CHAPTER 30 Pulmonary Hypertension

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KEY CONCEPTS

1. Pulmonary arterial hypertension (PAH) may be defined as a mean pulmonary artery pressure (PAPm) ≥25 mm Hg at rest with a pulmonary wedge pressure (also known as pulmonary artery occlusion pressure) ≤15 mm Hg measured by cardiac catheterization.
2. Idiopathic PAH (IPAH) is one of the most common forms of PAH. Fortunately, it is generally more responsive to therapy than secondary forms of PAH.
3. PAH is uncommon but increasing in prevalence.
4. The underlying cause of PAH is a complicated amalgam of endothelial cell dysfunction, a procoagulant state, platelet activation, constricting factors, loss of relaxing factors, cellular proliferation, hypertrophy, fibrosis and inflammation
5. PAH presents with exertional dyspnea, fatigue, weakness, complaints of general exertion intolerance, dyspnea at rest as the disease progresses, anginal chest pain, syncope.
6. Right-heart catheterization provides important prognostic information and can be used to assess pulmonary vasoreactivity prior to initiating therapy.
7. The goals of treatment are alleviation of symptoms, improvement in the quality of life, prevention of disease progression, and improvement in survival.
8. The general principle of PAH treatment is to attempt to correct the imbalance between vasoconstriction and vasodilation and prevent adverse thrombotic events to improve oxygenation and quality of life.
9. Nonpharmacologic therapy is frequently used to address comorbid conditions that often accompany PAH.
10. General care interventions in PAH include oral anticoagulants, diuretics, oxygen, and digoxin.
11. A small number of patients with IPAH who demonstrate a favorable response to acute vasodilator testing will do well with calcium channel blockers.
12. Sildenafil is a potent and highly specific phosphodiesterase-5 inhibitor that has been shown to reduce PAPm and improve functional class.
13. Prostacyclin analogs such as epoprostenol, treprostinil and iloprost induce potent vasodilation of all vascular beds.
14. Endothelin antagonists, bosentan and ambrisentan, improve exercise capacity, hemodynamics, and functional class in PAH.
15. Combination therapy in PAH may address more than one mechanism causing this disease. Combination therapy in uncontrolled trials has provided additional benefit (but at the risk of increased side effects).

1 Pulmonary arterial hypertension (PAH) may be defined as a mean pulmonary artery pressure (PAPm) ≥25 mm Hg at rest with a pulmonary wedge pressure (also known as pulmonary artery occlusion pressure) ≤15 mm Hg measured by cardiac catheterization.[1] PAH is a disorder that may occur either in the setting of a variety of underlying medical conditions or as a disease that uniquely affects the pulmonary circulation. Historically, medical treatment of PAH has been difficult. Idiopathic PAH (IPAH) was formerly known as primary pulmonary hypertension and carried a poor prognosis (medial survival 2.8 years) through the mid-1980s.[2] Prior to the availability of disease-specific or targeted drug therapy for IPAH, survival rates for 1, 3, and 5 years were 68%, 48%, and 34%, respectively.[3] Others have found similar survival rates in registry studies.[4,5] Since then a number of new therapeutic options have been developed which address this difficult to treat disease. 2 PAH may be classified into several types depending on etiology and diseases. Several sets of guidelines exist to aid clinicians in diagnosis and management of PAH.[1,2,6–9]

EPIDEMIOLOGY

3 The prevalence of PAH is estimated to be 50,000 to 100,000 individuals in the United States.[6] Unfortunately, only 15,000 to 20,000 of the afflicted patients have an established diagnosis of PAH and are currently receiving treatment. In a French registry study of more than 600 patients with PAH, Humbert et al. 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%).[5] Based on autopsy findings, PAH was found to occur in 0.13% of all patients autopsied and was more commonly found if patients had cirrhosis (0.73%).[7] (Through extrapolation of these autopsy findings to the entire U.S. population, there may be well over 1 million individuals with PAH in this country.)

TABLE 30-1 World Health Organization Classification of Pulmonary Hypertension

1.0 Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic (IPAH)
- 1.2 Familial (FPAH)
- 1.3 Associated with (APAH):
  - 1.3.1 Collagen vascular disease
  - 1.3.2 Congenital systemic-to-pulmonary shunts
  - 1.3.3 Portal hypertension
  - 1.3.4 Human immunodeficiency virus (HIV) infection
  - 1.3.5 Drugs and toxins
  - 1.3.6 Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
- 1.4 Associated with significant venous or capillary involvement
  - 1.4.1 Pulmonary venoocclusive disease (PVOD)
  - 1.4.2 Pulmonary capillary hemangiomatosis (PCH)
- 1.5 Persistent pulmonary hypertension of the newborn

2.0 Pulmonary hypertension with left heart disease
- 2.1 Left-sided atrial or ventricular heart disease
- 2.2 Left-sided valvular heart disease

3.0 Pulmonary hypertension associated with lung diseases and/or hypoxemia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Sleep-disordered breathing
- 3.4 Alveolar hypoventilation disorders
- 3.5 Chronic exposure to high altitude
- 3.6 Developmental abnormalities

4.0 Pulmonary hypertension as a result of chronic thrombotic and/or embolic disease
- 4.1 Thromboembolic obstruction of proximal pulmonary arteries
- 4.2 Thromboembolic obstruction of distal pulmonary arteries
- 4.3 Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)

5.0 Miscellaneous

Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Data from references 10 and 26.

ETIOLOGY

PAH originates with the interaction of a predisposing state and one or more inciting stimuli that has been referred to as the "multiple hit hypothesis." Two or more hits may consist of a genetic disorder combined with one or more other genetic or environmental exposure or comorbidity.[8] Once a permissive and provocative environment exists, multiple mechanisms can be activated leading to vascular constriction, cellular proliferation, and a prothrombotic state resulting in PAH and its sequelae.[9] PAH can be associated with numerous conditions (Table 30–1) as well as being an idiopathic condition (IPAH). The World Health Organization classification of PAH defines five groups: IPAH, PAH with left-heart disease, PAH associated with lung diseases and/or hypoxemia, PAH resulting from chronic thrombotic and/or embolic diseases, and miscellaneous PAH.[6,10] The incidence of IPAH is estimated to be 1 to 5 per 1 million in North America and Europe, with a marked female predominance (male-to-female ratio: 1:1.7) and a mean age at the time of recognition being approximately 36 years but with much variation.[9,11,12] Although uncommon in the United States, the commonest forms of PAH worldwide are probably schistosomiasis and sickle cell disease followed by congenital heart disease and pulmonary hypertension of early childhood. PAH is a common complication of sickle cell disease and is a major independent risk factor for death. Likely causative insults include hemolysis, chronic hypoxemia, thromboembolism, parenchymal and vascular injury as a result of sequestration of sickled erythrocytes, chronic liver disease, and asplenia.[13] Schistosomiasis affects millions of people throughout the world and in approximately 5% of infections, schistosomal eggs obstruct the lung vasculature, leading to PAH and cor pulmonale.[14] Drugs and toxins that definitively precipitate PAH include anorexic drugs such as aminorex, fenfluramine, and dexfenfluramine.[15] Other drugs considered to be very likely or possible causative agents for PAH include amphetamines, L-tryptophan, cocaine, and certain chemotherapeutic agents (mitomycin C, carmustine, etoposide, cyclophosphamide, bleomycin). Rapeseed oil is also associated with PAH. Mutations in the bone morphogenetic protein receptor II (BMPR2) gene have been identified in approximately 50% of patients with familial PAH and in 25% of patients with IPAH.[16] Genetic testing and professional genetic counseling should be offered to relatives of patients with FPAH, and patients with IPAH should be advised about the availability of genetic testing and counseling for their relatives (based on expert opinion and grade of recommendation E/A).[16] Table 30–2 lists the grading criteria for recommendations. Genetic counseling for family members at risk for FPAH is complicated because of decreased penetrance, variable age of onset, and inherent limitations of linkage studies.[16]

PATHOPHYSIOLOGY

4 The pathobiology of PAH involves several key biologic events, including endothelial cell dysfunction, a procoagulant state, platelet activation, constricting factors, loss of relaxing factors, cellular proliferation, hypertrophy, fibrosis, and inflammation—all combining to produce progressive and deleterious pulmonary vascular remodeling (Fig. 30–1).[17] Genetic substrates that are associated with PAH include BMPR2, activin-like kinase type-1, nitric oxide synthase (ec-NOS), carbamyl-phosphate synthase gene, and 5-hydroxytryptamine (serotonin) transporter (5-HTT).[9,15] (A mutation of BMPR2 receptor is an aberration of signal transduction in the pulmonary vascular smooth muscle cell that is postulated to alter apoptosis favoring cellular proliferation. Activin-like kinase type-1 receptors on endothelial cells is a transforming growth factor-β and is seen in hereditary hemorrhagic telangiectasia and PAH.[18]) 5-HTT is associated with pulmonary artery smooth muscle cell proliferation and is present in IPAH in the homozygous form in 65% of patients.[19] Dysregulation of serotonin (5-HT) synthesis mediated via tryptophan hydroxylases (Tph1 and Tph2) is closely linked to the hypoxic PAH phenotype in mice, and both Tph1 and Tph2 may contribute to PAH development.[20] Because of the recognized genetic component of PAH, family members should be screened for symptoms or for an established diagnosis

TABLE 30-2 Quality of the Evidence for the American College of Chest Physicians Guidelines for Pulmonary Artery Hypertension

	Net Benefit					
Quality of Evidence	***Substantial***	***Intermediate***	***Small/Weak***	***None***	***Conflicting***	***Negative***
Good	A	A	B	D	I	D
Fair	A	B	C	D	I	D
Low	B	C	C	I	I	D
Expert opinion	E/A	E/B	E/C	I	I	E/D

A, strong recommendation; B, moderate recommendation; C, weak recommendation; D, negative recommendation; I, inconclusive (no recommendation possible); E/A, strong recommendation based on expert opinion only; E/B, moderate recommendation based on expert opinion only; E/C, weak recommendation based on expert opinion only; E/D, negative recommendation based on expert opinion only.
McCrory DC, Lewis SZ. Methodology and grading for pulmonary hypertension evidence review and guideline development. Chest 2004;126(Suppl):11S–13S.

of PAH. Known or suspected exposure to human immunodeficiency virus (HIV) infection should be explored.[16]

Molecular and cellular mechanisms are mediated by a variety of biologically active compounds including prostacyclin (PGI_2), endothelin-1, nitric oxide, and serotonin. PGI_2 is a vasodilatory and anitproliferative substance that is produced by the endothelial cells and the synthesis of PGI_2 and its circulating levels are reduced in PAH. Furthermore, thromboxane, a vasoconstrictor, is increased in PAH. Endothelin-1 is produced in the endothelium and it possesses potent vasoconstrictor and mitogenic effects. Endothelin-1 levels are increased in PAH and clearance is reduced. Endothelin-1 acts via the endothelin receptors (ET_A and ET_B) to promote vascular smooth muscle proliferation and vasoconstriction. Plasma levels of endothelin-1 correlate with severity of PAH and prognosis.[21] Nitric oxide (NO) is produced in the endothelium via NO synthase and leads to vasodilation and opening of cell membrane potassium channels to allow potassium ion efflux, membrane depolarization and calcium channel inhibition. Voltage-dependent potassium channels (Kv 1.5) are inhibited by a number of stimuli that promote PAH, including hypoxia and fenfluramine, resulting in downregulated Kv 1.5 channels in patients with PAH. Entering calcium is a signal for release of sarcoplasmic calcium and activation of the contractile apparatus. NO promotes vasodilation through calcium channel inhibition. In PAH there is evidence of decreased NO synthase expression, thus promoting vasoconstriction and cell proliferation.[22] Alteration in NO is a potential therapeutic target and possible approaches include inhibition of phosphodiesterase-5 or calcium channel blockade. Elevated 5-HT has been observed and vasoconstriction mediated via the increased expression of the 5-HT_{1B} receptor is seen in PAH.[9]

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, serotonin, 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, hypoxia, and others, are thought to be involved. In IPAH endothelial dysfunction may occur as a result of proliferation of a monoclonal cell type leading to a plexiform lesion classically associated with this type of PAH. Sleep-disordered breathing and obstructive sleep apnea are associated with cardiovascular morbidity. The reported range of prevalence of PAH in sleep-disordered breathing is 17% to 53%.[23]

CLINICAL PRESENTATION[16]

CLINICAL PRESENTATION OF PULMONARY ARTERIAL HYPERTENSION

Symptoms

- Exertional dyspnea, fatigue, weakness, complaints of general exertion intolerance, dyspnea at rest as the disease progresses, anginal chest pain, syncope (Table 30–3).
- Symptoms of Related Conditions:

  Orthopnea, 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; a history of snoring by the patient's partner may be a consequence of sleep-disordered breathing and can be associated with PAH.

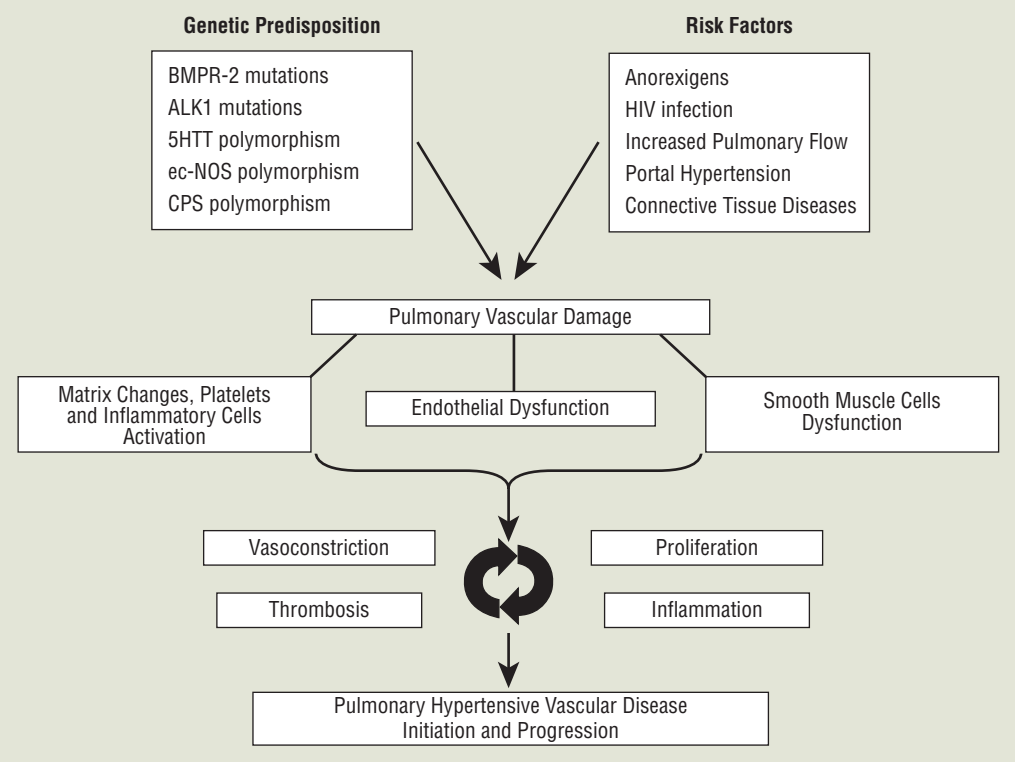

FIGURE 30-1. Pulmonary arterial hypertension; potential pathogenetic and pathobiologic mechanisms. (5-HTT, serotonin transporter gene; ALK 1, activin-receptor-like kinase 1 gene; BMPR-2, bone morphogenetic receptor 2 gene; CPS, carbamyl-phosphate synthase gene; ec-NOS, nitric oxide synthase gene; HIV, human immunodeficiency virus.) *(Reproduced with permission from Galie N, Torbicki A, Barst R. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. Eur Heart J 2004;25:2243–2278.)*

TABLE 30-3 World Health Organization Functional Classification of Pulmonary Arterial Hypertension (PAH)

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.

From Simonneau et al.[57]

Symptoms of Disease Progression

- Leg swelling, abdominal bloating and distension, anorexia, plethora, and more profound fatigue may develop as right ventricular dysfunction and tricuspid valve regurgitation evolve.

Signs

- Accentuated component of S_2 audible at the apex of the heart, early systolic ejection click, midsystolic ejection murmur, palpable left parasternal lift, right ventricular S_4 gallop and a prominent "a" wave.

Signs of Advanced Disease

- Diastolic murmur of pulmonary regurgitation and holosystolic murmur of tricuspid regurgitation, hepatojugular reflux, a pulsatile liver, right ventricular S_3 gallop, marked distension of jugular veins, peripheral edema, low blood pressure, diminished pulse pressure, cool extremities suggesting markedly reduced cardiac output and peripheral vasoconstriction; cyanosis (suggests right-to-left shunting), digital clubbing, rales, dullness, decreased breath sounds, accessory muscle use, wheezing, prolonged exhalation; peripheral venous insufficiency (suggests venous thrombosis or pulmonary thrombotic disease).

Diagnostic Tests

- Electrocardiogram for chamber enlargement, chest radiography to detect enlarged pulmonary arteries, Doppler echocardiography to calculate right ventricular/right atrial pressure and pulmonary diastolic pressure, pulmonary function testing and arterial blood oxygenation; ventilation–perfusion scanning, computed tomography, or magnetic resonance imaging can be used to exclude other diagnoses; right-heart catheterization may be used to confirm the presence of PAH and to guide therapy.
- Tests for connective disease or other risk factors.

5 The signs and symptoms of PAH are highly variable depending on the stage of the disease and comorbidities (see Table 30–3). In patients with a clinical suspicion of PAH, Doppler echocardiography should be performed as a noninvasive screening test that can detect PAH, although it may be imprecise in determining actual pressures compared to cardiac catheterization (quality of evidence: fair; benefit: substantial; strength of recommendation: A).[16] Echocardiography can also be used to assess treatment interventions and to follow disease progression. Because PAH commonly occurs in the setting of connective tissue disease, serologic markers for these diseases (e.g., scleroderma, systemic lupus erythematosus, rheumatoid arthritis, myositis) should be obtained to confirm or exclude these diagnoses (quality of evidence: expert opinion; benefit: intermediate; strength of recommendation: E/A). HIV is associated with an increased prevalence of PAH, ranging up to 0.5%, and HIV testing should be done in patients with unexplained PAH.[16] Chronic thromboembolic pulmonary hypertension should be evaluated with ventilation–perfusion lung scans or pulmonary angiography (quality of evidence: low; benefit: substantial; strength of recommendation: B). Pulmonary function testing and arterial blood oxygenation should be evaluated and the diffusing capacity of carbon monoxide may be particularly helpful in systemic sclerosis and PAH. Right-heart catheterization can confirm the presence of PAH and severity of disease, as well as guide therapy (quality of evidence: good; benefit: substantial; strength of recommendation: A). Right-heart catheterization is considered the "gold standard" because it establishes the diagnosis of PAH, evaluates pulmonary vasoreactivity, and guides treatment. In patients with PAH, serial determinations of functional class and exercise capacity, assessed by the 6-minute walk test, provide benchmarks for disease severity, response to therapy, and progression (quality of evidence: good; benefit: intermediate; strength of recommendation: A).[16]

6 Right-heart catheterization provides important prognostic information and can be used to assess pulmonary vasoreactivity with the administration of fast-acting, short-duration vasodilators to determine the extent of vascular smooth muscle constriction and vasodilator response to calcium channel blockers (quality of evidence: fair; benefit: substantial; strength of recommendation: A).[9] Table 30–4 lists commonly used agents and their dosing. The consensus definition of a positive response is defined as reduction of PAPm by at least 10 mm Hg to a value of 40 mm Hg or less, given that patients with this response are most likely to have a beneficial hemodynamic and clinical response to treatment with calcium channel blockers. Those failing to achieve this response are unlikely to improve with calcium channel blocker therapy, whereas those achieving this response may be treated with calcium channel blockers and followed closely for safety and efficacy. Patients most likely to respond to calcium channel blockers are those with IPAH. Based on a study conducted by Sitbon et al., only approximately 13% will display vasoreactivity.[24] A significant vasodilator response may reflect an earlier stage of disease or a qualitatively different disease process.[9]

TREATMENT

Pulmonary Arterial Hypertension

DESIRED OUTCOMES

7 The goals of treatment are alleviation of symptoms, improvement in the quality of life, prevention of disease progression, and

TABLE 30-4 Agent for Vasodilator Testing in Pulmonary Arterial Hypertension[9,15]

	Epoprostenol	Adenosine	NO
Route	IV	IV	Inhaled
Dose range	2–10 ng/kg/min	50–250 mcg/kg/min	10–80 ppm
Dosing increments	2 ng/kg/min every 15 minutes	50 mcg/kg/min every 2 minutes	10–80 ppm for 5 minutes
Common side effects	Headache, flushing, nausea	Chest tightness, dyspnea	None

NO, nitric oxide; IV, intravenous; ppm, parts per million.
From McLaughlin and McGoon,[9] and Galie et al.[15]

improvement in survival. While the first two outcomes are clearly obtainable based on data from randomized trials, it is less clear that survival can be improved, even considering new therapies developed in the past few years. In a meta-analysis performed by Macchia et al. of 16 trials involving 1,962 patients, no change in total mortality was seen.[25] Up to 80% of the patients were in functional classes III/IV, with a median walking distance of 330 meters at baseline. Overall, experimental treatments were associated with (a) a nonsignificant reduction in all-cause mortality (relative risk 0.70, 95% CI 0.41 to 1.22), (b) a minor but statistically significant improvement in exercise capacity of 42.8 m (95% CI 27.8 to 57.8), and (c) an improved dyspnea status by at least one functional class (relative risk 1.83, 95% CI 1.26 to 2.66). Changes in exercise capacity were not found to be predictive of a survival benefit.[25] Because most of the patients had advanced disease, the potential for a reduction in mortality may have been minimized and less-severely ill patients may have better outcomes. Individual trials do show survival benefit at least in the short-term (i.e., 3 years).[26]

GENERAL APPROACH TO TREATMENT

Treatment of PAH may be categorized into nonpharmacologic, surgical and pharmacologic interventions. 8 The principal endothelial abnormalities that are current pharmacologic therapeutic targets include (a) supplementing endogenous vasodilators; (b) inhibiting endogenous vasoconstrictors; and (c) reducing endothelial platelet interaction and limiting thrombosis. The principal endothelial abnormalities that are *potential* therapeutic targets include (a) reducing endothelial permeability to inhibit penetration of serum factors to the subendothelium; (b) preventing disordered endothelial growth and inappropriate angiogenesis by upregulating proapoptotic signaling/downregulating antiapoptotic signaling, and exploring the use of growth factor inhibitors; (c) metalloproteinase inhibitors, primarily elastase inhibitors to help maintain the integrity of the internal elastic lamina and to reduce activation of tenascin and growth factors in the underlying connective tissue matrix; (d) statins which lower cholesterol but also have potent antiproliferative and antiinflammatory effects with beneficial effects on pulmonary vascular remodeling in experimental models of PAH; and (e) growth of new pulmonary arteries.[11] Nonpharmacologic therapy can be quite broad and comorbidities often determine which form of nonpharmacologic therapy would be appropriate (e.g., use of positive airway pressure for patients with sleep-disordered breathing). Surgical therapy is indicated in certain situations and includes apical septostomy (usually performed in severely ill patients as a palliative bridge to lung transplantation), pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension, and lung or heart-lung transplantation.

8 NONPHARMACOLOGIC THERAPY

In patients with obstructive sleep apnea and PAH, treatment of obstructive sleep apnea with positive airway pressure therapy should be provided with the expectation that pulmonary pressures will decrease, although they may not normalize (quality of evidence: low; benefit: small/weak; strength of recommendation: C).[1] Pulmonary thromboendarterectomy for PAH caused by chronic, recurrent thromboembolic disease improves hemodynamics, functional status, and survival (quality of evidence: low; benefit: substantial; strength of recommendation: B). Pregnancy should be avoided or terminated in patients with PAH (quality of evidence: good; benefit: substantial; strength of recommendation: A). Immunization against influenza and pneumococcal disease should be provided according to standards for patients with serious cardiopulmonary disease. Hypoxia may aggravate vasoconstriction in patients with PAH and it is advisable to avoid hypobaric hypoxia starting with altitudes between 1,500 and 2,000 meters. Commercial airplanes are pressurized to equivalent altitude between 1,600 and 2,500 meters and supplemental oxygen in PAH patients should be considered.[15] Although there are no randomized trials to support limiting sodium intake, it seems reasonable that patients should adhere to a diet of 2,400 milligrams of sodium or less per day to avoid fluid retention (predisposing to right-heart failure).[9] Cardiopulmonary rehabilitation has been shown to improve functional status and is safe for patients with PAH.[27] Patients with PAH are highly sensitive to reduction in hemoglobin and anemia should be promptly treated.[15] Patients with long-standing hypoxia, such as those with right-to-left shunts, develop erythrocytosis and phlebotomies may be indicated to prevent complications of hyperviscosity. PAH patients are affected by a variable degree of anxiety and/or depression that can have a profound impact on their quality of life. Support groups and psychological counseling can be helpful to improve understanding and acceptance of the disease.[15]

Drugs to avoid in patients with PAH include drugs interacting with warfarin or that potentially increase the risk of gastrointestinal hemorrhage such as nonsteroidal antiinflammatory drugs (e.g., ibuprofen, aspirin) as anticoagulation in PAH is frequently considered. Nonsteroidal antiinflammatory drugs may also worsen renal function and are of particular concern in patients with low cardiac output or azotemia. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers may cause hypotension and right-heart failure and should be used with caution in PAH.

PHARMACOLOGIC THERAPY

The number of potential therapies for PAH have expanded dramatically in the past decade and there are now no less than six drugs for PAH in addition to adjunctive therapy with anticoagulation and oxygen, as well as other therapies to treat comorbidities. Figure 30–2 illustrates the current recommended treatment algorithm based on the most recent U.S. guidelines.[1]

General Pharmacologic Treatment

10 General care interventions include oral anticoagulants, diuretics, oxygen, and digoxin.[9] The rationale for oral anticoagulants in patients with PAH is based on the presence of traditional risk factors for venous thromboembolism, such as heart failure and sedentary lifestyle, as well as on the demonstration of thrombotic predisposition and thrombotic changes in the pulmonary microcirculation. The target international normalized ratio in most centers is 1.5 to 2.5; European targets are somewhat higher at 2.0 to 3.0. In recent trials, 50% to 85% of patients have been anticoagulated and the highest prevalence has been in IPAH patients in New York Heart Association classes III and IV.[15] Anticoagulation is recommended for patients with IPAH (level of evidence: fair; benefit: intermediate; grade of recommendation: B).[1]

Diuretics are used in patients with decompensated right-heart failure and with associated findings of increased central venous pressure, abdominal organ congestion, peripheral edema and ascites. Appropriate diuretic therapy in right-heart failure allows clear symptomatic and clinical benefits in patients with PAH (grade of recommendation: E/A). There are no randomized trials of diuretic therapy in PAH. Approximately 50% to 70% of patients with PAH receive diuretic therapy.

Although oxygen saturation should be maintained at approximately 90%, there are no data currently available regarding the effects of long-term oxygen treatment in PAH (level of evidence: expert opinion; benefit: substantial; grade of recommendation: E/A). Oxygen treatment in patients with PAH associated with shunts (Eisenmenger syndrome) is controversial and oxygen supplementation may have little effect in this situation.

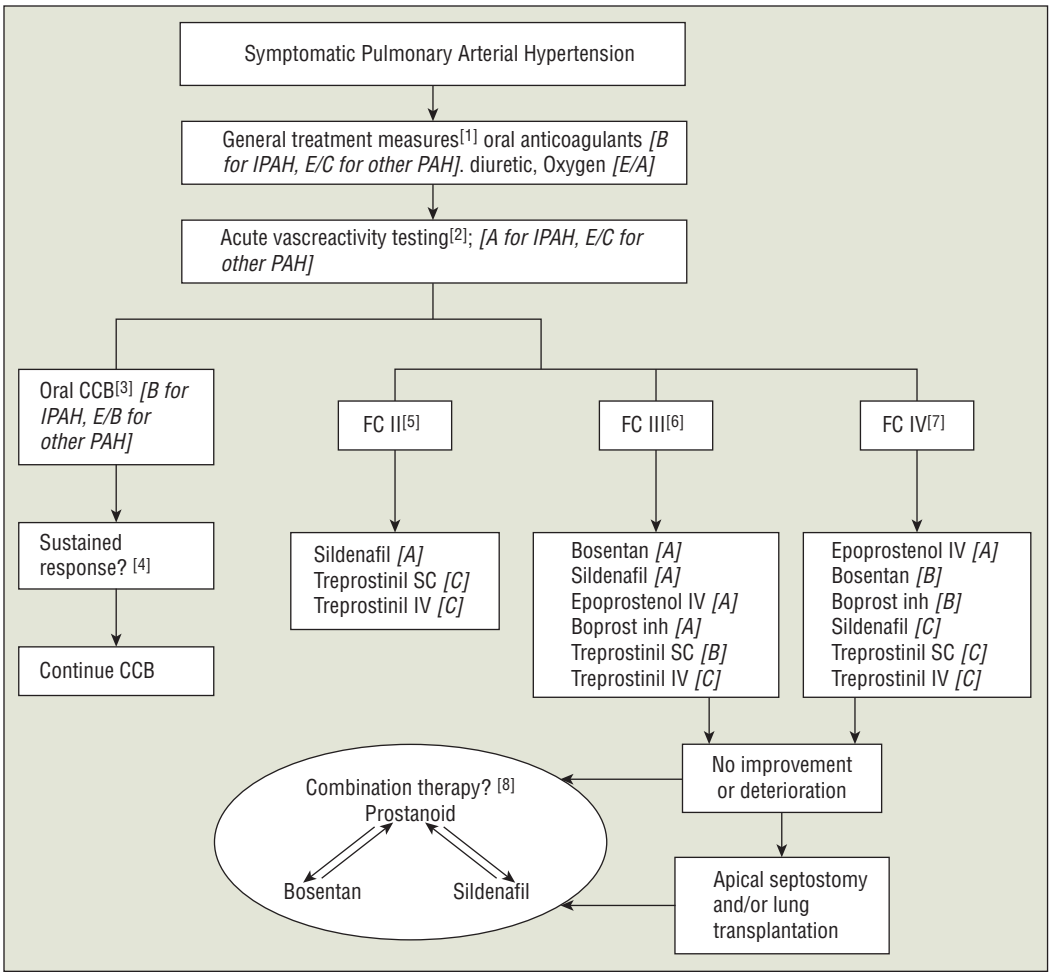

FIGURE 30-2. Treatment algorithm for pulmonary arterial hypertension (PAH). Designators [A], [B], [C], [D], [E/A], [E/B], and [E/C] are defined in Table 30–2. (CCB, calcium channel blocker; FC, functional class; IPAH, idiopathic pulmonary arterial hypertension.)

Digoxin use in PAH is based on judgment rather than scientific evidence of efficacy. Digoxin can be used for PAH patients with right-heart failure as adjunctive therapy along with diuretics to control symptoms. Digoxin may be useful in PAH patients who develop atrial flutter to slow ventricular rate. European guidelines give digoxin a recommendation of IIb with a level of evidence of C (usefulness is less-well established by evidence and consensus opinion). There are no long-term trials and benefit is uncertain. Optimal plasma concentrations for digoxin in PAH are unknown; however, in light of recent trials of digoxin in left systolic dysfunction, plasma concentrations should probably be in the range of 0.5 to 0.8 ng/mL.

Specific Pharmacologic Therapy

Calcium Channel Blockers ⓫ A small number of patients with IPAH demonstrating a favorable response to acute vasodilator testing (see clinical presentations page 3) will do well with calcium channel blockers (CCBs). As described previously, IPAH patients are most likely to respond to acute vasodilators and CCBs but the number responding on long-term treatment is small (approximately 7%).[24] Large reductions in PAPm predict a better response to long-term CCBs. The preferred drugs are dihydropyridine CCBs as they lack the negative inotropic effects seen with verapamil. Diltiazem may be used in patients with tachycardia to slow heart rate through atrioventricular node blockade. If left ventricular systolic dysfunction is present, diltiazem should not be used. Initial assessment for CCB therapy should occur after 3 months and if improvement in functional class to class I or II is not seen, additional or alternative PAH therapy should be instituted. CCBs should not be used empirically to treat PAH in the absence of demonstrated acute vasoreactivity (level of evidence: expert opinion; benefit: substantial; grade of recommendation: E/A). The doses of these drugs are relatively high—that is, up to 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.[15]

Phosphodiesterase Inhibitors ⓬ Sildenafil (Revatio) is a potent and highly specific phosphodiesterase-5 inhibitor that is approved for erectile dysfunction but also has been shown to reduce PAPm and improve functional class. Sildenafil exerts its pharmacologic effect by increasing the intracellular concentration of cyclic guanosine monophosphate, leading to vasorelaxation and antiproliferative effects on vascular smooth muscle cells. In a recent trial, sildenafil induced a significant reduction in mean pulmonary artery pressure and arteriolar resistance, and functional capacity improved (an average of +37 m). Sildenafil improved endothelial-dependent vasodilation, and reduced plasma concentrations of endothelin-1 (from 4.5±0.6 to 3.1±0.7 pg/mL; $p < 0.0001$) and von Willebrand factor (from 183.1±10.1 to 149.1±17.6 mU/mL; $p < 0.0001$).[28] In a year-long study, sildenafil in chronic thromboembolic pulmonary hypertension improved 6-minute walking distance and hemodynamics.[29] Other studies have found similar beneficial results.[30–32] The recommended dose is 20 mg by mouth three times per day; in clinical trials, however, much higher doses have been used. Common adverse effects 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, the drug should be stopped. Concurrent nitrate therapy may lead to excessive blood pressure reduction and this combination should be avoided. Based on the current U.S. guidelines, sildenafil is recommended for functional class II patients with PAH (level of evidence: good; benefit: substantial; grade of recommendation: A).[1]

Synthetic Prostacyclin and Prostacyclin Analogs 13 Prostacyclin is produced predominantly by endothelial cells and it induces potent vasodilation of all vascular beds. It is also a potent inhibitor of platelet aggregation and possesses cytoprotective and antiproliferative activities. Prostacyclin synthase expression is reduced in pulmonary arteries and urinary excretion of prostacyclin metabolites are reduced in PAH. Epoprostenol (Flolan) is a synthetic analog of prostacyclin and has a short half-life of 3 to 5 minutes; consequently, it must be given by continuous infusion. In controlled trials lasting up to 3 months, epoprostenol improved 6-minute walk time, hemodynamics, and clinical events.[33–35] Long-term epoprostenol is initiated at a dose 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, foot/leg pain, and, rarely, hypotension). Because the drug must be given by a pump to provide a continuous infusion, infection, catheter obstruction and sepsis are potential complications. A Centers for Disease Control and Prevention 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 1 infection every 3 years) when these drugs are given by the intravenous route. 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 and to avoid tolerance. Optimal doses are variable but are in the range of 20 to 40 ng/kg/min.[15] Observational series have documented an improvement in survival in patients with IPAH compared to either historical control or predicted survival based on the National Institutes of Health Registry equation.[35,36] Based on current U.S. guidelines, epoprostenol is indicated for functional class III (level of evidence: good; benefit: substantial; grade of recommendation: A).

Treprostinil (Remodulin) is a stable analog of prostacyclin given for subcutaneous or intravenous (IV) infusion with the major advantage over epoprostenol being ease of use and less potential for serious infections when used by the subcutaneous route. Treprostinil has been shown to improve 6-minute walk time and hemodynamics with outcomes that are similar to epoprostenol.[37,38] In clinical trials, the greatest exercise improvement was observed in patients who were more compromised at baseline and in patients 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 subcutaneous or IV route. If not tolerated, the dose should be reduced to 0.625 ng/kg/min and retitration attempted at 4 weeks. If transitioning from epoprostenol to treprostinil, start with 10% of the epoprostenol dose. Dose may be increased by 1.25 ng/kg/min but no more than 2.5 ng/kg/min per week. Infusion site pain is the most common side effect of treprostinil, leading to discontinuation of the treatment in 8% of patients and limiting dose increase in other patients.[15] Other side effects are similar to epoprostenol. Based on U.S. guidelines, treprostinil is recommended for functional class II (IV administration-level of evidence: low; benefit: small/weak; grade of recommendation: C), functional class III (IV administration-level of evidence: low; benefit: intermediate; grade of recommendation: C), and functional class IV (IV administration-level of evidence: low; benefit: intermediate; grade of recommendation: C).

Iloprost (Ilomedin, Ventavis) is a prostacyclin analog that is given by inhalation using a dosing system provided by the manufacturer (ADD system) with the initial inhaled dose being 2.5 mcg 6 to 9 times/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, randomized, double-blind, placebo-controlled trial, iloprost via inhalation provided at least a 10% improvement in 6-minute walking distance and improvement in functional class.[39] Iloprost may also be used as add-on therapy to bosentan.[40] Adverse effects are similar to other prostacyclin analogs with the exception of infectious complications related to catheter use for drug delivery. Inhaled iloprost is indicated for functional class III (level of evidence: good; benefit: intermediate; grade of recommendation: A), and functional class IV (level of evidence: fair; benefit: intermediate; grade of recommendation: B).

Endothelin Antagonists 14 Endothelin-1 (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 PAH patients. Bosentan (Tracleer) 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.[41,42] In one of the larger studies with bosentan, patients were started on 62.5 mg twice daily for 4 weeks followed by 125 mg or 250 mg twice daily for a minimum of 12 weeks.[41] Both doses were better than placebo and the higher dose provided greater improvement in 6-minute walking time. Increases in hepatic aminotransferases occurred in 10% of patients and were dose-dependent. 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 retention of bile salts that can be cytotoxic to hepatocytes.[43] Bosentan should be started at 62.5 mg twice daily in adults and adolescents for 4 weeks. If the body weight is more than 40 kg, increase the dose to 125 mg twice daily. If body weight is less than 40 kg, the maximum dose is 125 mg/day. If liver function tests 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 liver function tests return to pretreatment levels, bosentan may be continued or reintroduced if indicated. Liver function tests should be monitored at baseline and monthly and monthly pregnancy testing is required in females (category X). Bosentan is not recommended for children.

Ambrisentan (Letairis) is a once-daily selective ET_A receptor antagonist that improves exercise capacity and hemodynamics, and delays clinical worsening in PAH.[44–46] Similar to bosentan, ambrisentan has liver toxicity and is category X for pregnancy. Liver toxicity is thought to be somewhat less with ambrisentan (0.8% in 12-week trials and 2.8% for up to 1 year). Common side effects include peripheral edema, nasal congestion, flushing, and palpitations. Treatment should be initiated with 5 mg once daily and increased to 10 mg once daily if the lower dose is well tolerated. U.S. guidelines do not provide an evidenced-based recommendation for ambrisentan due to approval after guidelines publication but would likely have similar recommendations to those provided for bosentan.

Sitaxsentan (Thelin) is an orphan drug that is a selective, orally active ET_A receptor antagonist that improves exercise capacity, hemodynamics, and clinical events in IPAH and PAH at doses of 100 to 300 mg daily.[47–51] Sitaxsentan may increase the international normalized ratio because of inhibition of cytochrome P450 2C9 if patients are also taking warfarin. No recommendations currently exist for its use.

Combination Therapy 15 Combination therapy is an attractive option to address the multiple pathophysiologic mechanisms in PAH. Combination therapy can be pursued by the simultaneous initiation of two (or more) treatments or by the addition of a second (or third) agent if previous treatment has been insufficient. Bosen-

tan when combined with epoprostenol improved hemodynamics, exercise capacity, and functional class with a trend toward greater improvement in hemodynamics.[52] An increase in adverse effects was noted with combination therapy compared to epoprostenol alone. In patients with PAH who are deteriorating despite chronic treatment with prostanoids, the addition of bosentan or sildenafil results in improvement in pulmonary hemodynamics and exercise based on uncontrolled studies.[53,54] More specific information concerning drugs used for PAH are shown in Table 30–5.

Pharmacoeconomics

Although little pharmacoeconomic information is available for the management of PAH, treatment with treprostinil resulted in an expected savings of $2,610,642 and $2,781,438 from the ministries of health and societal perspectives, respectively. On a per-patient level, treatment with treprostinil resulted in an average annual savings of $14,504 and $15,452, respectively. The greatest savings with treprostinil came from reduced hospitalizations.[55] When nitric oxide was compared to extracorporeal membrane oxygenation in neonates with pulmonary hypertension and hypoxic respiratory failure, NO was found to be quite cost-effective.[56]

CLINICAL CONTROVERSIES

The use of combination therapy when monotherapy for PAH is no longer adequate is not well studied, but in uncontrolled trials, combinations of bosentan and epoprostenol and sildenafil to other therapy appears to provide additional improvement.

Calcium channel blockers can be effective in PAH, especially IPAH, but vasoreactivity testing should be performed first to ensure that calcium channel blockers can vasodilate the pulmonary artery vascular bed.

The exact sequencing of drug therapy for PAH remains a matter of individual clinician preference given the paucity of randomized trial data to support one drug over another in PAH which is worsening over time.

EVALUATION OF THERAPEUTIC OUTCOMES

Response to treatment in PAH can be objectively measured by the 6-minute walk distance, echocardiography to assess pulmonary pressures and right-heart catheterization as the gold standard to assess ventricular function and pulmonary pressures. Use of the functional classification system developed by the World Health Organization is clinically useful but correlations to hemodynamics may be imprecise. Other outcomes that are useful in clinical trials include hospitalization for exacerbations of PAH and the development of complications and death.

CONCLUSIONS

PAH is a challenging disease to manage; however, with the development of endothelin antagonists, phosphodiesterase inhibitors, and prostacyclin analogs, clinical improvement is possible in most patients, leading to a better quality of life and delay of disease progression. Patient education is important to improve acceptance of this disease and referral to specialty care centers may provide the best outcomes.

TABLE 30-5 Drug Class Information

Drug	Mechanism of Action	Pharmacokinetics	Adverse Events	Drug–Drug Interactions	Dosing
Calcium channel blockers					
Nifedipine extended release (Procardia XL, Nifedical XL, Adalat CC)	Blocks the influx of extracellular calcium, causing vasodilation; more potent vasodilator than diltiazem	Bioavailability 90% Extensive first-pass effect reduces bioavailability to 86% Metabolized by CYP3A4 Half-life 2–5 hours	Peripheral edema, headache, dizziness, constipation, flushing	Known inhibitors of CYP3A4 (e.g., amiodarone, erythromycin) Known 3A4 inducers (e.g., rifampin, carbamazepine)	Start at reduced dose of 30 mg orally twice daily and titrate to 120–240 mg daily
Diltiazem (Cardia XT, Cardizem CD, LA, SR, Taztia XT)	Blocks the influx of extracellular calcium, causing vasodilation	Bioavailability 80% Extensive first pass effect reduces bioavailability to 40% to 60% Metabolized by CYP3A4 Half-life 4–6 hours	Gastrointestinal effects, negative inotropic effects, headache, flushing, peripheral edema	Known inducers of CYP3A4 (e.g., rifampin, carbamazepine) Known inhibitors of CYP3A4 (e.g., amiodarone, erythromycin)	Start at reduced dose of 60 mg orally three times daily and titrate to 240–720 mg daily
Amlodipine (Norvasc)	Blocks the influx of extracellular calcium, causing vasodilation; more potent vasodilator than diltiazem	Bioavailability 52% to 88% 93% protein bound Metabolized by CYP3A4 Half-life 35 hours	Palpitations, peripheral edema, fatigue, dizziness, headache, flushing	Known inducers of CYP3A4 (e.g., rifampin, carbamazepine) Known inhibitors of CYP3A4 (e.g., amiodarone, erythromycin)	Start at reduced dose of 2.5 mg orally daily, titrated to maximum dose of 40 mg daily
Phosphodiesterase inhibitors					
Sildenafil (Revatio)	Increases the intracellular concentration of cyclic guanosine monophosphate (cGMP) resulting in vasorelaxation and antiproliferative effects on smooth muscle cells	Bioavailability 40% 96% protein bound Metabolized by CYP450 3A4 (major) and 2C9 (minor) Half-life 4 hours	Headache, flushing, dyspepsia, nasal congestion, dizziness, and rash	Known inhibitors of CYP3A4 and 2C9 (e.g., cimetidine, fluvoxamine) Known inducers of CYP3A4 (e.g., rifampin, carbamazepine) Concurrent use with nitrates potentiates hypotensive effects	20 mg orally three times daily, taken at least 4–6 hours apart; 50 mg twice daily may be appropriate for more severe cases No greater efficacy with higher doses

(continued)

TABLE 30-5 Drug Class Information (continued)

Synthetic prostacyclin and prostacyclin analogs					
Epoprostenol (Flolan)	Potent vasodilator of all vascular beds	Metabolized to 2 major and 14 minor metabolites Half-life 3–5 minutes Stable for 8 hours at room temperature	Flushing, jaw pain, diarrhea, headache, back ache, foot and leg pain, abdominal cramping, nausea, hypotension (rarely)	May increase risk of bleeding with anticoagulants Sympathomimetics antagonize vasodilatory effects Additive hypotensive effects with monoamine oxidase inhibitors	Starting dose 2–4 ng/kg/min IV, titrate up to 20–40 ng/kg/min
Treprostinil (Remodulin)	Direct vasodilator of systemic and pulmonary vascular beds and inhibits platelet aggregation	Metabolized hepatically via unknown CYP450 enzymes (dehydration, oxidation, glucuronidation) Half-life 4 hours	Cardiovascular dilation, diarrhea, nausea, headache, jaw pain, injection site pain, rash, and pruritus	May increase risk of bleeding with anticoagulants Sympathomimetics antagonize vasodilatory effects Additive hypotensive effects with monoamine oxidase inhibitors	Initially 1.25 ng/kg/min 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
Iloprost (Ventavis)	Dilates systemic and pulmonary arterial vascular beds, alters pulmonary vascular resistance and suppresses vascular muscle proliferation Potent endogenous inhibitor of platelet aggregation	Metabolized hepatically via beta oxidation of the carboxyl side chain Half-life 20–30 minutes	Flushing, hypotension, headache, nausea, trismus, cough, flu-like syndrome, jaw pain	Increased hypotensive effects when used with vasodilators and antihypertensive medications Anticoagulants and antiplatelet medications may increase the risk of bleeding	Initially 2.5 mcg inhaled six to nine times daily (dosing at ≥2 hour intervals while awake) May titrate to 5 mcg per dose with a maximum daily dose of 45 mcg
Endothelin antagonists					
Bosentan (Tracleer)	Competitive antagonist for type A and B endothelin receptors, which mediate vasoconstriction and vasodilation Lowers systemic vascular resistance, pulmonary vascular resistance and mean pulmonary arterial pressure	Bioavailability 50% >98% protein bound Metabolized by CYP2C9 and 3A4; also inducer of CYP 2C9, 3A4, and 2C19 Half-life 5 hours	Headache, flushing, abnormal hepatic enzymes, edema, reduced hemoglobin concentrations Black box warning to monitor serum aminotransferases at baseline and monthly during therapy	Known substrates of CYP3A4 (e.g., cyclosporine A, glyburide, hormonal contraceptives) Known substrates of CYP2C9 (e.g., warfarin)	Initially 62.5 mg orally twice daily for 4 weeks For patients weighing >40 kg, maximum dosage is 250 mg daily For patients weighing <40 kg, maximum dosage is 125 mg daily Available through Tracleer Access Program
Ambrisentan (Letairis)	Selective antagonist for type A endothelin receptors, which mediates vasoconstriction and vasodilation Lowers systemic vascular resistance, pulmonary vascular resistance and mean pulmonary arterial pressure	Bioavailability unknown 99% protein bound Metabolized by CYP3A4, 2C19, and uridine glucuronyltransferases, substrate of organic anion transport protein and P-glycoprotein Half-life-9 hours	Peripheral edema, flushing, palpitations, elevated hepatic enzymes, headache, nasal congestion	Cyclosporine will increase ambrisentan levels Known inhibitors of CYP3A4 (e.g., amiodarone, erythromycin) Known inhibitors of CYP2C19 (e.g., cimetidine, clopidogrel, efavirenz) Known inducers of CYP3A4 (e.g., carbamazepine, rifampin)	Initial dose 5 mg orally daily, titrated to maximum dose of 10 mg daily Available through Letairis Education and Access Program
Sitaxsentan (Thelin)	Selective antagonist for type A endothelin receptors, which mediates vasoconstriction and vasodilation Lowers systemic vascular resistance, pulmonary vascular resistance and mean pulmonary arterial pressure	Bioavailability >90% Moderate inhibitor of 2C9, 2C19, 3A4 Half-life 6.5 hours	Peripheral edema, nausea, decreased hemoglobin, fulminant hepatitis, increased aminotransferases, headache, dizziness	Increase risk of bleeding with warfarin	100–300 mg orally daily Not yet available in United States

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