Chapter 46: Pulmonary Arterial Hypertension

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KEY CONCEPTS

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1. Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary artery pressure (mPAP) ≥20 mm Hg at rest with a pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure ≤15 mm Hg and a pulmonary vascular resistance (PVR) >3 Wood units (24 MPa·s/m^3) measured by right heart catheterization.

2. Patients with PAH most commonly present with exertional dyspnea, fatigue, weakness, and exercise intolerance. As the disease progresses, symptoms of right heart dysfunction and failure, such as dyspnea at rest, lower extremity edema, chest pain, and syncope, may be present.

3. The definitive diagnosis of PAH is done with a right heart catheterization. The right heart catheterization provides important prognostic information and can be used to assess pulmonary vasoreactivity prior to initiating therapy.

4. Treatment goals are to achieve low-risk status; alleviate symptoms; improve quality of life, functional class, and exercise capacity; slow disease progression; and improve survival.

5. Nonpharmacologic therapy, including counseling on pregnancy avoidance, structured pulmonary or cardiac rehabilitation, immunizations, and low-sodium diets, should be provided to all patients with PAH.

6. Conventional therapy options for PAH include oral anticoagulants, diuretics, oxygen, and digoxin.

7. Prostacyclin analogs such as epoprostenol, treprostinil, and iloprost induce potent vasodilation of pulmonary vascular beds. These therapies can be administered through different routes, including oral, inhaled, subcutaneous, and intravenous. Intravenous therapies are typically reserved for high-risk patients and are used in combination with endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and riociguat. Only epoprostenol has demonstrated improved survival.

8. Oral combination therapy is recommended initially for patients with PAH at low-to-intermediate risk for mortality at 1 year. Options include endothelin-receptor antagonists, phosphodiesterase-5 inhibitors, riociguat, and selexipag. These agents improve exercise capacity, functional class, and hemodynamics in PAH.

9. Calcium channel blockers (CCBs) are only considered in a small number of patients who have a positive response to acute vasoreactivity testing. A small number of patients have a long-term response to CCBs.

BEYOND THE BOOK

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The mechanism of action of medications used in pulmonary arterial hypertension (PAH) is directly tied to the pathophysiology of the disease. Create a concept map of the site of action of the major medication classes utilized in PAH—prostacyclin analogs, endothelin-receptor antagonists (ERAs), phosphodiesterase-5 inhibitors, and guanylate cyclase stimulators. This activity is intended to prepare you to understand the role of the medications in the treatment of PAH as well as to increase critical thinking skills related to evaluating side effects and monitoring parameters of these medications.

INTRODUCTION

1 Pulmonary arterial hypertension (PAH) is a group of conditions relating to elevated blood pressure measured within the pulmonary arteries. Pulmonary hypertension (PH) is not a specific diagnosis; rather it is a complex group of disorders relating to the pulmonary circulation. PH is classified into five groups according to the World Health Organization (WHO); see Table 46-1.[1] PAH, or Group 1 PH, is a progressive disease characterized by an elevation in pulmonary arterial pressure and pulmonary vascular resistance. PAH may be defined as a mean pulmonary artery pressure (mPAP) ≥20 mm Hg at rest, with a pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure ≤15 mm Hg and a pulmonary vascular resistance (PVR) >3 Wood units (24 MPa·s/m^3) measured by cardiac catheterization.[1-3]

TABLE 46-1

World Health Organization Classification of Pulmonary Hypertension

Group 1—Pulmonary Arterial Hypertension (PAH)

• Idiopathic (IPAH)
• Heritable
  ○ BMPR-2
  ○ Other mutations: ALK-1, ENG, SMAD9, CAV1, KCNK3
• Medications and toxin-induced PAH
• PAH associated with
  ○ Connective tissue diseases
  ○ HIV infection
  ○ Portal hypertension
  ○ Congenital heart diseases
  ○ Schistosomiasis
• PAH long-term responders to calcium channel blockers
• PAH with overt features of venous/capillaries (PVOD/PCH) involvement
• Persistent pulmonary hypertension (PH) of the newborn

Group 2—PH due to Left Heart Disease
• PH due to heart failure with preserved ejection fraction or heart failure with reduced ejection fraction • Valvular disease • Congenital/acquired cardiovascular conditions leading to post-capillary PH
Group 3—PH due to Lung Diseases and/or Hypoxia
• Obstructive pulmonary disease

- Restrictive lung disease
- Other lung diseases with a mixed restrictive and obstructive pattern
- Hypoxia without lung disease
- Developmental lung disorders

Group 4—PH due to pulmonary artery obstructions

- Chronic thromboembolic pulmonary hypertension (CTEPH)
- Other pulmonary artery obstructions
  - Sarcoma or angiosarcoma
  - Other intravascular tumors
  - Arteritis without connective tissue disease
  - Congenital pulmonary arteries stenosis
  - Parasites (hydatidosis)

Group 5—Pulmonary Hypertension with Unclear and/or Multifactorial Mechanisms

- Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders
- Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, Gaucher disease, glycogen storage disease, neurofibromatosis
- Others: fibrosing mediastinitis, chronic renal failure (with/without dialysis)
- Complex congenital heart disease

ALK-1, activin receptor-like kinase type-1; BMPR-2, bone morphogenetic protein receptor 2; CAV1, caveolin-1; ENG, endoglin; EIF2AK4, eukaryotic translation initiation factor 2 alpha kinase 4; HIV, human immunodeficiency virus; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary hemangiomatosis.

Data from Reference 1.

PAH may occur in the setting of underlying medical conditions or as an idiopathic disease (idiopathic PAH [IPAH]). Historically, medical treatment of PAH has been limited due to lack of effective, targeted therapy. Without medical therapy, IPAH portends a poor prognosis (median survival 2.8 years) after diagnosis.[4] Prior to the availability of disease-specific therapy for IPAH, survival rates at 1, 3, and 5 years were 68%, 48%, and 34%, respectively.[5] Since the approval of epoprostenol in 1995, a number of new therapeutic options have been developed. A recent study shows survival rates at 1 and 3 years were 85% and 68%, respectively, in patients with PAH, and 91% and 74%, respectively, in patients with IPAH.[6] Overall 5-year survival rates in that registry were 65% in previously diagnosed patients versus 61% in newly diagnosed patients with PAH.[7]

EPIDEMIOLOGY

The prevalence of PAH is 15 to 26 patients per million individuals.[8] One registry study found that the most common cause of PAH was IPAH (approximately 40%), followed by PAH associated with connective tissue diseases (15.3%), congenital heart disease (11.3%), portal hypertension (10.4%), and familial PAH (FPAH) (3.9%).[9] The US-based REVEAL (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management) registry found that 46% of PAH was idiopathic, 25% was associated with connective tissue diseases, and 10% was associated with congenital heart diseases.[10] The incidence of IPAH is 2.0 to 7.6 per 1 million in North America and Europe, with a marked female predominance (male-to-female ratio, 1:1.7), and mean age at the time of recognition is approximately 37 years, although there is considerable variation.[11]

The diagnosis of PAH is growing due to increased awareness and knowledge of the disease state, leading to earlier and improved evaluation and identification. Based on recent registry data, PAH is now being diagnosed more commonly in older patients, with a mean age at diagnosis ranging from 50 to 65 years.[11]

ETIOLOGY

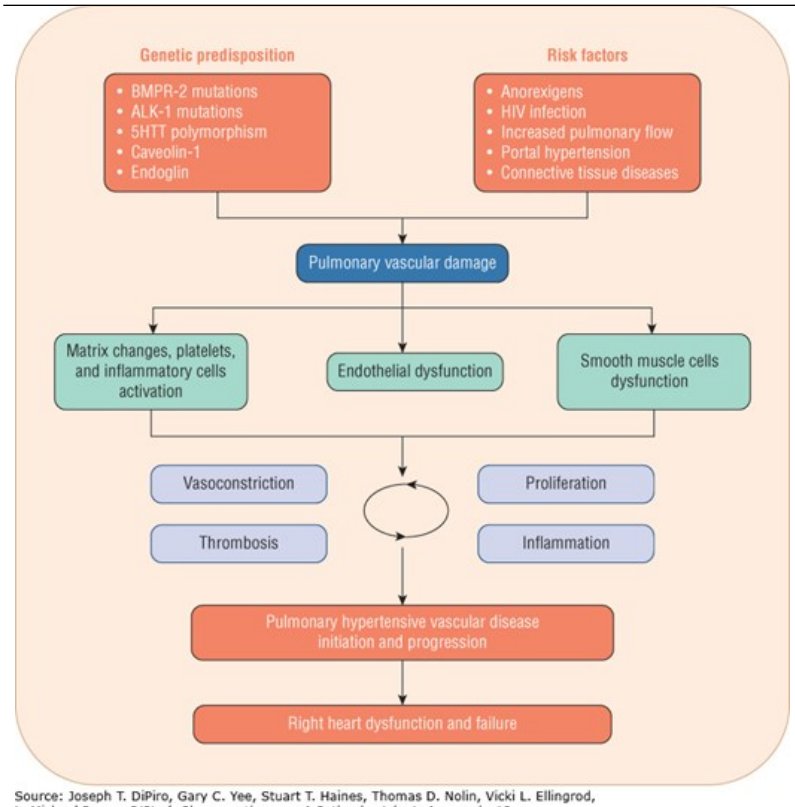
PAH most often originates with a predisposing state and one or more inciting factors that could be genetic or environmental exposures.[12] Once a permissive environment exists, multiple mechanisms can be activated leading to vascular constriction, cellular proliferation, and a prothrombotic state resulting in PAH and its sequelae.[13] PAH can be associated with numerous conditions as well as being an idiopathic condition (IPAH). Although uncommon in the United States, the most common form of PAH worldwide is schistosomiasis followed by congenital heart disease and pulmonary hypertension of early childhood.[2] Rheumatologic diseases such as scleroderma, systemic lupus erythematosus, rheumatoid arthritis, and myositis are also associated with the development of PAH. Patients with scleroderma who develop PAH, between 7% and 12% of patients, have markedly worse outcomes in comparison to other PAH subgroups. Patients with human immunodeficiency virus (HIV) infection can develop PAH with a prevalence of 0.5%. In patients with liver disease, portal hypertension may cause concurrent pulmonary hypertension in 2% to 6% of patients.[2] Multiple medications and toxins have been associated with PAH but those that definitively precipitate PAH include anorexigens such as aminorex, fenfluramine, benfluorex, and dexfenfluramine.[1,3,11] Other precipitants include toxic rapeseed oil and selective serotonin reuptake inhibitors (SSRIs), specifically in newborns of pregnant patients exposed to SSRIs after 20 weeks of gestation.[2,3] Other medications considered to be likely or possible causative agents for PAH include amphetamines, L-tryptophan, cocaine, interferon α and β, leflunomide, and certain chemotherapeutic agents (dasatanib, mitomycin C, carmustine, etoposide, cyclophosphamide, bleomycin).[1-3] Heritable PAH (HPAH) includes both IPAH with germline mutations and familial cases without an identified mutation. Germline mutations seen in PAH include bone morphogenetic protein receptor 2 (BMPR-2) and activin receptor-like kinase 1 (ALK-1). About 75% of patients with HPAH have BMPR-2 mutations.[14] Genetic testing for these mutations may be offered, and professional genetic counseling should be provided at expert centers.[2,14]

PATHOPHYSIOLOGY

PAH is characterized by progressive vasoconstriction of the small pulmonary arteries that eventually leads to right ventricular hypertrophy and failure. The right ventricle is thin-walled and accustomed to the much lower pressures of the pulmonary system and, therefore, does not have the reserve that the left ventricle does.[15] Regardless of etiology, all subgroups of PAH are based on similar clinical and pathologic physiology. The pathobiology of PAH involves several key biologic events, including endothelial cell dysfunction, thrombotic lesions, platelet activation, the gain of constricting factors, loss of relaxing factors, intimal proliferation, medial hypertrophy, fibrosis, and inflammation—all combining to produce progressive and deleterious vascular remodeling (Fig. 46-1).[16,17] Multiple genetic mutations are known to contribute to the pathophysiology of PAH, including BMPR-2, ALK-1, Caveolin-1, KCNK3, nitric oxide synthase (ec-NOS), and 5-hydroxytryptamine (serotonin [5-HT]) transporter (5-HTT).[2,16,18]

FIGURE 46-1

Pathophysiology of pulmonary arterial hypertension. Pulmonary arterial hypertension; potential pathogenetic and pathobiologic mechanisms. (5-HTT, serotonin transporter gene; ALK-1, activin receptor-like kinase 1 gene; BMPR-2, bone morphogenetic receptor 2 gene; HIV, human immunodeficiency virus.) *(Reproduced from Galiè N, Torbicki A, Barst R, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J. 2004;25(24):2243–2278.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Molecular, cellular, and genetic mechanisms are mediated by a variety of biologically active compounds, including prostacyclin (PGI_2), endothelin-1 (ET-1), nitric oxide (NO), and 5-HT. PGI_2 is a vasodilatory and antiproliferative substance that is produced by the endothelial cells. The synthesis of PGI_2 and its circulating levels is reduced in PAH. Furthermore, thromboxane, a vasoconstrictor, is increased in PAH. ET-1 is produced in the endothelium and possesses potent vasoconstrictor and mitogenic effects. ET-1 levels are increased in PAH, and clearance is reduced. ET-1 acts via the endothelin receptors (ET_A and ET_B) to promote vascular smooth muscle proliferation and vasoconstriction.[17,19] Plasma levels of ET-1 are correlated with the severity of PAH and prognosis.[20] NO is produced in the endothelium via NO synthase, leading to vasodilation. NO also leads to the opening of potassium channels in the cell membrane, allowing potassium efflux, membrane depolarization, and calcium channel inhibition. In PAH, there is evidence of decreased NO synthase expression, leading to vasoconstriction and cell proliferation.[21] Elevated 5-HT has been observed and vasoconstriction mediated via the increased expression of the $5\text{-}HT_{1B}$ receptor is seen in PAH.[2]

Autoantibodies, proinflammatory cytokines, and inflammatory infiltrates may also participate in the pathogenesis of PAH. Coagulation is disordered in PAH as evidenced by increased levels of von Willebrand factor, plasma fibrinopeptide A, plasminogen activator inhibitor-1, 5-HT, and thromboxane. Furthermore, tissue plasminogen activator, thrombomodulin, NO, and PGI_2 are decreased, leading to an imbalance favoring thrombosis. Endothelial dysfunction is the common denominator of mechanisms for PAH, and a variety of injuries, such as shear stress, inflammation, toxins, and hypoxia, are thought to be involved.[2,16]

CLINICAL PRESENTATION

2 The signs and symptoms of PAH are highly variable depending on the stage of the disease and comorbidities. The impact of these signs and symptoms on functional capacity can be generally described using the WHO functional classification (Table 46-2). Symptoms are often related to right ventricular dysfunction and may include exertional dyspnea, fatigue, and weakness.[3] As the disease progresses, patients may experience dyspnea at rest, chest pain, presyncope, syncope, lower extremity edema, and abdominal bloating and distension. On physical examination, patients with PAH may have an accentuated component of S_2 audible at the apex of the heart, midsystolic ejection murmur, palpable left parasternal lift, right ventricular

S_4 gallop, and a prominent "a" wave.[2] Hepatojugular reflux, a diastolic murmur of pulmonary regurgitation, and a systolic murmur of tricuspid regurgitation may be present in advanced disease.[2] Patients with an increased risk of mortality are more likely to have a higher WHO functional class, older age, male gender, higher brain natriuretic peptide (BNP), higher right atrial pressure, and lower cardiac output. In contrast, patients with a decreased risk of mortality are more likely to have a lower WHO functional class, higher 6-minute walking distance (6MWD), lower BNP, and higher cardiac output.[13]

TABLE 46-2

World Health Organization Functional Classification of Pulmonary Arterial Hypertension

Class	Description
I	Patients with PAH in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope
II	Patients with PAH who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope
III	Patients with PAH who have marked limitation of physical activity. There is no discomfort at rest, but less than normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope
IV	Patients with PAH who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest, and symptoms are increased by almost any physical activity

Data from Reference 4.

3 Several comorbidities and environmental factors play a role in the development of PAH and must be evaluated when establishing an initial diagnosis of PAH (Fig. 46-2). If PAH is suspected, a noninvasive screening test (eg, Doppler echocardiography) may detect increased pulmonary pressures. However, diagnosis of PAH requires additional testing.[22,23] Echocardiography is also useful in evaluating specific causes of pulmonary hypertension, such as a cardiac shunt or left-sided heart disease. Echocardiography can also be used to assess treatment interventions and to follow disease progression.[2] However, right heart catheterization is the definitive study to diagnose PAH and evaluate patients who are worsening clinically.[18]

Right heart catheterization is used to assess pulmonary vasoreactivity in patients with idiopathic, heritable, or medication-induced PAH. This test involves the administration of fast-acting vasodilators to determine the extent of vascular smooth muscle constriction and predict vasodilator response to calcium channel blockers (CCBs; class of recommendation I, level of evidence C).[4] Table 46-3 lists the classes of recommendations [COR] and levels of evidence [LOE], and Table 46-4 lists agents commonly used for vasoreactivity testing and their doses. The consensus definition of a positive vasoreactivity response is defined as a reduction of mPAP by at least 10 mm Hg to a value of 40 mm Hg or less with an unchanged or increased cardiac output.[24] Patients with a positive vasoreactivity response (approximately 13% of patients on initial testing) are most likely to have a beneficial hemodynamic and clinical response. These patients may be able to be treated with CCBs. However, about half of these patients lose an acute vasodilator response when tested 1 year later.[25] Therefore, even this small group of patients who may be treated with CCBs must be followed closely for safety and efficacy. If the patient loses the acute vasodilator response on follow-up assessment, they should be switched to different PAH therapy. Patients who have a negative response on initial vasodilator testing are not candidates for treatment with CCBs.[2,26]

FIGURE 46-2

Diagnostic algorithm of pulmonary arterial hypertension. (PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; CT, computed tomography; RV, right ventricular; mPAP, mean pulmonary artery pressure; CTEPH, chronic thromboembolic pulmonary hypertension; HIV, human immunodeficiency virus; PVOD/PCH, pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis; RHC, right heart catheterization.) *(Adapted from Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines forthe diagnosis and treatment of pulmonary hypertension. Eur Respir*

J. 2015;46:903–975.)

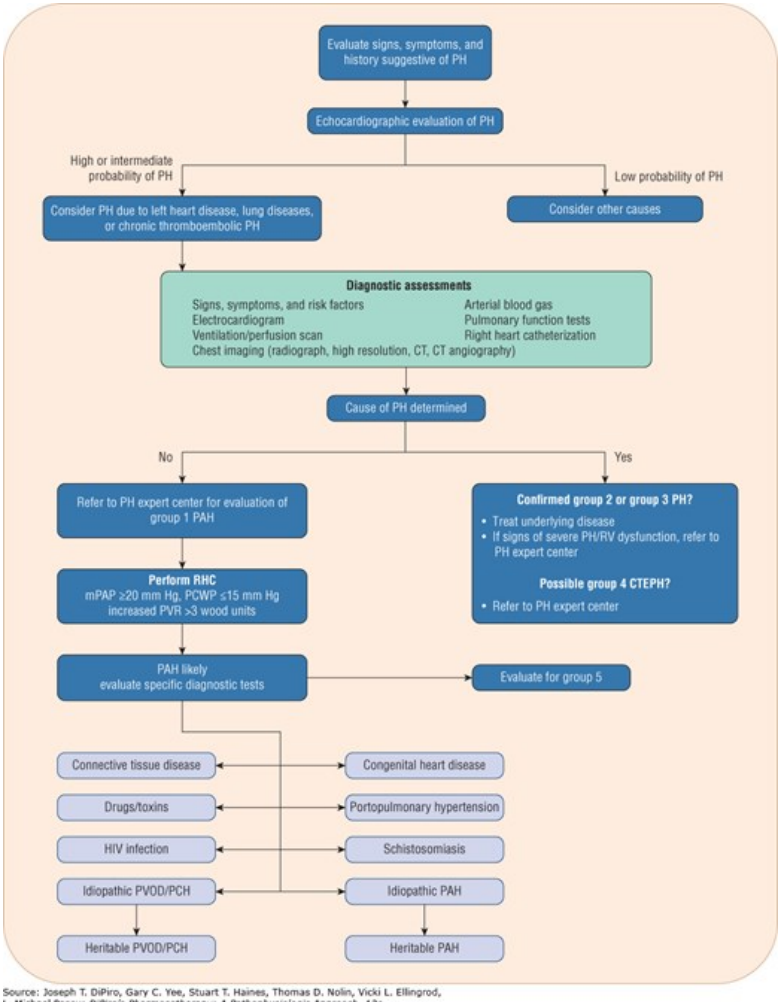


TABLE 46-3

Classes of Recommendations and Levels of Evidence[a]

Classes of Recommendations (CORs)	Definition	Suggested Wording to Use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/Is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that a given treatment or procedures is not useful/effective, and in some cases may be harmful.	Is not recommended
Levels of Evidence (LOE)	**Definition**	
A	Data derived from multiple randomized clinical trials or meta-analyses.	
B	Data derived from a single randomized clinical trial or large nonrandomized studies.	
C	The consensus opinion of the experts and/or small studies, retrospective studies, registries.	

[a]Classes of Recommendations and Levels of Evidence are consistent between the ESC/ERS Guidelines and the WHO Guidelines.

Data from Reference 4.

TABLE 46-4

Agents for Vasodilator Testing in Pulmonary Arterial Hypertension

	Nitric Oxide	Epoprostenol	Adenosine
Route	Inhaled	Intravenous	Intravenous
Dose range	10-80 ppm	2-10 ng/kg/min	50-250 mcg/kg/min
Dosing increments	10-80 ppm for 5 minutes	2 ng/kg/min every 15 minutes	50 mcg/kg/min every 2 minutes
Common side effects	None	Headache, flushing, nausea	Chest tightness, dyspnea

Data from Reference 27.

Because PAH commonly occurs in the setting of connective tissue disease, serologic markers should be obtained to confirm or exclude these diagnoses.[2,28] Liver function tests (LFTs) should also be evaluated due to the increased risk for PAH in patients with cirrhosis and portal hypertension and as a baseline for certain PAH therapies. HIV is associated with an increased prevalence of PAH, and HIV testing should be done as part of the initial

PAH workup.[2] CTEPH should be evaluated with ventilation-perfusion lung scans and/or pulmonary angiography. Pulmonary function testing and arterial blood oxygenation should be evaluated. The diffusing capacity of carbon monoxide may be particularly helpful in patients with systemic sclerosis and PAH.[2]

In patients with PAH, serial determinations of functional class, exercise capacity (assessed by the 6MWD), and serial biomarkers (ie, BNP) provide benchmarks for disease severity, response to therapy, and progression.[2,28] These variables can be used to determine the risk level in patients and may aid in prognosis. Table 46-5 outlines the calculation of low-, intermediate-, and high-risk patients based on these factors, which is essential for determining initial therapy and assessing treatment response. Risk assessment tools continue to be developed and refined (such as REVEAL 2.0 and REVEAL Lite 2) to use the most predictive variables to assess risk while also simplifying the assessment to promote routine use in daily clinical practice.[29,30] Table 46-6 provides guidelines for initial and follow-up assessments and their timing.

TABLE 46-5

Risk Assessment in Pulmonary Arterial Hypertension

Determinants of Prognosis[a] (estimated 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[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6-minute walk distance	>440 m	165-440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 mL/min/kg (>65% pred.) Ve/VCO_2 slope <36	Peak VO_2 11-15 mL/min/kg (35%-65% pred.) Ve/VCO_2 slope 36-44.9	Peak VO_2 <11 mL/min/kg (<35% pred.) Ve/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/L (14.5 pmol/L) NT-proBNP <300 ng/L (35.4 pmol/L)	BNP 50-300 ng/L (14.5-86.7 pmol/L) NT-proBNP 300-1,400 ng/L (35.4-165 pmol/L)	BNP >300 ng/L (86.7 pmol/L) NT-proBNP >1,400 ng/L (165 pmol/L)
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18-26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Hemodynamics	RAP <8 mm Hg CI ≥2.5 L/min/m^2 (0.042 L/s/m^2) SvO_2 >65% (0.65)	RAP 8-14 mm Hg CI 2.0-2.4 L/min/m^2 (0.033-0.040 L/s/m^2) SvO_2 60%-65% (0.60-0.65)	RAP >14 mm Hg CI ≤2.0 L/min/m^2 (0.033 L/s/m^2) SvO_2 <60% (0.60)

WHO, World Health Organization; VO_2, oxygen consumption; Ve, ventilation; VCO_2, volume of exhaled carbon dioxide; NT, n-terminal; BNP, b-type natriuretic peptide; CMR, cardiac magnetic resonance; RA, right atrial, RAP, right atrial pressure; CI, cardiac index; SvO_2, venous oxygen saturation.

[a]Most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and are used to guide therapeutic decisions, but applications to individual patients must be done carefully. One must also note that most of these variables have been validated for IPAH and the cut-off values used above may not apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

[b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in the otherwise stable patient.

[c]Repeated episodes of syncope, even with little or regular physical activity.

Data from Reference 4.

TABLE 46-6

Suggested Assessment and Timing for the Follow-up of Patients with Pulmonary Arterial Hypertension

	At Baseline	Every 3-6 Months	Every 6-12 Months[1]	3-6 Months After Changes in Therapy[1]	In Case of Clinical Worsening
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnea score	+	+	+	+	+
CPET	+		+		+[a]
Echocardiogram	+		+	+	+
Basic labs[b]	+	+	+	+	+
Extended labs[c]	+		+		+
Blood gas analysis[d]	+		+	+	+
Right heart catheterization	+		+[e]	+[f]	+[f]

[a]Intervals to be adjusted according to patient needs.

[b]Basic labs includes complete blood count, INR (in patients receiving vitamin K antagonists), serum creatinine, sodium, potassium, AST/ALT (in patients receiving ERAs), bilirubin, and BNP/NT-proBNP

[c]Extended labs includes TSH, troponin, uric acid, iron status (iron, ferritin, soluble transferrin receptor), and other variables according to individual patient need.

[d]From arterial or arterialized capillary blood; may be replaced by peripheral oxygen saturation in stable patients or if BGA is not available.

[e]Some centers perform RHCs at regular intervals during follow-up.

[f]Should be considered.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BGA, blood gas analysis; BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise testing; Echo, echocardiography; ECG, electrocardiogram; ERAs, endothelin-receptor antagonists; FC, functional class; INR, international normalized ratio; lab, laboratory assessment; NT-proBNP, N-terminal pro-brain natriuretic peptide; RHC, right heart catheterization; TSH, thyroid stimulating hormone; 6MWT, 6-minute walking test.

Data from Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2015;43:903–975.

CLINICAL PRESENTATION: Pulmonary Arterial Hypertension

Symptoms

- Exertional dyspnea
- Fatigue
- Weakness
- Exertional chest pain
- Complaints of general exertion intolerance
- Dyspnea at rest as the disease progresses
- Syncope
- Lower extremity edema

Symptoms of Related Conditions

- Paroxysmal nocturnal dyspnea as a result of left-sided heart disease
- Raynaud's phenomenon, arthralgia, or swollen hands and other symptoms of connective tissue disease
- Orthopnea

Symptoms of Disease Progression

- Leg swelling
- Abdominal bloating and distension
- Anorexia
- Profound fatigue
- May develop as right ventricular dysfunction and tricuspid valve regurgitation evolve

Signs of Advanced Disease

- Diastolic murmur of pulmonary regurgitation
- A pansystolic murmur of tricuspid regurgitation
- Hepatojugular reflux
- Right ventricular S_3 gallop
- Marked distension of jugular veins
- Peripheral edema
- Hypotension
- Cool extremities suggesting markedly reduced cardiac output and peripheral vasoconstriction

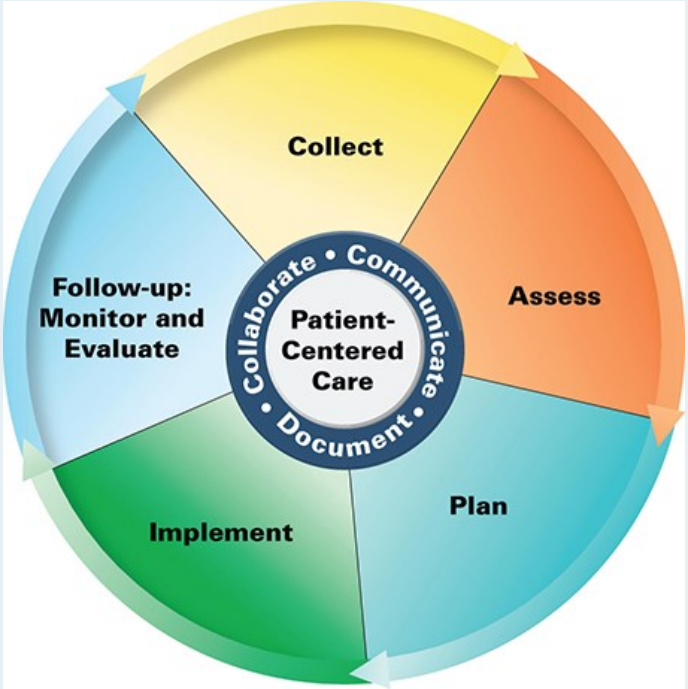
TREATMENT

Desired Outcomes

4 Specific goals in the treatment of PAH include lowering risk, improving quality of life and symptoms, and preventing disease progression and mortality.[13] Trials in the PAH population have undergone a change over the last decade. In the past, outcomes were predominantly focused on improvement in hemodynamic parameters and exercise tolerance.[31,32] However, more recent studies have focused on clinical outcomes, particularly combined clinical worsening. This outcome may differ among clinical trials but typically includes outcomes such as hospitalization, progression of symptoms, treatment escalation to prostacyclin therapy, transplantation, atrial septostomy, and death.[31]

PATIENT CARE PROCESS

Patient Care Process for Pulmonary Arterial Hypertension



Collect

- Patient characteristics (eg, age, race, gender, pregnancy status)
- Patient history: past medical (eg, connective tissue diseases), family (eg, family history of pulmonary arterial hypertension), social (eg, use of cocaine or amphetamines)
- Current medications (eg, particularly anorexigen use such as fenfluramine)
- Immunization history (eg, influenza, pneumococcal vaccination)
- Socioeconomic factors that may affect access to treatment
- Lifestyle assessment: smoking status, exercise, diet, alcohol intake, sexual activity
- Symptoms (eg, exertional dyspnea or chest pain, syncope, volume overload) and WHO functional class (Table 46-2)

- Objective data (Table 46-6)
  - Height, weight, BMI, blood pressure, and heart rate
  - Echocardiography and electrocardiogram
  - Right heart catheterization (with acute vasoreactivity testing if idiopathic, heritable, or anorexigen-associated PAH)
  - Labs (eg, AST/ALT, BNP)

Assess

- Rule out secondary causes (eg, left heart disease [Group 2], lung diseases and/or hypoxia [Group 3], CTEPH hypertension [Group 4], PH with unclear multifactorial mechanisms [Group 5])
- Assess groups with special considerations such as pregnant women
- Presence of comorbid conditions: atrial tachyarrhythmias, depression, anxiety, anemia
- Current medications that may affect PAH-targeted therapy (eg, drug-drug interactions)
- Recommended treatment options based on risk assessment (see Fig. 46-3 and Table 46-5)
- Appropriateness and effectiveness of current PAH therapy (eg, current risk status [Table 46-5], WHO functional class [Table 46-2], exercise capacity, change in pulmonary pressures, if any)

Plan*

- Therapeutic lifestyle changes (eg, diet and nutrition)
- Medication therapy regimen including specific PAH medication, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Table 46-7)
- Evaluate current therapy for drug-drug interactions at each visit (see Table 46-9)
- Monitoring parameters including efficacy (eg, risk status [Table 46-5], WHO functional class [Table 46-2], exercise capacity, change in pulmonary pressures), safety (medication-specific adverse effects [Table 46-8]), and time frame (3-month initial follow-up intervals, followed by 6-12 month intervals once at goal) (see Table 46-6)
- Patient education (eg, the purpose of treatment, dietary and lifestyle modification, medication therapy, immunizations, counseling on pregnancy and air travel)
- Self-monitoring of weight, exercise, diet, medication adherence/adverse effects
- Referral to PAH specialty center for coordination of care

Implement*

- Provide patient education regarding all elements of the treatment plan
- For parenteral prostacyclin analogs, coordinate with specialty company to ensure appropriate education on agents, including reconstitution, safety, back-up supplies
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up and time frame to achieve goals of therapy (eg, low-risk status [Table 46-5], improvement in WHO functional class [Table 46-2] and exercise capacity, symptom improvement, euvolemia [see Table 46-6])

- Educate patient on when to seek medical care (eg, worsening edema or dyspnea)

Follow-up: Monitor and Evaluate

- Determine response to PAH therapy and volume management
- Presence of medication-induced adverse effects (eg, elevated transaminases on ERAs, headache, flushing, edema, pump issues with parenteral prostacyclin analogs [see Table 46-8])
- Routine pregnancy screening for females (especially if receiving ERAs or riociguat)
- The occurrence of PAH worsening (eg, worsening symptoms or hospitalizations for PAH)
- Patient adherence to the treatment plan

**Collaborate with patient, caregivers, and other healthcare professionals.*

General Approach to Treatment

Treatment of PAH may be categorized into nonpharmacologic, pharmacologic, and surgical interventions. The principal pathophysiologic abnormalities that are current pharmacologic therapeutic targets include the following: (1) supplementing endogenous vasodilators, (2) inhibiting endogenous vasoconstrictors, and (3) reducing endothelial platelet interaction and limiting thrombosis. Nonpharmacologic therapy can be quite broad and should be used when clinically appropriate. Surgical therapy is indicated in certain situations and includes atrial septostomy, pulmonary thromboendarterectomy for CTEPH, and lung or heart-lung transplantation (for disease that is not responsive to medical therapy). Bilateral lung and lung-heart transplantation improves survival rates in patients with PAH.[4]

Selection of targeted pharmacologic therapy should consider many factors, such as disease severity, safety profile, cost, and patient preference.[3] In 2019, the Sixth World Symposium on Pulmonary Hypertension published an updated series on PAH recommendations.[3] These guidelines recommend combination therapy as initial management for many patients with PAH, particularly WHO functional class II and higher. For patients on monotherapy with an inadequate response, an additional agent should be added to current therapy. Many patients with PAH will require combination therapy with two or three medications. Specific combination therapies will be discussed later on in this chapter.

Not all patients with PAH should be started on combination therapy. Those who are considered low risk may have improvement in symptoms with monotherapy. Other patient groups who may be candidates for monotherapy initially include those with multiple comorbidities, those at higher risk of adverse events, and populations of patients who were not included in the randomized controlled trials of initial combination therapy, such as patients with HIV or portal hypertension.[33]

Nonpharmacologic Therapy

5 Nonpharmacologic therapy is frequently used to address comorbid conditions that often accompany PAH. Patients with PAH should be counseled on several important points. Pregnancy should be avoided due to high morbidity and mortality rates in females with PAH during pregnancy and in the postpartum course (COR I, LOE C).[3,4] Immunization against influenza and pneumococcal disease should be provided (COR I, LOE C).[3,4] Hypoxemia may aggravate pulmonary vasoconstriction in patients with PAH; therefore, patients with PAH may require supplemental oxygen (COR IIa, LOE C), particularly when using air travel.[4] Patients should adhere to a low-sodium diet to avoid fluid retention predisposing to right heart failure.[34] Counseling on smoking cessation should be provided to all patients who are active smokers. Cardiopulmonary rehabilitation improves functional status, exercise capacity, and quality of life in patients with PAH.[3]

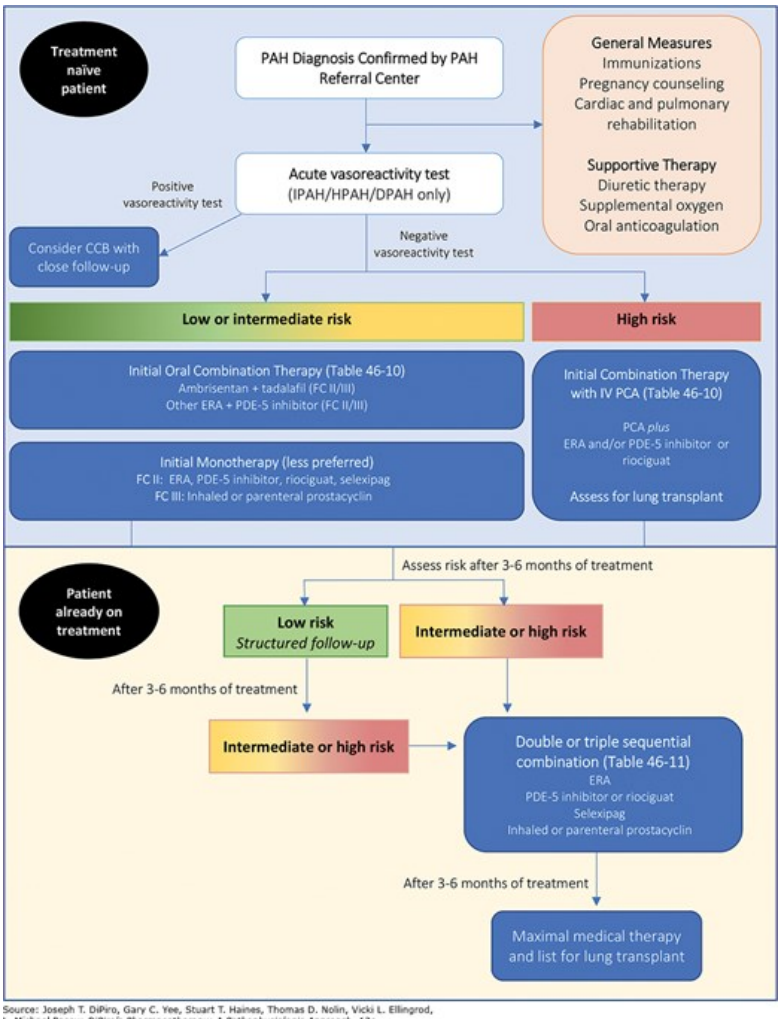
Pharmacologic Therapy

The number of potential therapies for PAH has expanded dramatically in the last decade. In addition to adjunctive background therapy, multiple

medications have been developed specifically for the treatment of PAH. Figure 46-3 illustrates the recommended treatment algorithm based on the most recent guidelines.[3,33]

FIGURE 46-3

Treatment algorithm. (CCB, calcium channel blocker; DPAH, drug-induced pulmonary arterial hypertension; ERA, endothelin receptor antagonist; FC, functional class; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; PCA, prostacyclin analog; PDE, phosphodiesterase.) *(Reprinted from Risk stratification and medical therapy of pulmonary arterial hypertension. Galiè N, Channick RN, Frantz RP et al. European Respiratory Journal Jan 2019, 53 (1) 1801889; DOI: 10.1183/13993003.01889-2018. Published 24 January 2019.)*



Conventional Pharmacologic Treatment

6 Conventional therapy includes oral anticoagulants, diuretics, oxygen, and digoxin.[33] Anticoagulation with warfarin may be considered on a case-by-case basis in patients with idiopathic, heritable, or drug-induced PAH (COR IIb, LOE C).[4] The rationale for oral anticoagulants is based on the presence of traditional risk factors for venous thromboembolism, such as heart failure and immobility, as well as thrombotic changes in the pulmonary microcirculation. Meta-analyses of small cohort studies demonstrate a 31% mortality risk reduction with anticoagulation.[35] However, recent observational studies report conflicting results regarding the benefit of anticoagulation in IPAH and associated PAH (APAH).[36,37] When warfarin is used, the target international normalized ratio (INR) in most centers is 1.5 to 2.5.[2,24] Anticoagulation is not recommended for patients with APAH due to HIV or portal hypertension.[33]

Loop diuretics such as furosemide are helpful adjunctive therapy in patients with decompensated right heart failure and associated findings of increased central venous pressure, abdominal organ congestion, peripheral edema, and ascites.[2] Appropriate diuretic therapy in right heart failure and volume overload provides symptomatic and clinical benefits in patients with PAH (COR I, LOE C).[4] Patients should be maintained at as close to a euvolemic state as possible.

Oxygen therapy with a goal oxygen saturation greater than 90% (0.90) may be beneficial in some patients with a PaO_2 <60 mm Hg (8.0 kPa), although no data exist regarding long-term benefit of oxygen treatment in PAH (COR I, LOE C).[4] Oxygen treatment is controversial in patients with PAH associated with shunts (ie, Eisenmenger's syndrome).

Digoxin may be used for patients with PAH with right heart failure as adjunctive therapy along with diuretics to control symptoms as well as in patients with atrial arrhythmias (COR I, LOE C).[4] There are no long-term trials, and clinical benefit is uncertain. Optimal plasma concentrations are unknown; however, based on data for digoxin use in heart failure with reduced ejection fraction, the typical target concentration is between 0.5 and 0.8 ng/mL (µg/L; 0.64 and 1 nmol/L). Patients on digoxin should receive periodic monitoring of potassium and renal function.

Lastly, iron-deficiency anemia is commonly reported in patients with PAH and may lead to decreased exercise capacity. Treatment of iron-deficiency anemia with iron replacement is recommended in patients with PAH (COR II, LOE b).[3,4] Anxiety and depression are frequent comorbidities in patients with PAH, occurring in up to 50%, with negative effects on perception of symptoms and quality of life. Appropriate counseling and treatment should be offered.[38]

Targeted Pharmacologic Therapy

The first medication, epoprostenol, developed to specifically target the disease process causing PAH was approved in 1995. Since then, there has been a surge in the availability of medication therapy for the treatment of PAH with five classes of medications now available. Specific pharmacologic therapy targets the disease process while conventional therapy is used for the management of symptoms and/or comorbid conditions. Specific information concerning individual medications used for PAH is shown in Tables 46-7–46-9.

TABLE 46-7

Dosing Recommendations for Common Treatments for Pulmonary Arterial Hypertension

Medication	Initial Dose	Usual Range	Other
Epoprostenol	2-4 ng/kg/min by IV infusion	Titrate up to 20-40 ng/kg/min	
Treprostinil (IV or SC)	1.25 ng/kg/min by continuous subcutaneous or IV infusion	Decrease to 0.625 ng/kg/min if not tolerated Increase by no more than 1.25 ng/kg/min weekly for the first 4 weeks of therapy and no more than 2.5 ng/kg/min weekly for the duration of therapy	
Treprostinil (inhaled)	Three inhalations (18 mcg) four times daily during waking hours (approximately 4 hours apart)	Reduce to one to two breaths if three breaths not tolerated; increase to three breaths when tolerance improves The goal maintenance dose is nine breaths (54 mcg) per treatment four times daily; titrate by increasing three breaths at 1- to 2-week intervals as tolerated	

Treprostinil (oral)	0.25 mg every 12 hours or 0.125 mg every 8 hours	Titrate dose in increments of 0.25-0.5 mg every 12 hours or 0.125 mg every 8 hours every 3-4 days The maximum dose is determined by tolerability Avoid abrupt discontinuation; if not tolerated, decrease dose stepwise in 0.25-0.5 mg increments	If unable to continue oral therapy temporarily while inpatient, consider initiation of IV or SC treprostinil; 1/5 of the total daily oral dose is an estimate of total daily parenteral dose
Iloprost	2.5 mcg inhaled six to nine times daily (dosing at ≥2-hour intervals while awake)	Titrate to 5 mcg per dose with a maximum daily dose of 45 mcg	
Bosentan	62.5 mg orally twice daily	Increase to 125 mg orally twice daily	Available through Tracleer Access Program
Ambrisentan	5 mg orally daily	Titrate to maximum dose of 10 mg daily	Available through Letairis Education and Access Program
Macitentan	10 mg orally daily	Maximum dose of 10 mg orally daily	Available through Opsumit Risk Evaluation and Mitigation Strategy Program
Sildenafil	20 mg orally three times daily, taken at least 4-6 hours apart	Maximum FDA-approved dose is 20 mg orally three times a day; higher doses frequently used clinically	
Tadalafil	40 mg orally once daily, with or without food	40 mg orally once daily	Not recommended to divide the dose
Riociguat	0.5-1 mg orally three times daily	Maximum dose is 2.5 mg orally three times daily Titrate by 0.5 mg every 2 weeks to maximum tolerated dose; dose limited by hypotension	Use is contraindicated with PDE-5 inhibitors due to the risk of hypotension Available through Adempas Risk Evaluation and Mitigation Program
Selexipag	200 mcg orally twice daily	Titrate to maximally tolerated dose in 200 mcg increments; maximum dose 1,600 mcg orally twice daily	

IV, intravenous; SC, subcutaneous; FDA, Food and Drug Administration; PDE-5, phosphodiesterase-5.

TABLE 46-8

Monitoring Recommendations for Adverse Drug Reactions

Medication	Adverse Drug Reaction	Monitoring Parameter	Comments
Synthetic Prostacyclin and Prostacyclin Analogs			
Epoprostenol, Treprostinil (IV/SC/oral)	Pain (chest and jaw), flushing, headache	Patient reported symptoms	Occurs with dose titration; titrate to balance efficacy and adverse effect
	GI (nausea, vomiting, diarrhea, anorexia)	Patient reported symptoms	
	Hypotension	Blood pressure	Occurs with dose titration; additive hypotensive effects with other antihypertensives, vasodilators, and diuretics
	Thrombocytopenia	Platelets; signs and symptoms of bleeding	Monitor with concurrent anticoagulant and antiplatelet agents
Treprostinil (SC-specific)	SC site pain	Local pain at SC administration site	Frequent site rotation may improve; may also use cool compresses, lidocaine-based creams or patches, or pluronic lecithin organogel (PLO) to relieve pain
Treprostinil (inhaled)	Cough and throat irritation	Patient reported symptoms	
Iloprost	Cough and throat irritation	Patient reported symptoms	
Prostacyclin IP Receptor Agonist			
Selexipag	Pain (chest and jaw), flushing, headache	Titrate to balance efficacy and adverse effect	Occurs with dose titration
	GI (nausea, diarrhea)	Patient reported symptoms	
	Anemia	Hemoglobin	Monitor at baseline and then periodically throughout treatment
	Hyperthyroidism	Thyroid stimulating hormone	May monitor if associated symptoms
Endothelin-Receptor Antagonists			
Bosentan, Ambrisentan, Macitentan	Anemia	Hemoglobin	Usually resolves after the first 3 months of therapy
	Edema	Edema on physical exam	May require a dose increase of diuretic therapy

Bosentan (specific)	Hepatotoxicity	Baseline and monthly liver function tests required	Black box warning for liver injury
Phosphodiesterase-5 Inhibitors			
Sildenafil, Tadalafil	Headache	Patient reported symptoms; occurs due to vasodilation	
	Nasal congestion	Patient reported symptoms	
	Hypotension	Blood pressure	Concurrent use with nitrates potentiates effects
	Visual changes	Consider baseline exam; repeat exam if visual changes occur	
Soluble Guanylate Cyclase Stimulator			
Riociguat	Headache	Patient reported symptoms	
	Hypotension	Blood pressure	
	Peripheral edema	Edema on physical exam	
	Major bleeding	Hemoglobin and hematocrit Signs and symptoms of bleeding	
	Gastroesophageal reflux disease (GERD)	Patient reported symptoms; heart burn/reflux symptoms	

IV, intravenous; SC, subcutaneous; GI, gastrointestinal.

TABLE 46-9

Potentially Significant Drug Interactions with Pulmonary Arterial Hypertension Medications

PAH Medication	Mechanism of Interaction	Interacting Medication	Interaction
Ambrisentan	Unknown	Cyclosporine Ketoconazole	Caution is required in the coadministration of ambrisentan with ketoconazole and cyclosporine.
Bosentan	CYP3A4 inducer	Sildenafil	Sildenafil levels fall 50%; bosentan levels increase 50%. May not require dose adjustments of either medication.
	CYP3A4 substrate	Cyclosporine	Cyclosporine levels fall 50%; bosentan levels increase fourfold. Combination contraindicated.
	CYP3A4 substrate	Erythromycin	Bosentan levels increase. May not require dose adjustment of bosentan during a short

			course.
	CYP3A4 substrate	Ketoconazole	Bosentan levels increase twofold.
	CYP3A4 substrate + bile salt pump inhibitor	Glibenclamide	Increase incidence of elevated aminotransferases. Potential decrease of hypoglycemic effect of glibenclamide. Combination contraindicated.
	CYP2C9 & CYP3A4 substrate	Fluconazole, amiodarone	Bosentan levels increase considerably. Combination contraindicated.
	CYP2C9 & CYP3A4 inducers	Rifampin, phenytoin	Bosentan levels decrease by 50%. Need for dose adjustment uncertain.
	CYP2C9 inducer	HMG CoA reductase inhibitors	Simvastatin levels reduce 50%; similar effects likely with atorvastatin. Cholesterol level should be monitored.
	CYP2C9 inducer	Warfarin	Increases warfarin metabolism, may need to adjust warfarin dose. Intensified monitoring of warfarin recommended following initiation but dose adjustment usually unnecessary.
	CYP2C9 & CYP3A4 inducers	Hormonal contraceptives	Hormone levels decrease. Contraception unreliable.
Macitentan			Not yet determined.
Selexipag			Not yet determined.
Sildenafil[47]	CYP3A4 substrate	Bosentan	Sildenafil levels fall 50%; bosentan levels increase 50%. May not require dose adjustments of either medication.
	CYP3A4 substrate	HMG CoA reductase inhibitors (statins)	May increase simvastatin/atorvastatin levels through competition for metabolism, Sildenafil levels may increase. Possible increased risk of rhabdomyolysis.
	CYP3A4 substrate	HIV protease inhibitors	Ritonavir and saquinavir increase sildenafil levels markedly.
	CYP3A4 inducer	Phenytoin	Sildenafil levels may fall.
	CYP3A4 substrate	Erythromycin	Sildenafil levels increase. May not require dose adjustment for a short course.
	CYP3A4 substrate	Ketoconazole	Sildenafil levels increase. May not require dose adjustment.
	CYP3A4 substrate	Cimetidine	Sildenafil levels increase. May not require dose adjustment.
	cGMP	Nitrates, Nicorandil Molsidomine	Profound systemic hypotension, combination contraindicated.
Tadalafil[48]	CYP3A4 substrate	Bosentan	Tadalafil exposure decreases by 42%, no significant changes in bosentan levels.[48] May not

			require dose adjustment.
	cGMP	Nitrates, Nicorandil	Profound systemic hypotension, combination contraindicated.
Riociguat[18]	cGMP	Sildenafil, other PDE-5 inhibitors	Hypotension, severe side effects, combination contraindicated.
	cGMP	Nitrates, Nicorandil	Profound systemic hypotension, combination contraindicated.

HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HIV, human immunodeficiency virus; GMP, guanosine monophosphate.

Data from Reference 4.

Synthetic Prostacyclin and Prostacyclin Analogs

7 PGI_2 is produced predominantly by endothelial cells, inducing potent vasodilation of all vascular beds. It is also a potent inhibitor of platelet aggregation and possesses cytoprotective and antiproliferative activities. PGI_2 synthase expression is reduced in pulmonary arteries. Epoprostenol is a synthetic analog of PGI_2 and has a short half-life of 3 to 5 minutes; consequently, it must be given by continuous intravenous (IV) infusion. Initiation of epoprostenol should be done in a hospital setting at low doses ranging from 2 to 4 ng/kg/min and increased at a rate limited by side effects (flushing, headache, diarrhea, jaw pain, backache, abdominal cramping, extremity pain, and hypotension). During initiation and initial titration of epoprostenol, patients may require inotropic and/or blood pressure support for hemodynamic stability.[39] The two available products, Flolan® (generic formulation available) and Veletri®, have unique stability and reconstitution parameters; both pharmacists and patients should be aware of the differences and follow the manufacturer recommendations. Due to the short half-life of epoprostenol, it is recommended that the patient have backup supplies of both the medication and infusion pump, as interruption of therapy may lead to life-threatening pulmonary vasoconstriction.[40] Because the medication must be administered by continuous infusion with a central venous catheter and pump, bacteremia and catheter obstruction are potential complications. One study found that bloodstream infections occurred with epoprostenol and treprostinil in the range of 0.3 to 2.1 per 1,000 medicine days (approximately one infection every 3 years) when these medications are given IV.[41] The target dose for the first 2 to 4 weeks is around 10 to 15 ng/kg/min, and periodic dose increases are then required to maximize efficacy. Maintenance doses are variable but are often in the range of 25 to 80 ng/kg/min.[4] Multiple observational studies have documented an improvement in survival in patients with IPAH treated with epoprostenol.[4,42,43] Based on current guidelines, epoprostenol is indicated for WHO functional class III and IV (COR I, LOE A).[3,4]

Treprostinil is a stable analog of PGI_2 administered by subcutaneous (SC) or IV infusion and approved for WHO functional class II, III, and IV.[44] The major advantages of treprostinil over epoprostenol include ease of use and increased safety due to a longer half-life. Because of the longer half-life, the risk of rebound vasoconstriction that may occur if therapy is interrupted is lower, resulting in an improved safety profile.[19] Treprostinil improves 6MWD and hemodynamics with outcomes that are similar to epoprostenol.[45,46] In clinical trials, the greatest exercise improvement was observed in patients who were more compromised at baseline and who could tolerate doses in the upper quartile (>13.8 ng/kg/min). The initial dose for treprostinil is 1.25 ng/kg/min by either the SC or IV route. If not tolerated, the dose should be reduced to 0.625 ng/kg/min and dose titration again attempted at 4 weeks. Infusion site pain is common with the SC route and can occur in up to 85% of patients, leading to discontinuation of treatment in 8% of patients and limiting upward dose titration.[4] Patients unable to tolerate SC can be transitioned to IV treprostinil.[24] Transitions between prostacyclin agents or routes should be performed in an inpatient setting at an expert referral center. Bloodstream infections, primarily due to gram-negative pathogens, are more likely with IV treprostinil than with IV epoprostenol.[47] The use of the diluent used for epoprostenol, which has a more basic pH, to reconstitute IV treprostinil may decrease rates of bloodstream infections to a rate similar to that seen with epoprostenol.[48] Other adverse drug reactions are similar to epoprostenol. Based on international guidelines, treprostinil is recommended for WHO functional class III (SC administration—COR I, LOE B; IV administration—COR IIa, LOE C) and functional class IV (SC and IV administration—COR IIb, LOE C).[3,4]

To prevent complications and use of pumps and central venous catheters for PGI_2 analog administration, aerosolized formulations were developed. The first approved formulation, iloprost (Ventavis), is a PGI_2 analog that is given by inhalation using a dosing system provided by the manufacturer (ADD system). The initial inhaled dose is 2.5 mcg six to nine times per day up to every 2 hours during waking hours. The dose should be titrated and maintained at 5 mcg/dose if tolerated. In a 3-month clinical trial, iloprost via inhalation provided at least a 10% improvement in 6MWD and improvement in functional class.[49] Inhaled iloprost can be cumbersome to use as each inhalation dose can take 4 to 10 minutes to administer, and multiple inhalations are required for a full dose. Patients should also be instructed to have a backup supply as iloprost has a short half-life, similar to epoprostenol.[24] Adverse effects are similar to other PGI_2 analogs, including cough, headache, flushing, and jaw pain. Inhaled iloprost is indicated for functional class III (COR I, LOE B) and functional class IV (COR IIb, LOE C), although many clinicians prefer using PAH medications given via the IV or SC route in patients with more severe disease.[3]

The second aerosolized formulation, inhaled treprostinil, was approved by the Food and Drug Administration (FDA) in July 2009 to improve exercise capacity in functional class III patients. In a clinical trial, patients receiving inhaled treprostinil experienced a 20 m improvement in 6MWD compared with those on placebo. All patients included in the trial were concurrently receiving bosentan or sildenafil for at least 3 months.[50] An open-label extension of the trial found that inhaled treprostinil provided sustained benefit and was safe and efficacious over a 2-year period.[51] The approved dosing of inhaled treprostinil is three breaths (18 mcg each) four times daily during waking hours. The dose may be titrated based on patient tolerance at 1- to 2-week intervals to a maximum dose of nine breaths four times daily. Inhaled treprostinil requires less time to administer, but the formulation is more complicated to prepare than inhaled iloprost.[24] While inhaled treprostinil avoids the infusion-related complications of the other PGI_2 analogs, use is cautioned in patients with acute pulmonary infections or underlying lung disease. The most common adverse effects seen in clinical trials include throat irritation, cough, headache, nausea, dizziness, and flushing. Inhaled treprostinil may also cause systemic hypotension, and patients should be monitored carefully if they are concurrently on diuretics, antihypertensives, or other vasodilators. Inhaled treprostinil is indicated for patients with WHO functional class III (COR I, LOE B) and IV (COR IIb, LOE C).[3,4]

Finally, the first oral prostacyclin analog, sustained-release treprostinil (Orenitram), was approved by the FDA in December 2013 for patients with WHO functional class II and III PAH. Oral treprostinil monotherapy for 12 weeks was associated with a significant increase of 23 m in 6MWD.[52] No differences were observed between treprostinil and placebo in time to clinical worsening or WHO functional class. Two randomized controlled trials followed evaluating the use of oral treprostinil in addition to ERAs and/or phosphodiesterase-5 inhibitors (PDE-5i). Neither study demonstrated a significant improvement in 6MWD with oral treprostinil therapy.[53,54] The average increase in 6MWD did correspond to treprostinil dose, with patients receiving higher doses demonstrating more improvement. Adverse events in studies included headache, nausea, diarrhea, and jaw pain; it is not well-tolerated overall, resulting in a high discontinuation rate of over 30%. Like other prostacyclin analogs, oral treprostinil inhibits platelet aggregation and may increase the risk of bleeding, especially in patients treated with anticoagulants. Oral treprostinil must be taken with food to improve absorption and cannot be crushed due to the osmotic release formulation. Oral treprostinil is indicated for patients with WHO functional class III (COR IIb, LOE B).[4]

Prostacyclin IP Receptor Agonist

Selexipag is a novel prostacyclin IP receptor agonist that was approved for use in patients with WHO functional class II and III PAH in 2015. Selexipag works by agonizing the prostacyclin IP receptor coupled with G_s protein, leading to increased cyclic adenosine monophosphate and relaxation of vascular smooth muscle. This leads to pulmonary vasodilation, as well as antiproliferative effects on smooth muscle cells and inhibition of platelet aggregation. The initial clinical trial evaluating the use of selexipag showed efficacy in decreasing pulmonary vascular resistance and improving cardiac index and 6MWD.[55] In a large clinical trial, patients with IPAH and APAH treated with selexipag experienced less disease progression, fewer hospitalizations for PAH, and reduced complications from PAH compared to placebo.[56] These outcomes were similar in patients on no background therapy and when added to background eERAs, PDE-5i, or both. This finding supports the use of triple oral combination therapy.[57] Similar benefits were seen with selexipag in a subgroup of patients with PAH associated with connective tissue diseases.[58] An additional substudy of this trial demonstrated that patients initiating therapy within 6 months of their PAH diagnosis demonstrated more pronounced reduction of morbidity and mortality with the addition of oral selexipag, further supporting oral combination therapy early in the disease.[59] Dose titration is similar to the prostacyclin analogs where the patient is initiated on a starting dose and titrated to the maximum tolerated dose. The initial starting dose is 200 mcg orally twice daily; this dose can be increased by 200 mcg twice daily increments to a maximum dose of 1,600 mcg twice daily. The median dose tolerated

was 1,000 mcg twice daily in the clinical trial.[56] Patients with treatment interruptions greater than 3 days require re-titration of selexipag. Adverse drug reactions are common, especially during dose titration, and similar to those caused by prostacyclin analogs, including flushing, headache, diarrhea, nausea, jaw pain, and myalgias. Selexipag may also cause anemia; periodic monitoring of the complete blood cell count is warranted. Selexipag has also been associated with an increased incidence of hyperthyroidism. Current guidelines do not provide a recommendation on the role of selexipag in therapy.

Endothelin-Receptor Antagonists

ET-1, a peptide produced primarily by the vascular endothelial cells, is characterized as a powerful vasoconstrictor and mitogen for smooth muscle. Activation of the ET-1 system has been shown in both plasma and lung tissue of patients with PAH. There are three FDA-approved oral ERAs available for the treatment of PAH—bosentan, ambrisentan, and macitentan. All ERAs are orally administered and teratogenic. Patients must be enrolled in a Risk Evaluation and Mitigation Strategy (REMS) program for all ERAs. All ERAs can cause liver toxicity, although the incidence is highly variable across the class. ERAs are metabolized through cytochrome p450 (CYP) enzyme system and are, therefore, targets for drug-drug interactions, requiring providers to evaluate for potential drug-drug interactions.[44]

Ambrisentan is a once-daily selective ET_A receptor antagonist that improves exercise capacity and hemodynamics and delays clinical worsening in PAH.[60,61] Two large trials demonstrated a significant improvement in functional capacity with ambrisentan (at doses of 2.5, 5, and 10 mg daily) compared to placebo.[44,61] However, a greater response was seen with higher doses. All doses were well tolerated, and no patients on therapy experienced an increase in LFTs more than three times the upper limit of normal. Unlike bosentan, liver toxicity occurs rarely with ambrisentan (0.8% in 12-week trials and 2.8% for up to 1 year).[4] Common side effects include peripheral edema, nasal congestion, flushing, anemia, and palpitations. Treatment should be initiated with 5 mg once daily and increased to 10 mg once daily, if required. Ambrisentan is recommended for WHO functional class II and III (COR I, LOE A/B) as well as functional class IV (COR IIb, LOE C).[4]

Macitentan (Opsumit) is a once-daily dual ERA. In a phase III clinical trial, patients with PAH (primarily functional class II and III), including those on stable therapy with oral or inhaled prostanoids, CCBs, or oral PDE-5i, were randomized to macitentan 3 mg daily, 10 mg daily, or placebo.[62] Both macitentan doses demonstrated statistically significant decreases in composite events related to PAH or death compared to placebo, primarily due to less frequent worsening of PAH (defined as a decrease in 6MWD, worsening symptoms, and need for additional treatment). Increased LFTs occurred with similar frequency in all groups, about 3.5%-4.5%. More patients in the macitentan groups experienced nasopharyngitis, headache, and anemia than with placebo. The FDA-approved dose is 10 mg by mouth daily. Macitentan is recommended for WHO functional class II and III (COR I, LOE B) as well as functional class IV (COR IIb, LOE C).[4]

Bosentan is an orally active dual ET_A and ET_B receptor antagonist that improves exercise capacity, functional class, hemodynamics, echocardiographic and Doppler variables, and time to clinical worsening.[63-65] In one of the larger studies with bosentan, patients were started on 62.5 mg twice daily for 4 weeks followed by 125 or 250 mg twice daily for a minimum of 12 weeks. Both doses improved 6MWD, WHO functional class, and increased time to clinical worsening compared to placebo. Increases in hepatic aminotransferases occurred in 9% of patients and were dose-dependent.[64] The mechanism of increased liver enzymes is thought to be competition by bosentan and its metabolites with the biliary excretion of bile salts, resulting in the retention of bile salts that can be cytotoxic to hepatocytes. Because of this toxicity, bosentan is only available through a distribution program.[24] Bosentan should be started at 62.5 mg twice daily for 4 weeks. After 4 weeks of therapy, the dose should be increased to 125 mg twice daily. If LFTs are confirmed to be in the range of three to five times the upper limit of normal, reduce the daily dose or interrupt treatment. If LFTs return to pretreatment levels, bosentan may be continued or reintroduced if indicated. LFTs should be monitored at baseline and monthly thereafter. A complete blood count should be monitored every 3 months as bosentan has been associated with anemia. Bosentan is indicated for WHO functional class II and III (I-A/B) as well as functional class IV (COR IIb, LOE C).[1,4]

Phosphodiesterase Inhibitors

There are two PDE-5i available for the treatment of PAH—sildenafil and tadalafil. PDE-5i increase the intracellular concentration of cyclic guanosine monophosphate, leading to vasorelaxation and antiproliferative effects on vascular smooth muscle cells. PDE-5i commonly cause headaches and flushing as well as systemic hypotension. Both are contraindicated in combination with nitrates and riociguat due to increased risk of hypotension.

Sildenafil and tadalafil both interact with bosentan, which is a potent CYP3A4 inducer.[66] Bosentan can decrease sildenafil and tadalafil concentrations by up to 50%, necessitating higher doses of PDE-5i when used in combination. PDE-5i are unique compared to other PAH therapies, as they are the only class that does not require enrollment in a REMS program nor acquisition through a specialty pharmacy.[62]

Sildenafil is a potent and highly specific PDE-5i that is approved for erectile dysfunction but also reduces mPAP and improves functional class. In one clinical trial, sildenafil added to conventional therapy significantly improved 6MWD and hemodynamic parameters at 12 weeks compared with placebo.[67] The FDA-approved dose is 20 mg orally three times per day; however, much higher doses are routinely used clinically. Common adverse drug reactions include headaches, flushing, epistaxis, dyspepsia, and diarrhea. Changes in vision have been reported, including blue-tinted vision and sudden loss of vision. In the event of sudden loss of vision, sildenafil should be stopped. Current guidelines recommend sildenafil for WHO functional class II and III patients with PAH (COR I, LOE A) in addition to functional class IV patients (COR IIb, LOE C).[4]

Another PDE-5i, tadalafil, was approved by the FDA in 2009 for the treatment of PAH. In a trial of patients with symptomatic PAH, more than 50% of whom were treated with bosentan at baseline, tadalafil 40 mg daily significantly improved exercise capacity, quality of life, and time to clinical worsening.[68] Treatment-naïve patients demonstrated not only greater improvement in exercise capacity than those on bosentan therapy but also greater improvement in all secondary outcomes. One possible explanation is decreased tadalafil levels as bosentan is a potent CYP3A4 inducer.[66] The most common adverse drug reactions were headache, myalgia, and flushing. Similar to sildenafil, tadalafil can also cause vision changes and dyspepsia. The recommended dose is 40 mg by mouth once a day.[68] Current guidelines recommend tadalafil for functional class II and III (COR I, LOE B) and functional class IV (COR IIb, LOE C).[4]

Guanylate Cyclase Stimulator

Riociguat is a soluble guanylate cyclase stimulator approved by the FDA in 2013. Riociguat works synergistically with nitric oxide and directly stimulates soluble guanylate cyclase. In a phase 3 study of patients with PAH, many of whom were on an ERA or non-IV prostacyclin analog at baseline, riociguat 2.5 mg by mouth three times daily improved 6MWD, hemodynamic parameters, and WHO functional class compared to placebo.[69] Syncope, the most frequent serious adverse event, occurred in 1% of riociguat patients compared to 4% in the placebo group. The recommended starting dose is 1 mg orally, three times daily (TID), titrated by 0.5 mg TID every 2 weeks to a maximum dose of 2.5 mg by mouth TID. An initial starting dose of 0.5 mg TID may be used in patients with baseline hypotension. The use of riociguat is contraindicated in patients treated with PDE-5i due to the additive risk of hypotension. Riociguat is teratogenic and female patients must go through a REMS program to receive the medication. Smoking status should also be evaluated prior to initiation of riociguat because smoking reduces riociguat concentrations by 50% to 60%, potentially requiring dose adjustment to achieve the same effect. Riociguat is recommended for WHO functional class II and III (COR I, LOE B), functional class IV (COR IIb, LOE C), and is also approved for patients with Group 4 CTEPH.[4]

Calcium Channel Blockers

Since such a small number of patients with PAH have a positive response to acute vasodilator testing, CCBs are infrequently used. Approximately 13% of patients with IPAH will demonstrate an acute vasodilator response and may be initiated on CCB therapy. However, the number responding to long-term therapy is low (7%).[25] For the small group of patients that are long-term responders (at least 1 year on CCB monotherapy), a new clinical classification was added to the guidelines in group 1 PAH (Table 46-1).[1] Many long-term responders will lose the response to CCBs; therefore, patient response should be monitored closely with follow-up hemodynamic assessment with vasoreactivity testing. CCBs should not be used in the absence of demonstrated acute vasoreactivity.[3] If used in patients without acute vasoreactivity, CCBs are associated with systemic hypotension leading to reflex tachycardia, sympathetic stimulation, and right ventricular ischemia, ultimately increasing patient morbidity.[4] When used, dihydropyridine CCBs are preferred as they lack the negative inotropic effects seen with verapamil. Diltiazem may be used in patients who also have tachycardia to slow heart rate through atrioventricular node blockade. If left ventricular systolic dysfunction is present, diltiazem and verapamil should not be used. Assessment of CCB therapy should occur soon after initiation, and if improvement in functional class to class I or II is not seen, additional or alternative PAH therapy must be initiated. In acute responders, CCBs may be used in WHO functional class I to IV (COR I, LOE C).[4] Compared to CCB doses used to treat other conditions (eg, hypertension), doses for PAH are relatively high—that is, up to 20 to 30 mg/day for amlodipine, 120 to 240 mg/day for nifedipine, and 240 to 720 mg/day for diltiazem. However, initial doses should be much lower and titrated upward to response.[4] The most common adverse drug reaction is peripheral edema.

Combination Therapy

Combination therapy is an attractive treatment option that targets multiple pathophysiologic mechanisms in PAH. This approach improves hemodynamics, symptoms, and exercise capacity. A significant portion of patients require combination therapy with either two- or three-drug regimens. Two meta-analyses found that combination therapy decreased time to clinical worsening by 35% to 40%.[32,70] Several trials have evaluated different combination therapies. The first-line recommended combination therapy in treatment-naïve patients is an ERA with a PDE-5i. In a clinical trial of patients with newly diagnosed PAH, initial combination therapy with ambrisentan and tadalafil was associated with a significant reduction in time to clinical failure and PAH hospitalizations compared to either therapy alone.[71] Peripheral edema, headache, nasal congestion, and anemia were more common in the combination group than either monotherapy group. However, there was no difference in medication discontinuation due to adverse events.[71] This initial combination is considered a class I recommendation (LOE B) for WHO functional class II and III patients and a class IIb recommendation (LOE C) for WHO functional class IV patients.[4]

While not specifically evaluated as initial combination therapy, the addition of macitentan to a PDE-5i or nonparenteral prostanoid therapy delayed clinical worsening in one trial.[72] Another study found a 40% decrease in clinical worsening when selexipag was added to background therapy; clinical improvements were similar regardless of the type of background therapy (ERA, PDE-5i, or a combination).[73] In a post hoc analysis, investigators found a more profound effect in patients who were started on selexipag within 6 months of diagnosis.[74] Sildenafil added to epoprostenol provided significant improvements in clinical outcomes and delay in clinical worsening.[75] Riociguat combined with ERAs showed benefit at 12 weeks.[69]

Current guidelines state the combination therapies with the strongest evidence and guideline support include the following: macitentan and sildenafil, riociguat and bosentan, and selexipag and ERA and/or PDE-5i.[33] A recent study compared an initial triple therapy (macitentan, tadalafil, and selexipag) to initial dual therapy (macitentan and tadalafil) in patients with PAH and found no difference in pulmonary vascular resistance but reduced the risk of disease progression with initial triple therapy.[76] Adverse drug reactions occurring more frequently in the triple therapy group included headache, diarrhea, nausea, pain in extremity, jaw pain, and vomiting.[76]

Tables 46-10 and 46-11 show current treatment recommendations for initial combination and sequential combination therapy, respectively.

TABLE 46-10

Recommendations for Efficacy of Initial Medication Combination Therapy for Pulmonary Arterial Hypertension (Group 1) According to World Health Organization Functional Class

Treatment	WHO-FC II		WHO-FC III		WHO-FC IV	
	COR	LOE	COR	LOE	COR	LOE
Ambrisentan + tadalafil[a]	I	B	I	B	IIb	C
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C
Bosentan + sildenafil + iv epoprostenol	-	-	IIa	C	IIa	C
Bosentan + iv epoprostenol	-	-	IIa	C	IIa	C
Other ERA or PDE-5i + sc treprostinil			IIb	C	IIb	C
Other ERA or PDE-5i + other iv prostacyclin analogs			IIb	C	IIb	C

ERA, endothelin-receptor antagonist; iv, intravenous; PDE-5i, phosphodiesterase type 5 inhibitor; RCT, randomized controlled trial; sc, subcutaneous; WHO-FC, World Health Organization functional class; COR, class of recommendation; LOE, level of evidence.

[a]Time to clinical failure as primary endpoint in RCTs or medications with demonstrated reduction in all-cause mortality (prospectively defined).

TABLE 46-11

Recommendations for Efficacy of Sequential Medication Combination Therapy for Pulmonary Arterial Hypertension (Group 1) According to World Health Organization Functional Class

Treatment	WHO-FC II		WHO-FC III		WHO-FC IV	
	COR	LOE	COR	LOE	COR	LOE
Macitentan added to sildenafil[a]	I	B	I	B	IIa	C
Riociguat added to bosentan	I	B	I	B	IIa	C
Selexipag added to ERA[b] and/or PDE-5i[a]	I	B	I	B	IIa	C
Sildenafil added to epoprostenol	-	-	I	B	IIa	B
Treprostinil inhaled added to sildenafil or bosentan	IIa	B	IIa	B	IIa	C
Iloprost inhaled added to bosentan	IIb	B	IIb	B	IIb	C
Tadalafil added to bosentan	IIa	C	IIa	C	IIa	C
Ambrisentan added to sildenafil	IIb	C	IIb	C	IIb	C
Bosentan added to epoprostenol	-	-	IIb	C	IIb	C
Bosentan added to sildenafil	IIb	C	IIb	C	IIb	C
Sildenafil added to bosentan	IIb	C	IIb	C	IIb	C
Other double combinations	IIb	C	IIb	C	IIb	C
Other triple combinations	IIb	C	IIb	C	IIb	C
Riociguat added to sildenafil or other PDE-5i	III	B	III	B	III	B

EMA, European Medicines Agendy; ERA, endothelin-receptor antagonist; PAH, pulmonary arterial hypertension; PDE-5i, phosphodiesterase type 5 inhibitor; RCT, randomized controlled trial; WHO-FC, World Health Organization functional class; COR, class of recommendation; LOE, level of evidence.

[a]Time to clinical failure as primary endpoint in RCTs or medications with demonstrated reduction in all-cause mortality (prospectively defined).

[b]This medication was not approved by the EMA at the time of publication of these guidelines.

Fusion Protein

An emerging treatment option in development is sotatercept. Sotatercept is a fusion protein composed of the extracellular domain of the human activin receptor type IIA linked to the Fc domain of human IgG1.[77] Sotatercept impairs activation in the transforming growth factor ß (TGF-ß) pathway, thereby restoring the balance between proproliferative and antiproliferative pathways. Mutations in the TGF-ß pathway, specifically BMPR2, are present in 70% to 80% of heritable PAH and in 10% to 20% of IPAH.[14] In a phase 2 trial, sotatercept dosed at 0.3 mg/kg or 0.7 mg/kg SC every 3 weeks

reduced pulmonary vascular resistance at 24 weeks in patients with PAH on background therapy, the majority of whom were on double or triple therapy while many others were on intravenous prostacyclin therapy.[77] Thrombocytopenia occurred in 6% of the lower dose group and 12% in the higher dose. An increase in hemoglobin was also seen in 3% of patients on the lower dose and 17% of patients on higher dose, perhaps because the TGF-ß pathway is involved in hematopoiesis. In 2020, the FDA granted Breakthrough Therapy status for sotatercept for the treatment of PAH, and phase 3 trials are ongoing.

Special Populations

Pregnancy

Pregnancy confers an increased risk of mortality in patients with PAH. Guidelines recommend encouraging patients with PAH to actively avoid pregnancy.[4] There is no consensus on the best birth control method for patients with PAH, but the use of two methods should be considered. Estrogen-containing products should be avoided. Patients who do become pregnant need to be referred as soon as possible to a PH center where there are expert high-risk obstetricians and PAH specialists who have experience in this area.[4] All ERAs (bosentan, ambrisentan, and macitentan) are teratogenic, as is riociguat. These medications should be discontinued immediately if a patient becomes pregnant and therapy needs to be adjusted. Monthly pregnancy tests are required for use of ERAs and riociguat. It is also important to note that bosentan may decrease the efficacy of oral birth control medications (Table 46-9).

Evaluation of Therapeutic Outcomes

All patients with PAH, regardless of risk status, should be reevaluated within 3 to 6 months of starting therapy.[33] Current guidelines recommend the use of a comprehensive risk assessment tool to assess prognosis and inform therapy (Table 46-5). Additionally, recent studies have reported successful use of refined risk assessment tools that use the most predictive variables and simplify assessment for clinicians.[29,30] If a patient has achieved a low-risk status, therapy should be continued. If a patient is considered intermediate risk, additional therapy should be considered. This may result in initial combination therapy escalating to triple therapy in some patients. Patients who are high risk on follow-up should be initiated on IV prostacyclin therapy and referred for lung transplant evaluation. Table 46-6 provides recommendations regarding specific baseline and follow-up assessments and when they should be performed.

CONCLUSION

PAH is an uncommon disease state with complex therapies. Significant advances have been made in elucidating the pathogenesis of PAH as well as in the evaluation and treatment of these patients over the past three decades. With targeted therapies such as ERAs, PDE-5i, and PGI_2 analogs, clinical improvement is possible in most patients, leading to a higher quality of life and delayed disease progression. Patient education is important to improve acceptance of this disease and referral to specialty care centers may provide the best outcomes.

ABBREVIATIONS

6MWD	6-minute walking distance
5-HT	serotonin
5-HTT	5-hydroxytryptamine transporter
ALK-1	activin receptor-like kinase 1
APAH	associated pulmonary arterial hypertension
BMPR-2	bone morphogenetic protein receptor 2

BNP	brain natriuretic peptide
CCB	calcium channel blocker
COR	class of recommendation
CTEPH	chronic thromboembolic pulmonary hypertension
CYP	cytochrome p450
ERA	endothelin-receptor antagonist
ET-1	endothelin-1
FDA	Food and Drug Administration
HIV	human immunodeficiency virus
HPAH	heritable pulmonary arterial hypertension
INR	international normalized ratio
IPAH	idiopathic pulmonary arterial hypertension
IV	intravenous
LOE	level of evidence
LFT	liver function test
NO	nitric oxide
NOS	nitric oxide synthase
PAH	pulmonary arterial hypertension
PAP	pulmonary artery pressure
PCWP	pulmonary capillary wedge pressure
PDE-5i	phosphodiesterase-5 inhibitors
PGI2	prostacyclin
REMS	Risk Evaluation and Mitigation Strategy
SC	subcutaneous
SSRIs	selective serotonin reuptake inhibitors
TGF-β	transforming growth factor-β

WHO	World Health Organization

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SELF-ASSESSMENT QUESTIONS

1. Pulmonary hypertension can be defined as a mean pulmonary artery pressure of ≥____ mm Hg at rest with a pulmonary capillary wedge pressure equal to or less than 15 mm Hg measured by right heart catheterization.

   A. 10

   B. 15

   C. 20

   D. 25

2. Which of the following symptoms is *not* suggestive of pulmonary arterial hypertension?

   A. Exertional chest pain

   B. Syncope

   C. Lower extremity edema

   D. Wheezing

3. Which of the following pathophysiologic abnormalities is a target of current pharmacologic treatments for PAH?

   A. Supplementing endogenous vasodilators

   B. Increasing endothelial platelet interaction and limiting thrombosis

   C. Reducing levels of serotonin

   D. Supplementing endogenous vasoconstrictors

4. Patients who are unresponsive to acute vasoreactivity testing are *not* candidates for which class of medication therapy?

   A. Calcium channel blockers

   B. Endothelin antagonists

   C. Phosphodiesterase inhibitors

   D. Prostacyclin analogs

5. A 34-year-old female presents to your clinic with increasing dyspnea with mild exertion for 2 years, chest tightness, occasional ankle edema, and a recent episode of near syncope. The patient denies paroxysmal nocturnal dyspnea, orthopnea, wheezing, or palpitations but does report a 15-lb (6.8 kg) weight gain over the last year. Past medical history includes having two children without pregnancy complications. The patient has no known medication allergies and is not currently taking any medications. Family history is significant for type 2 diabetes mellitus. Physical examination: The patient is 5 ft 5 in. (165 cm) and 180 lb (81.6 kg) with a body mass index of 30 kg/m^2. Heart rate is 86 beats/minute with a blood pressure of 128/74 mm Hg.

   Significant findings: Jugular venous pressure is 12 cm. Normal S_1 and S_2, 3/6 tricuspid murmur; 1+ lower extremity edema.

   Imaging: Chest x-ray and electrocardiogram are ordered.

   On the basis of the clinical presentation, what diagnostic test would be the most appropriate to order now?

   A. Pulmonary angiography

   B. Echocardiography

   C. Doppler ultrasound of lower extremity

   D. Coronary angiography

6. Which of the following medications is associated with significant elevations in aminotransferases, requiring baseline and monthly monitoring?

   A. Epoprostenol

   B. Amlodipine

C. Sildenafil

D. Bosentan

7. A patient presenting with no discomfort at rest but increased dyspnea, fatigue, and chest pain on mild physical exertion is classified in which World Health Organization functional class?

A. Class I

B. Class II

C. Class III

D. Class IV

Use the following case to answer questions 8 and 9:

A 28-year-old female presents to your clinic with increasing dyspnea with mild exertion for 1 year, chest tightness, and occasional ankle edema, consistent with World Health Organization Class II pulmonary arterial hypertension. The patient denies paroxysmal nocturnal dyspnea, orthopnea, wheezing, or palpitations but does report an 8-lb (3.6 kg) weight gain over the last year. The patient has no known drug allergies and is not currently taking any medications. The patient has previously been found unresponsive to acute vasoreactivity testing and is currently low-risk status.

8. What is the *most* appropriate initial treatment for this patient?

A. Sildenafil 100 mg orally daily

B. Epoprostenol 2 ng/kg/min continuous infusion

C. Ambrisentan 5 mg orally daily and tadalafil 40 mg orally daily

D. Amlodipine 5 mg orally daily

9. Which of the following drugs should this patient avoid?

A. Ibuprofen

B. Digoxin

C. Furosemide

D. Acetaminophen

10. Which of the following agents is *not* used for acute vasoreactivity testing in pulmonary arterial hypertension?

A. Epoprostenol

B. Nitroglycerin

C. Adenosine

D. Nitric oxide

11. Which of the following best describes the mechanism of action of epoprostenol?

A. A competitive antagonist of endothelin receptors, causing vasodilation of the pulmonary vasculature

B. Phosphodiesterase inhibition, causing an increase in cyclic guanosine monophosphate leading to vasorelaxation

C. Inhibition of influx of extracellular calcium, leading to vasodilation

D. Direct vasodilation of pulmonary vascular beds as well as inhibition of platelet aggregation

12. Infection, catheter obstruction, and sepsis are potentially serious complications of which of the following medications?

A. Bosentan

B. Sildenafil

C. Treprostinil

D. Diltiazem

13. TP is a 68-year-old female with PAH. The patient describes worsening symptoms lately. The patient used to be able to walk the dog around the block but is no longer able to do so without feeling exhausted. The patient feels shortness of breath and fatigue even when resting in a recliner. Upon assessment, the patient is categorized as high risk and is currently treated with sildenafil 40 mg orally three times daily. Which agent is most appropriate to add now?

A. Epoprostenol

B. Ambrisentan

C. Riociguat

D. Selexipag

14. Women of child-bearing age with pulmonary arterial hypertension should be counseled on the risks of pregnancy. Which of the following medications is teratogenic in pregnancy?

A. Macitentan

B. Amlodipine

C. Epoprostenol

D. Selexipag

15. Epoprostenol is indicated for patients with PAH in which of the following WHO functional classifications?

A. WHO functional class I and II

B. WHO functional class II and III

C. WHO functional class II, III, and IV

D. WHO functional class III and IV

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** Current guidelines defined pulmonary arterial hypertension as mean pulmonary artery pressure of ≥20 mm Hg at rest with a pulmonary capillary wedge pressure equal to or less than 15 mm Hg measured by right heart catheterization. See the "Introduction" section for more information.

2. **D.** Exertional dyspnea, chest pain, and lower extremity edema are all common symptoms of pulmonary arterial hypertension. Wheezing is not a characteristic symptom and is more common with obstructive lung diseases, such as asthma or chronic obstructive pulmonary disease. See the "Clinical Presentation" box for more information.

3. **C.** Reducing levels of serotonin is not a current target of pharmacologic treatment for PAH. Multiple medication classes either target supplementing endogenous vasodilators or inhibiting endogenous vasoconstrictors. Prostacyclin analogs and selexipag are examples of medication classes that supplement endogenous vasodilators and reduce endothelial platelet aggregation, while endothelin-receptor antagonists are an example of agents that inhibit endogenous vasoconstrictors. See the "Pharmacologic Therapy" section for more information.

4. **A.** Patients who have a negative acute vasoreactivity test should not receive therapy with a calcium channel blocker. The use of calcium channel blockers in patients with a negative acute vasoreactivity test on right heart catheterization may lead to increased patient morbidity. See "Calcium Channel Blockers" section for more information.

5. **B.** Echocardiography is the most commonly used assessment for initial screening of patients who may have pulmonary arterial hypertension. Echocardiography is useful because it is less invasive than right heart catheterization (which will still be required for definitive diagnosis) and may also rule out other causes.

6. **D.** Bosentan is the most likely medication to cause elevations in transaminases. Bosentan has a US-boxed warning requiring practitioners to monitor liver function tests at baseline and monthly thereafter in all patients on therapy. Elevated transaminases and hepatotoxicity are not as likely with the other endothelin-receptor antagonists (ambrisentan and macitentan) so they do not carry the same warning. See Table 46-8 for more information.

7. **B.** This patient shows symptoms on mild exertion but no discomfort at rest, which is characteristic of WHO functional class II. See Table 46-2 for more information.

8. **C.** The most appropriate therapy to initiate this patient is on oral combination therapy with ambrisentan 5 mg po daily and tadalafil 40 mg orally daily. Amlodipine is not appropriate because the patient had negative acute vasoreactivity test. While sildenafil is an appropriate agent, the dose is too high and not at the appropriate frequency; the normal starting dose of sildenafil is 20 mg PO TID. In addition, initial oral combination therapy is now recommended in low and intermediate risk patients. Lastly, epoprostenol and other prostacyclin analogs are reserved for high-risk patients. See Table 46-7 and FIGURE 46-3 for more information.

9. **A.** Ibuprofen and other NSAIDs should be avoided in patients with PAH due to worsening edema and heart failure.

10. **B.** Nitroglycerin is not used for acute vasoreactivity testing in pulmonary arterial hypertension. See Table 46-4 for more detailed information on the other three agents that are indicated for acute vasoreactivity testing.

11. **D.** Epoprostenol is a prostacyclin agent that causes direct vasodilation to pulmonary vascular beds. See "Synthetic Prostacyclin and Prostacyclin Analogs" section for more information. Endothelin-receptor antagonists such as bosentan, ambrisentan, and macitentan are competitive antagonists of endothelin receptors. Sildenafil and tadalafil inhibit phosphodiesterase-5, while calcium channel blockers inhibit the influx of extracellular calcium.

12. **C.** Infection, catheter obstruction, and sepsis are potentially serious complications of the parenteral prostacyclin agents, including treprostinil and epoprostenol. See "Synthetic Prostacyclin and Prostacyclin Analogs" section for more information.

13. **A.** The patient is currently high risk and on sildenafil treatment. The most appropriate therapy to add is a parenteral prostacyclin analog like epoprostenol. Sildenafil and riociguat are contraindicated in combination due to additive risk of hypotension. See FIGURE 46-3 and Table 46-11 for more information on double and sequential treatment in patients already on therapy.

14. **A.** The endothelin-receptor antagonists, such as macitentan, and the soluble guanylate cyclase stimulator, such as riociguat, are teratogenic and contraindicated in pregnancy.

15. **D.** Epoprostenol is reserved for high-risk patients with more severe functional classes, including WHO functional class III and IV. See "Synthetic Prostacyclin and Prostacyclin Analogs" section and FIGURE 46-3 for more information.