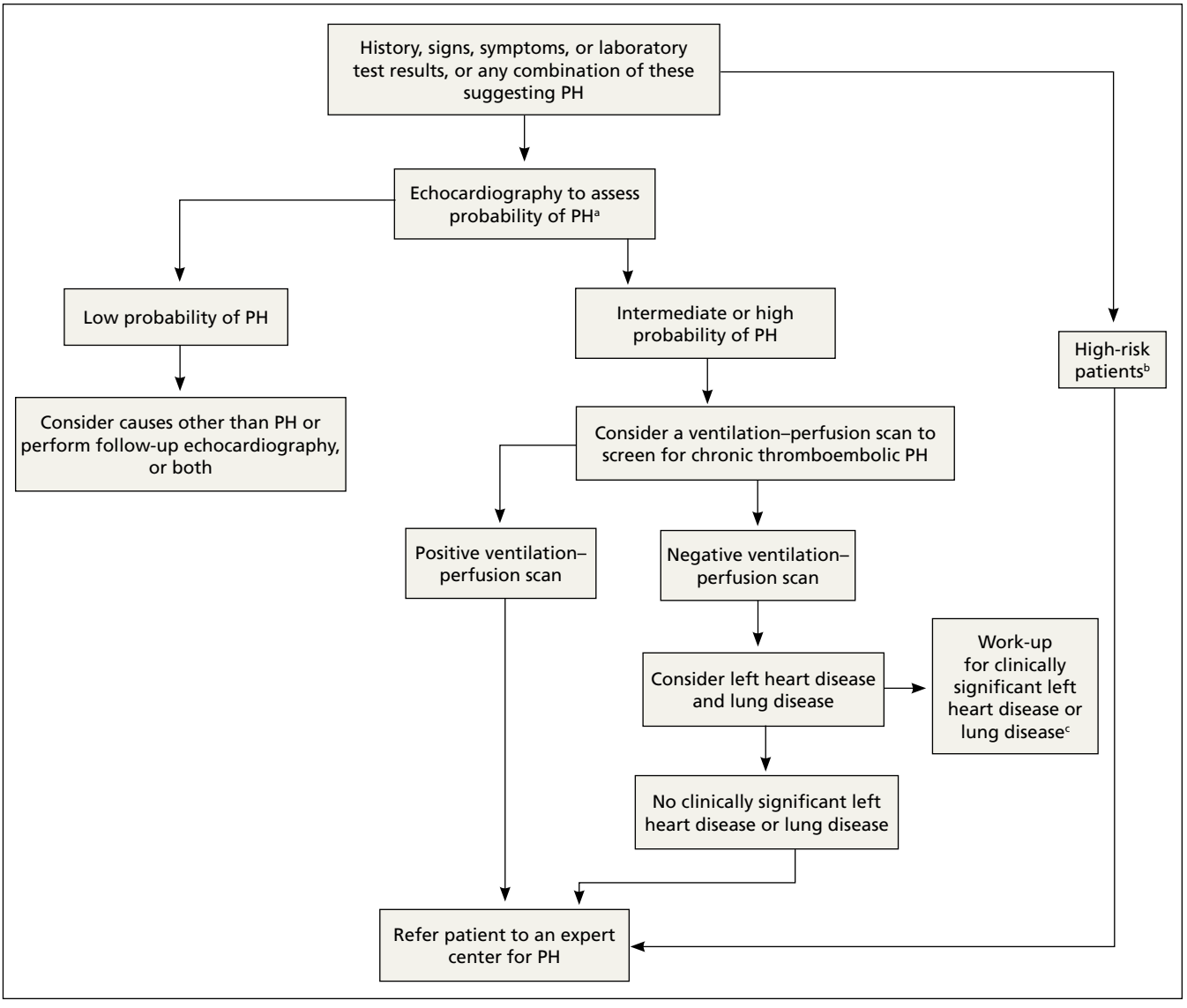
Electrocardiographic findings of PH are demonstrated by signs of left ventricular hypertrophy, especially in Group 2 PH. Upright R waves in V_1-V_2 with deeper S waves in V_5-V_6 might represent right ventricular hypertrophy or right heart strain. Frequent premature atrial contractions and multifocal atrial tachycardia are also associated with PH.[7]

Brain natriuretic peptide (BNP) or N-terminal (NT) proBNP. The level of BNP might be elevated in PH, but its role in the diagnostic process has not been established. BNP can, however, be used to monitor treatment effectiveness and prognosis.[15] A normal electrocardiogram in tandem with a normal level of BNP or NT-proBNP is associated with a low likelihood of PH.[6]

Transthoracic echocardiography (TTE) is the initial evaluation tool whenever PH is suspected. Echocardiographic findings suggestive of PH include a combination of tricuspid regurgitation velocity > 2.8 m/s (**FIGURE 2**); estimated pulmonary artery systolic pressure > 35 mm Hg in younger adults and > 40 mm Hg in older adults; right ventricular hypertrophy or strain; or a combination of these. Other TTE findings suggestive of PH are related to the ventricles, pulmonary artery, inferior vena cava, and right atrium

FIGURE 1

Diagnostic work-up based on echocardiographic probability of PH[13,14]



PH, pulmonary hypertension.

[a] See **TABLE 3**.[16]

[b] High-risk patients are those with warning signs including rapid progression of symptoms, severely reduced exercise capacity, pre-syncope or syncope on mild exertion, or signs of right heart failure.

[c] With pulmonary function testing and chest computed tomography.

(**TABLE 2**[6]). The probability of PH based on TTE findings is categorized as low, intermediate, or high (see **TABLE 2**[6] and **TABLE 3**[16] for details).

Older guidelines, still used by some, rely on the estimated pulmonary artery systolic pressure (ePASP) reading on echocardiography.[13,17] However, studies have reported poor correlation between ePASP readings and values obtained from RHC.[18]

TTE also provides findings of left heart disease, such as left ventricular systolic and diastolic dysfunction and left-sided valvular pathology. Patients with suspected PH in whom evidence of left heart disease on TTE is insufficient for making the diagnosis should

receive further evaluation for their possible status in Groups 3-5 PH.

Ventilation–perfusion (VQ) scan. If CTEPH is suspected, a VQ scan should be performed. The scan is highly sensitive for CTEPH; a normal VQ scan excludes CTEPH. Computed tomography (CT) of the chest is not helpful for identifying chronic thromboembolism.[13]

Coagulation assays. When CTEPH is suspected, coagulopathy can be assessed by measuring anticardiolipin antibodies, lupus anticoagulant, and anti-β-2-glycoprotein antibodies.[13]

Chest CT will show radiographic findings in greater detail. An enlarged pulmonary artery (diameter ≥ 29 mm) or a ratio ≥ 1 of the diameter of the main pulmonary artery to the diameter of the ascending aorta is suggestive of PH.

Other tests. Overnight oximetry and testing for sleep-disordered breathing, performed in an appropriate setting, can be considered.[13,14,19]

Pulmonary function testing with diffusion capacity for carbon monoxide, high-resolution chest CT, and a 6-minute walk test (6MWT) can be considered in patients who have risk factors for chronic lung disease. Pulmonary function testing, including measurement of the diffusing capacity of the lungs for carbon monoxide, arterial blood gas analysis, and CT, is used to aid in interpreting echocardiographic findings in patients with lung disease in whom PH is suspected.

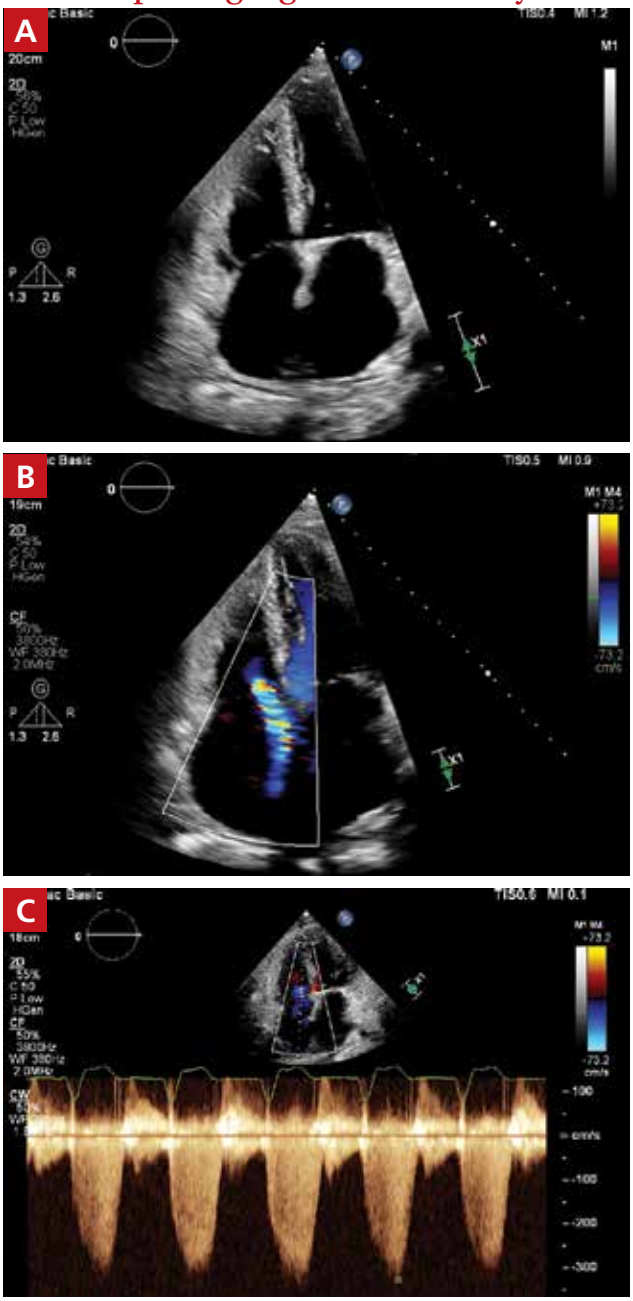
Testing for comorbidities. A given patient's predisposing conditions for PH might already be known; if not, laboratory evaluation for conditions such as sickle cell disease, liver disease, thyroid dysfunction, connective tissue disorders (antibody tests of antinuclear antibody, rheumatoid factor, anticentromere, anti-topoisomerase, anti-RNA polymerase III, anti-double stranded DNA, anti-Ro, anti-La, and anti-U1-RNP), and vasculitis (anti-neutrophil cytoplasmic autoantibodies) should be undertaken.

Analysis of stool and urine for *Schistosoma* spp parasites can be considered in an appropriate clinical setting.[13]

Right heart catheterization. Once alternative diagnoses are excluded, RHC is recommended to make a definitive diagnosis and assess the contribution of left heart disease. Vasoreactivity—defined as a reduction in mPAP ≥ 10 mm Hg to reach an absolute value of mPAP ≤ 40 mm Hg with increased

FIGURE 2

Echocardiographic images of tricuspid regurgitation velocity



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Echocardiography in this patient shows (**A**) right ventricle and bi-atrial dilation in an apical 4-chamber view; (**B**) Doppler view of tricuspid regurgitation; and (**C**) continuous wave Doppler view of a tricuspid regurgitation jet, which is used to assess peak and mean pulmonary artery pressures.

TABLE 2

Additional echocardiographic signs that suggest, and are used to assess the probability of, PH[6a]

Echocardiographic signs from ≥ 2 categories (A, B, C) should be present to alter the level of echocardiographic probability of PH.

Category		
A	B	C
Ventricles	Pulmonary artery	Inferior vena cava and right atrium
Basal diameter ratio of right ventricle to left ventricle > 1.0	Right ventricular outflow Doppler acceleration time < 105 m/sec *or* Midsystolic notching *or both*	Diameter of inferior cava > 21 mm with decreased inspiratory collapse (< 50% with a sniff or < 20% with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index > 1.1 in systole *or* in diastole) *or both*	Early diastolic pulmonary regurgitation velocity > 2.2 m/sec	Right atrial area (end-systole) > 18 cm^2
Ratio of tricuspid annular plane systolic excursion to systolic pulmonary arterial pressure < 0.55 mm/mm Hg	Diameter of pulmonary artery > diameter of aortic root *or* Diameter of pulmonary artery > 25 mm	

PH, pulmonary hypertension.

[a] In addition to tricuspid regurgitation velocity.

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or unchanged cardiac output—is assessed during RHC by administering nitric oxide or another vasodilator. This definition of vasoreactivity helps guide medical management in patients with PAH.[7,20]

6MWT. Once the diagnosis of PH is made, a 6MWT helps establish baseline functional performance and will help you to monitor disease progression.

Who can benefit from screening for PH?

Annual evaluation of the risk of PAH is recommended for patients with systemic sclerosis or portal hypertension[13] and can be considered in patients who have connective tissue disease with overlap features of systemic sclerosis.

Assessment for CTEPH or chronic thromboembolic pulmonary disease is recommended for patients with persistent or new-onset dyspnea or exercise limitation after pulmonary embolism.

Screening echocardiography for PH is recommended for patients who have been referred for liver transplantation.[6]

How risk is stratified

Risk stratification is used to manage PH and assess prognosis.

At diagnosis. Application of a 3-strata model of risk assessment (low, intermediate, high) is recommended.[6] Pertinent data to determine risk include signs of right heart failure, progression of symptoms and clinical manifestations, report of syncope, WHO functional class, 6MWT, cardiopulmonary exercise testing, biomarkers (BNP or NT-proBNP), echocardiography, presence of pericardial effusion, and cardiac magnetic resonance imaging.

TABLE 3

When PH is suspected: Echocardiographic probability of PH findings in symptomatic patients[16]

Peak tricuspid regurgitant velocity (m/sec)	Other echocardiographic signs of PH[a]	Echocardiographic probability of PH
≤ 2.8 or unmeasurable	No	Low
≤ 2.8 or unmeasurable	Yes	Intermediate
2.9-3.4	No	
2.9-3.4	Yes	High
> 3.4	Not required	

PH, pulmonary hypertension.

[a] See **TABLE 2**.[6]

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At follow-up. Use of a 4-strata model (low, intermediate–low, intermediate–high, and high risk) is recommended. Data used are WHO functional class, 6MWT, and results of either BNP or NT-proBNP testing.[6]

When to refer

Specialty consultation[21-23] is recommended for:

- all patients with PAH
- PH patients in clinical Groups 2 and 3 whose disease is disproportionate to the extent of their left heart disease or hypoxic lung disease
- patients in whom there is concern about CTEPH and who therefore require early referral to a specialist for definitive treatment
- patients in whom the cause of PH is unclear or multifactorial (ie, clinical Group 5).

What are the options for managing PH?

Management of PH is based on the cause and classification of the individual patient's disease.

Treatment for WSPH Group 1

Patients require referral to a specialty clinic for diagnosis, treatment, and monitoring of progression.[10]

First, regrettably, none of the medications approved by the US Food and Drug Administration for treating PAH prevent progression.[7]

Patients with idiopathic, hereditary, or drug-induced PAH with positive vasoreactivity are treated with a calcium channel blocker (CCB). The dosage is titrated to optimize therapy for the individual patient.

The patient is then reassessed after 3 to 6 months of medical therapy. Current treatment is continued if the following goals have been met:

- WHO functional classification is I or II
- BNP < 50 ng/L or NT-proBNP < 300 ng/L
- hemodynamics are normal or near-normal (mPAP ≤ 30 mm Hg and PVR ≤ 4 WU).

If these goals have *not* been met, treatment is adjusted by following the algorithm described below.

The treatment algorithm for idiopathic-, heritable-, drug-induced, and connective tissue disease–associated PAH highlights the importance of cardiopulmonary comorbidities and risk strata at the time treatment is initiated and then during follow-up.

Cardiopulmonary comorbidities are conditions associated with an increased risk of left ventricular diastolic dysfunction, including obesity, hypertension, diabetes, and coronary artery disease. Pulmonary comorbidities can include signs of mild parenchymal lung disease and are often associated with a low carbon monoxide diffusing capacity (< 45% of predicted value).

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Drugs and toxins associated with pulmonary arterial hypertension include aminorex, fenfluramine, dexfenfluramine, benfluorex, methamphetamines, dasatinib, and toxic rapeseed oil.

The nonspecificity of presenting symptoms of pulmonary hypertension—dyspnea, fatigue, chest pain, near syncope, syncope, lower-extremity edema—can lead to a delay in diagnosis.

The management algorithm proceeds as follows:

- For patients *without* cardiopulmonary comorbidities and who are at low or intermediate risk, treatment of PAH with an endothelin receptor antagonist (ERA) plus a phosphodiesterase-5 (PDE5) inhibitor is recommended.
- For patients *without* cardiopulmonary comorbidities and who are at high risk, treatment with an ERA, a PDE5 inhibitor, and either an IV or subcutaneous prostacyclin analogue (PCA) can be considered.
- Patients in either of the preceding 2 categories should have regular follow-up assessment; at such follow-up, their risk should be stratified based on 4 strata (see "How risk is stratified," page 78):
  - *Low risk*: Continue initial therapy.
  - *Low-to-intermediate risk*: Consider adding a prostacyclin receptor agonist to the initial regimen *or* switch to a PDE5 inhibitor or a soluble guanylate cyclase stimulator.
  - *Intermediate-to-high or high risk*: Consider adding a PCA (IV epoprostenol or IV or subcutaneous treprostinil). In addition, or alternatively, have the patient evaluated for lung transplantation.
- For patients *with* cardiopulmonary comorbidity—in any risk category—consider oral monotherapy with a PDE5 inhibitor or an ERA. Provide regular follow-up and individualize therapy.[6]

Treatment for WSPH Groups 2 and 3

Treatment is focused on the underlying cause of PH:

- Patients who have left heart disease with either severe pre-capillary component PH or markers of right ventricular dysfunction, or both, should be referred to a PH center.
- Patients with combined pre-capillary and postcapillary PH in whom pre-capillary PH is severe should be considered for an individualized approach.
- Consider prescribing the ERA bosentan in specific scenarios (eg, the Eisenmenger syndrome of left-right shunting resulting from a congenital cardiac defect) to improve exercise capacity. If PAH persists after corrected adult congenital heart disease, follow the PAH treatment algorithm for Group 1 patients (described earlier).
- For patients in Group 3, those who have severe PH should be referred to a PH center.
- Consider prescribing inhaled treprostinil in PH with interstitial lung disease.

Treatment for WSPH Group 4

Patients with CTEPH are the only ones for whom pulmonary endarterectomy (PEA), the treatment of choice, might be curative. Balloon angioplasty can be considered for inoperable cases[6]; these patients should be placed on lifelong anticoagulant therapy.

Symptomatic patients who have inoperable CTEPH or persistent recurrent PH after PEA are medically managed; the agent of choice is riociguat. Patients who have undergone PEA or balloon angioplasty and those receiving pharmacotherapy should be followed long term.

Treatment for WSPH Group 5

Management of these patients focuses on associated conditions.

Which medications for PAH?

CCBs. Four options in this class have shown utility, notably in patients who have had a positive vasoreactivity test (see "How best to approach evaluation and diagnosis?," page 75):

- *Nifedipine* is started at 10 mg tid; target dosage is 20 to 60 mg, bid or tid.
- *Diltiazem* is started at 60 mg bid; target dosage is 120 to 360 mg bid.
- *Amlodipine* is started at 5 mg/d; target dosage is 15 to 30 mg/d.
- *Felodipine* is started at 5 mg/d; target dosage is 15 to 30 mg/d.

Felodipine and amlodipine have longer half-lives than other CCBs and are well tolerated.

ERA. Used as vasodilators are ambrinsentan (starting dosage, 5 mg/d; target dosage, 10 mg/d), macitentan (starting and target dosage, 10 mg/d), and bosentan (starting dosage, 62.5 mg bid; target dosage, 125 mg bid).

Nitric oxide–cyclic guanosine monophosphate enhancers. These are the PDE5 inhibitors sildenafil (starting and target dosages, 20 mg tid) and tadalafil (starting dosage, 20 or 40 mg/d; target dosage, 40 mg/d), and the guanylate cyclase stimulant riociguat (starting dosage, 1 mg tid; target dosage, 2.5 mg tid). All 3 agents enhance production of the potent vasodilator nitric oxide, production of which is impaired in PH.

Prostanoids. Several options are available:

- Beraprost sodium. For this oral prostacyclin analogue, starting dosage is 20 µg tid; target dosage is the maximum tolerated dosage (as high as 40 µg tid).
- Extended-release beraprost. Starting dosage is 60 µg bid; target dosage is the maximum tolerated dosage (as high as 180 µg bid).
- Oral treprostinil. Starting dosage is 0.25 mg bid or 0.125 mg tid; target dosage is the maximum tolerated dosage.
- Inhaled iloprost. Starting dosage of this prostacyclin analogue is 2.5 µg, 6 to 9 times per day; target dosage is 5 µg, 6 to 9 times per day.
- Inhaled treprostinil. Starting dosage is 18 µg qid; target dosage is 54 to 72 µg qid.
- Epoprostenol is administered by continuous IV infusion, at a starting dosage of 2 ng/kg/min; target dosage is determined by tolerability and effectiveness (typically, 30 ng/kg/min).
- IV treprostinil. Starting dosage 1.25 ng/kg/min; target dosage is determined by tolerability and effectiveness, with a typical dosage of 60 ng/kg/min.

Combination treatment with the agents listed above is often utilized.

Selexipag. This oral selective nonprostainoid prostacyclin receptor agonist is started at 200 µg bid; target dosage is the maximum tolerated, as high as 1600 µg bid.

Supportive therapy

The need for oxygen should be addressed in patients with hypoxia in any setting—resting, exercise induced, and nocturnal.[24] Patients with an arterial blood oxygen pressure < 60 mm Hg (SaO_2 < 90 mm Hg) should be on long-term oxygen therapy.[6]

Diuretics are beneficial in patients with chronic fluid retention from PH that is related to right ventricular failure.[24]

Pulmonary rehabilitation and exercise. Contrary to common belief that exercise training is contraindicated in patients with PH, exercise training has emerged in the past decade as an effective tool to improve exercise capacity, ventilatory efficiency, and quality of life. While a patient is training, oxygen saturation, measured by pulse oximetry, should be maintained at > 90% throughout the exercise session to avoid hypoxic pulmonary artery vasoconstriction.[25]

A patient who does not qualify for pulmonary or cardiac rehabilitation should be referred for physical therapy.[24]

Ongoing follow-up in primary care

Instruct patients not to abruptly discontinue medications that have been prescribed for PH. Ongoing follow-up and monitoring involves assessing right heart function, exercise tolerance, and resting and ambulatory oximetry. Testing for the level of BNP provides prognostic information and allows assessment of treatment response.[15] The frequency of 6MWT, echocardiography, and RHC is decided on a case-by-case basis.

Other considerations

Pregnancy. PAH often affects patients of childbearing age. Because PAH-associated maternal mortality and the risk to the fetus during pregnancy are high, pregnancy is not recommended for patients with PAH. After a diagnosis of PAH in a patient of childbearing age, counseling should be offered at an expert center. Advice on effective contraception methods should be given early on.[10,26-29]

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Common physical findings in pulmonary hypertension include an increased P2 heart sound, high-pitched holosystolic murmur from tricuspid regurgitation, and pulmonic insufficiency murmur.

Pulmonary hypertension in the pediatric population

The onset of pulmonary hypertension (PH) in children can occur at any age and be of quite different causes than in adults. In newborns, pulmonary pressure drops rapidly during the week after delivery; in some cases, however, pressures remain elevated (> 20 mm Hg) despite healthy lungs. These asymptomatic newborns require close monitoring.[32]

Etiology. Pediatric PH can be persistent or transient. Prominent causes of persistent or progressive PH in children are pulmonary arterial hypertension (PAH) associated with congenital heart disease and developmental lung disease, such as bronchopulmonary dysplasia and idiopathic PAH. Major categories of congenital heart disease that cause PH are shunting lesions and left heart disease associated with elevated atrial pressure. Other causes are rare.[33]

Persistent PH of the newborn (PPHN) and PH due to diaphragmatic hernia are common causes of transient PH.[34] In PPHN, pulmonary vascular resistance remains abnormally high after birth, resulting in right-to-left shunting of the circulation that, in turn, leads to hypoxemia unresponsive to usual measures. In most cases, signs of respiratory distress and hypoxia are noted within the first 24 hours of life. The most common cause of PPHN is infection.[35]

Evaluation. The typical diagnostic work-up of suspected pediatric PH is similar to what is undertaken in the adult population—varying, however, according to the specific suspected cause. As in adults, right heart catheterization remains the gold standard of diagnosis, and should be conducted at a pediatric PH expert center. As with adult patients, infants and children with PH should be managed by a multidisciplinary expert team.

Management. PAH-targeted medications (see "What are the options for managing PH?," page 79) are used to treat PAH in children.[36]

Surgery. Every patient with clinically significant PH is at increased risk of perioperative morbidity and death.[30,31] Guidelines recommend that these patients avoid nonessential surgery; if surgery is necessary, care should be provided at a PH expert center.[10]

Patients with severe PH should consider surgery for any indication carefully, discussing with the care team their risk and exploring nonsurgical options. Cardiothoracic surgical and liver transplantation services might have highly specific criteria for treating patients with PH, but other essential and nonessential surgeries require individualized risk stratification. Surgery for patients with severe PH and right ventricular dysfunction should be performed at a center equipped to handle high-risk patients.

Other preventive measures. Patients with PAH should[6,10]:

- remain current with immunization against influenza virus, SARS-CoV-2, and pneumococcal pneumonia
- avoid high altitudes
- use supplemental oxygen during air travel to keep arterial oxygen saturation > 91%.

Lung transplantation. Patients eligible for transplantation who (1) are at intermediate-to-high risk or high risk or (2) have a REVEAL (*R*egistry to *EV*aluate *E*arly *A*nd *L*ong-term pulmonary arterial hypertension disease management) risk score > 7, and who have had an inadequate response to oral combination therapy, should be referred for evaluation for lung transplantation. Placement on the list for lung transplantation is also recommended for patients at high risk of death and who have a REVEAL risk score ≥ 10 despite medical therapy, including a subcutaneous or IV prostacyclin analogue.[6]

PH in infants and children

The Pediatric Task Force of the 6th WSPH has applied the new definition proposed for adult PH (> 20 mm Hg mPAP) to children and infants > 3 months of age (see "Pulmonary hypertension in the pediatric population," at left[32-36]). JFP

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