Treatments and strategies to optimize the comprehensive management of patients with pulmonary arterial hypertension

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ABSTRACT

The management of pulmonary arterial hypertension (PAH) should aim to provide vasodilation of the pulmonary arteries, treat right ventricular failure, improve functional capacity and quality of life, and improve survival, if possible. Data from right heart catheterization and an estimation of vasoresponsiveness together guide treatment for PAH. The judicious use of calcium channel blockers, prostacyclin analogues, anticoagulation, and endothelin receptor antagonists forms the current basis of therapy. Three drugs—the prostacyclin analogues epoprostenol and treprostinil and the endothelin receptor antagonist bosentan—are currently approved for the primary treatment of PAH and have been clinically shown to improve outcomes. Coumarin derivatives, epoprostenol, and, in selected patients, calcium channel blockers are the only drugs associated with improved survival, and only epoprostenol has been shown to improve survival in a prospective randomized trial. Knowledge of the supportive therapies, indications for surgical intervention, and emerging drug therapies should provide the working armamentarium for clinicians treating this rare but devastating disease.

The comprehensive management of patients with pulmonary arterial hypertension (PAH) generally includes the following goals:

- Vasodilation of the pulmonary arteries to reduce pulmonary artery pressure
- Treatment of right ventricular failure
- Improvement in functional capacity and quality of life
- Improved survival.

These goals are most efficiently and effectively achieved using a team approach centered on collaboration among the various physicians involved and a pulmonary hypertension center, including a pulmonary hypertension coordinator (see the article by Mughal et al in this supplement). In the present article, we review the various therapeutic options available for patients with PAH and issues involved in the comprehensive management of these patients. The simplified algorithm in **Figure 1** provides an overview of the management of these patients.

GENERAL CONSIDERATIONS IN THE APPROACH TO PULMONARY HYPERTENSION

Pulmonary arterial hypertension has diverse origins and may occur as a primary disease (primary pulmonary hypertension) or as a complication of systemic, pulmonary, or cardiac conditions,[1] as described earlier in this supplement. Most of the discussion in this article relates to patients with prima-

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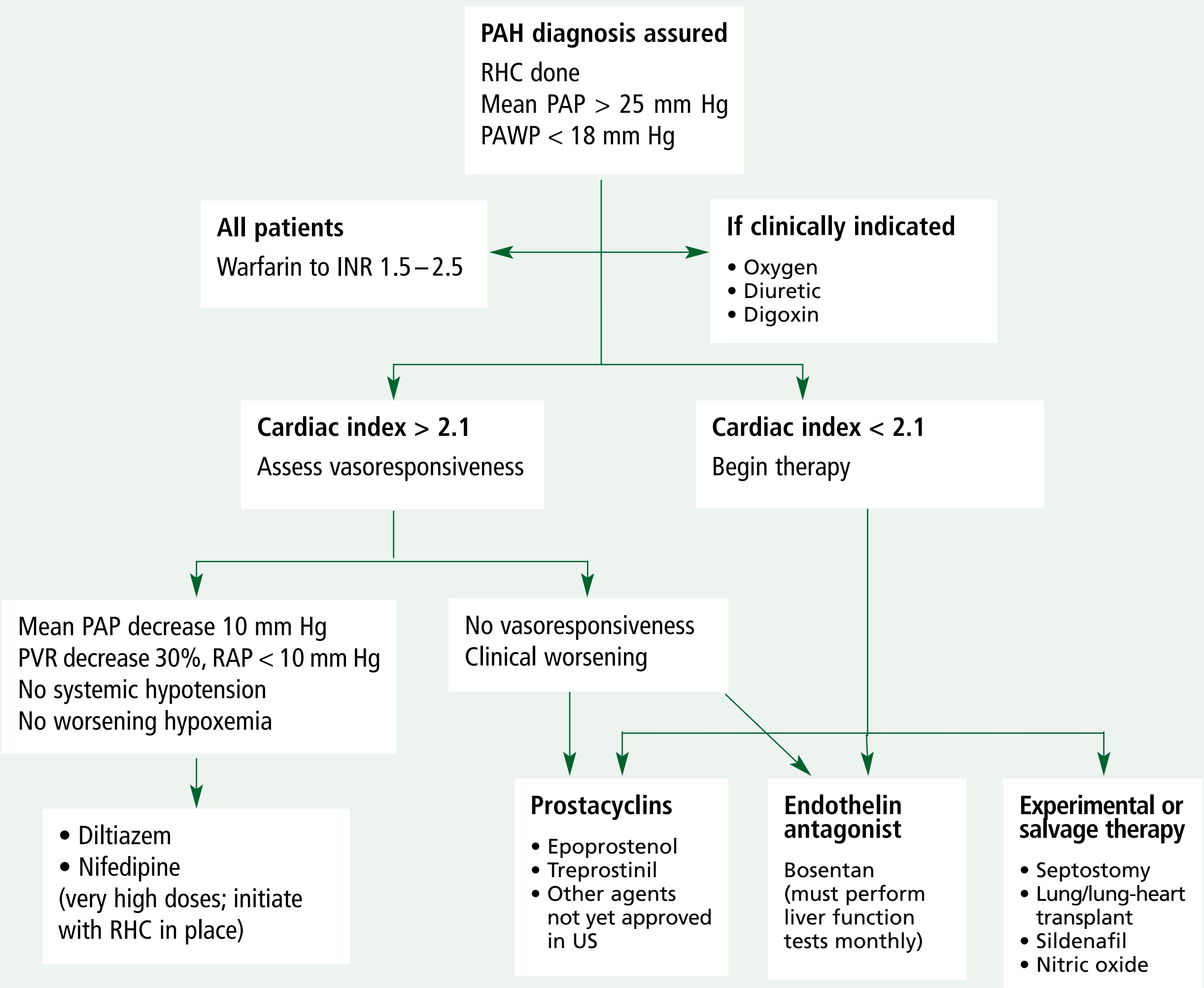

PAH = pulmonary arterial hypertension; RHC = right heart catheterization; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; INR = international normalized ratio; PVR = pulmonary vascular resistance; RAP = right atrial pressure

Figure 1. Algorithm for the management of patients with pulmonary arterial hypertension.

ry pulmonary hypertension, although many studies have included patients with other categories of PAH **(Table 1)**.

Secondary causes of pulmonary hypertension should be thoroughly investigated since most cases have an underlying etiology. Although some of these secondary causes may have distinguishing clinical features, a high index of suspicion is needed to make a correct and timely diagnosis of PAH, owing to its insidious onset and progression, nonspecific symptoms, and varied underlying causes.[1,2]

Although echocardiography is a useful noninvasive method of estimating the right ventricular systolic pressure,[3,4] all patients should undergo right heart catheterization for accurate measurement of hemodynamic parameters and to guide the selection of appropriate therapy.

■ ESTIMATE OF VASORESPONSIVENESS

Before vasodilator therapy is initiated for PAH, patients should be identified as “responders” or

TABLE 1
Classification of pulmonary arterial hypertension

1. Primary pulmonary hypertension
   - Sporadic
   - Familial
2. Pulmonary arterial hypertension related to:
   - Collagen vascular disease
   - Congenital systemic to pulmonary shunts
   - Portal hypertension
   - HIV infection
   - Drugs
     —Anorexigens
     —Other (rapeseed oil, cocaine, L-tryptophan, etc)
   - Persistent pulmonary hypertension of the newborn
   - Other

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"nonresponders" by measuring the change in pulmonary artery pressure and pulmonary vascular resistance in response to short-acting vasodilators such as inhaled nitric oxide,[5] intravenous prostacyclin,[6] or adenosine.[7] A decrease of 10 mm Hg in mean pulmonary artery pressure and a 25% decrease in pulmonary vascular resistance[8] is considered a positive response so long as it occurs with a stable or increased cardiac index and without a significant decrease in systemic blood pressure or oxygen saturation.[9] Because there is a 20% to 25% spontaneous variability in pressures and resistances,[10] it is reasonable to require at least a 30% reduction in pulmonary vascular resistance in order to call a vasodilator response positive.[11] Patients with a positive response are more likely to benefit from long-term vasodilator therapy[11–14] and to have fewer side effects.[11,15] Patients without an acute vasodilator response also appear to have vascular endothelial remodeling that limits vasodilatation,[16] but they still derive clinical benefit from long-term vasodilator therapy with epoprostenol.[17–19]

■ CALCIUM CHANNEL BLOCKERS

Calcium channel blockers were the first medications associated with an improvement in survival in patients with primary pulmonary hypertension. Some authors recommend at least a 50% decrease in pulmonary vascular resistance and near normalization of mean pulmonary artery pressure in response to a vasodilator trial when assessing a patient's candidacy for calcium channel blocker therapy.[20] Calcium channel blockers are best reserved for patients with a preserved cardiac index and documented vasoreactivity. Unfortunately, vasoreactivity is uncommon, existing in approximately 30% of patients.[21]

Studies have shown that high-dose calcium channel blocker therapy in carefully selected patients (ie, those with a 20% reduction in mean pulmonary artery pressure during acute titration of nifedipine or diltiazem) is associated with reducations in pulmonary artery pressure, pulmonary vascular resistance, and symptoms, as well as improved survival at 5 years.[12,13,22] Doses up to 720 mg/day of diltiazem or 240 mg/day of nifedipine were used as long-term therapy after the initial dose escalation.

Notably, patients with a right atrial pressure greater than 10 mm Hg may not derive benefit from calcium channel blocker therapy.[23]

■ PROSTACYCLIN ANALOGUES

Prostaglandins, including prostacyclin, are powerful vasodilators that have antiplatelet activity and may also contribute to pulmonary vascular endothelial remodeling.[23–27] Several prostacyclin analogues are in clinical use for pulmonary hypertension throughout the world, but only epoprostenol (Flolan) and treprostinil (Remodulin) are approved by the Food and Drug Administration (FDA) for use in the United States.

Epoprostenol is delivered by continuous intravenous infusion because of its short half-life in the circulation (3 to 5 minutes). Its main mechanism of action is a dose-dependent vasodilation that begins within a few minutes of the start of infusion. Through its actions on the arachidonic acid pathway, epoprostenol also can inhibit platelet aggregation and reduce the risk of in situ thrombosis.

Reports in the 1980s[28,29] suggested a significant sustained benefit from epoprostenol in patients with primary pulmonary hypertension. In 1996, a randomized prospective trial demonstrated the sustained effect of epoprostenol over a 3-month period in 81 patients with severe primary pulmonary hypertension (New York Heart Association [NYHA] class III or IV).[18] The mean pulmonary artery pressure decreased by 8% in the epoprostenol group while rising by 3% in the conventional therapy group. Additionally, epoprostenol therapy was associated with significant improvements in cardiac index, pulmonary vascular resistance, 6-minute walk distance, and quality-of-life measures over the 12-week period. All of the patients who died were in the conventional therapy arm **(Figure 2)**.

Several other trials of epoprostenol have shown a sustained increase in cardiac output with reduction in pulmonary vascular resistance[30] and improvement in survival at 1, 3, and 5 years compared with historical controls.[18,31] The beneficial effects of epoprostenol can be seen even in patients without acute reduction of pulmonary artery pressure and vascular resistance.[18,19] McLaughlin et al[30] showed that the greater the reduction in pulmonary vascular resistance with acute adenosine challenge, the lower the pulmonary vascular resistance with long-term epoprostenol therapy, but even those patients with no response to the initial challenge had a reduction in pulmonary vascular resistance and an improvement in symptoms.

Epoprostenol may delay or eliminate the need for lung transplantation in some instances.[32] This drug also has benefited patients with PAH secondary to connective tissue diseases,[27] congenital heart defects,[25] portopulmonary hypertension,[23] chronic thromboembolic pulmonary hypertension,[33] HIV infection,[26] use of anorectic agents,[34] and sarcoidosis.[30,35]

Dosing of epoprostenol is based on actual body weight and is calculated in ng/kg/min. Treatment is usually started with insertion of a pulmonary artery catheter to monitor hemodynamic changes with drug titration. Optimal dosing follows either of two strategies. In one strategy, the dose may be increased if the patient experiences symptoms (ie, the lowest tolerated dose is used). The second strategy is to continue increasing the dose as long as the toxicities from treatment are tolerable. These strategies have not been compared directly.

Epoprostenol typically is initiated at a dose of 2 to 4 ng/kg/min, which is titrated up, based on side effects, toward a target dose of 8 to 15 ng/kg/min in the initial 4 to 5 weeks. Interpatient variability makes the notion of an "ideal dose" somewhat nebulous, but a recent report suggests that most patients remain on stable doses between 22 and 45 ng/kg/min.[36] Epoprostenol is delivered via a permanent central catheter, which can subject the patient to significant risk of infection[37] and thrombosis.

Changes in volume status will change the volume of distribution and may result in over- or underdosing. Symptoms of epoprostenol toxicity include flushing, jaw claudication, abdominal cramping, diarrhea, nausea/emesis, headache, and arthralgia; these symptoms abate with time, indicating drug tolerance.[38] Acute discontinuation of therapy for any reason may result in a rapid increase in pulmonary vascular resistance and pulmonary artery pressure, as well as potentially acute right ventricular failure and death.

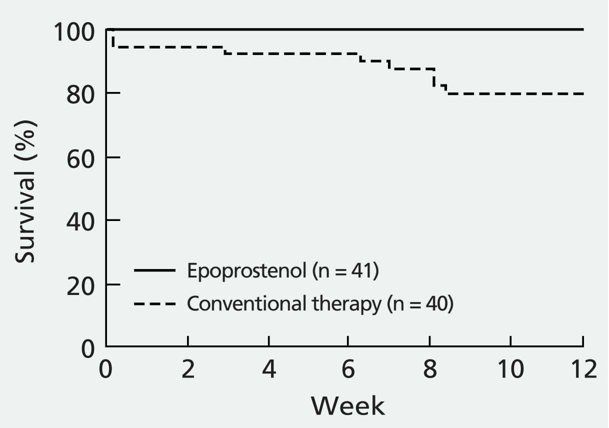


Figure 2. Survival among 41 patients treated with epoprostenol and 40 patients receiving conventional therapy in a randomized prospective trial.[18] Estimates were made by the Kaplan–Meier product-limit method. The two-sided *P* value from the log-rank test was 0.003. Reprinted with permission from reference 18. Copyright © 1996 Massachusetts Medical Society.

Treprostinil is the prostacyclin analogue that is available for subcutaneous infusion. A recent prospective, randomized, 12-week study compared treprostinil with placebo in 470 patients with PAH (mainly primary pulmonary hypertension).[39] Treprostinil recipients showed a small improvement compared with placebo recipients in 6-minute walk distance (16 meters) and significant improvement in mean right atrial pressure, mean pulmonary artery pressure, cardiac index, pulmonary vascular resistance, mixed venous oxygen saturation, and quality-of-life measures. However, significant pain at the infusion site was a major problem, occurring in 85% of patients and causing study discontinuation in 8%. There are currently no data showing mortality benefits.

■ ENDOTHELIN RECEPTOR ANTAGONISTS

The biology of endothelin-1 and its receptors (endothelin receptors A and B) has been the focus of intense research in recent years. Endothelin-1 is the most potent known endogenous vasoconstrictor. It

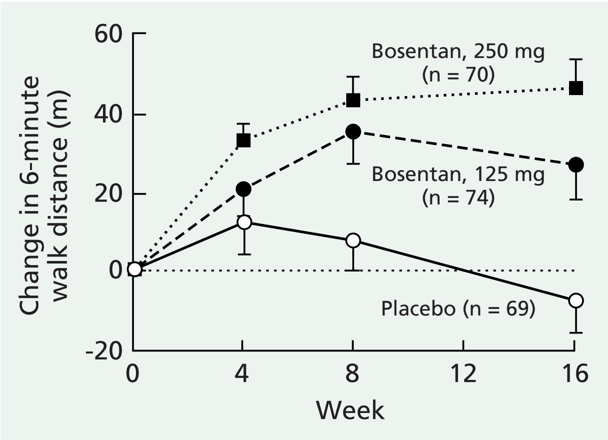
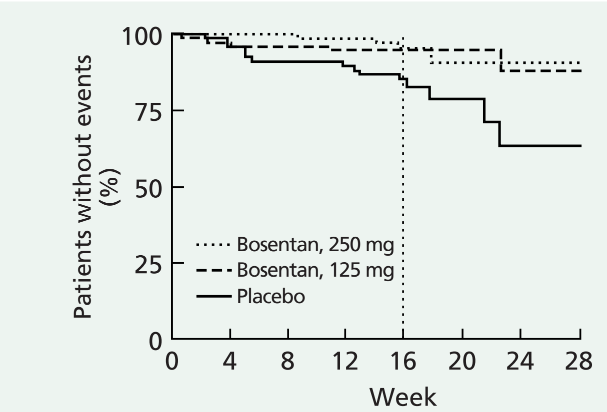


Figure 3. Mean (± SE) change in 6-minute walk distance from baseline to week 16 in patients treated with one of two doses of bosentan or placebo in a randomized prospective trial.[50] *P* < 0.01 for the comparison between the 125-mg dose of bosentan and placebo, and *P* < 0.001 for the comparison between the 250-mg dose and placebo. There was no significant difference between the two bosentan groups. Reprinted with permission from reference 50. Copyright © 2002 Massachusetts Medical Society.



Placebo	69	68	63	62	48	10	7	3
Bosentan, 125 mg	74	72	71	70	55	18	14	7
Bosentan, 250 mg	70	70	70	68	48	13	11	6

Figure 4. Kaplan–Meier estimates of the proportion of patients with clinical worsening in a randomized, prospective, placebo-controlled study of bosentan.[50] Clinical worsening was defined by the combined end point of death, lung transplantation, hospitalization, or discontinuation of the study treatment. *P* < 0.05 for the comparison of the bosentan groups with the placebo group at weeks 16 and 28. There was no significant difference between the two bosentan groups. Reprinted with permission from reference 50. Copyright © 2002 Massachusetts Medical Society.

exhibits smooth muscle mitogenic, proinflammatory, and profibrotic properties via actions on its receptors located on vascular endothelial cells and bronchial smooth muscle cells.[40] Recent evidence suggests that the vasoconstrictive action of endothelin-1 can be mediated via both endothelin receptors.[41]

Endothelin-1 has a prominent role in various forms of pulmonary hypertension. Elevated endothelin-1 levels have been found in patients with primary pulmonary hypertension[42]; PAH associated with scleroderma[43] and systemic lupus erythematosus[44]; and pulmonary hypertension due to chronic hypoxic lung diseases,[45] congenital heart diseases,[46] and congestive heart failure.[47] Endothelin-1 levels are associated with disease severity and have been shown to decrease with epoprostenol therapy.[48]

Bosentan. Because the fibrotic effects of endothelin-1 seem to be mediated via the B receptors, blockade of the B receptors with the dual endothelin receptor antagonist bosentan (Tracleer) may be desirable. Bosentan is currently the only proven effective oral therapy for PAH, as well as the only endothelin receptor antagonist that is commercially available in the United States.

Bosentan has been studied in two randomized, placebo-controlled, double-blind studies involving patients with class III or IV PAH according to the World Health Organization functional classification, which is a modification of the NYHA classification for heart failure. The first study[49] was a 12-week trial in which bosentan was associated with an improvement, compared with placebo, in 6-minute walk distance, functional capacity, score on the Borg dyspnea index, pulmonary artery pressure, pulmonary vascular resistance, and cardiac output.

The larger Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE-1)[50] enrolled 213 patients with PAH (primary pulmonary hypertension or PAH due to connective tissue diseases) who were in WHO functional classes III or IV. Patients were randomized in a 1:1:1 ratio to placebo, bosentan 125 mg twice daily, or bosentan 250 mg twice daily. At 16 weeks, patients in the combined bosentan groups walked 44.2 meters farther than those in the placebo group (95% confidence interval, 21–67 meters) **(Figure 3)** and had greater improvements in their WHO functional class and Borg dyspnea scores. Clinical worsening was noted in 20% of patients in the placebo group compared with 6% of patients in the bosentan groups **(Figure 4)**.

A recent study has also shown an improvement in right ventricular systolic function and left ventricular early diastolic filling and reverse ventricular remodeling with bosentan therapy in patients with PAH.[51]

Although bosentan and treprostinil seem to show equivalent overall efficacy, there was a much smaller magnitude of improvement in 6-minute walk distance in the pivotal treprostinil study[39] than in studies of bosentan, which might be attributable to differences in study cohorts. Whereas the bosentan studies consisted mostly of patients with PAH related to connective tissue disease, most patients in the treprostinil study had primary pulmonary hypertension, although there were some with PAH associated with congenital disease or connective tissue disease. Also, the treprostinil study had some patients with a NYHA classification as low as II, and infusion-site pain made it difficult to reach higher doses in some patients.[39]

A dose-related rise in hepatic aminotransferase levels was noted in bosentan-treated patients in the BREATHE-1 study (3% incidence for patients receiving 125 mg twice daily, 7% for those receiving 250 mg twice daily) but resolved with dose reduction or drug discontinuation.[50] Serum aminotransferase levels must be measured in patients before starting bosentan therapy and monthly thereafter.

Because of the risk of fetal damage with bosentan use, patients should take special care not to become pregnant while on this medication.

Bosentan is approved by the FDA for all forms of PAH in patients in WHO functional classes III or IV **(Table 2)**. Adding bosentan to the regimen of patients already on epoprostenol may be a reasonable strategy in highly symptomatic patients who are deteriorating on symptom-limited doses of epoprostenol, but any recommendation for such combination therapy awaits further evidence. The practice of using bosentan to "wean patients off" epoprostenol is also currently under study.

Sitaxsentan, a specific endothelin A receptor antagonist, is currently also under study in patients with PAH.[52] This investigational agent also is administered orally. Theoretically, sitaxsentan blocks the vasoconstrictive effects of the endothelin A receptor while allowing the vasodilative effects of endothelin B receptor stimulation.

TABLE 2
World Health Organization functional classification of pulmonary hypertension

Class I—Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Class II—Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class III—Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest, but less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV—Patients with pulmonary hypertension who are unable to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea , fatigue, or both may be present even at rest. Discomfort is increased by any physical activity.

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OTHER VASODILATORS

Additional prostacyclin analogues are currently not available in the United States, but the possible benefits of the orally administered beraprost and the inhaled iloprost are under study in Europe.

Nitric oxide is a potent pulmonary vasodilator that is produced in the pulmonary endothelium by the metabolism of L-arginine; it has a key role in pulmonary vascular tone.[53] Inhaled nitric oxide has been used to treat persistent pulmonary hypertension of the newborn[54] as well as adult PAH. In view of its short half-life, its main role to date has been to determine vasodilator responsiveness in patients with PAH.[5,55] Long-term use of inhaled nitric oxide has also been described in patients with primary pulmonary hypertension,[56] but its clinical application has been limited because of the compound's short half-life.

Phosphodiesterase-5 (PDE-5) inhibitors act by causing cyclic GMP levels to increase, which appears to regulate pulmonary vascular tone via nitric oxide. There has been significant enthusiasm for use of the PDE-5 inhibitor sildenafil (Viagra) in PAH because it can reduce pulmonary artery pressure and pulmonary vascular resistance without significantly reducing systemic blood pressure, and also because it is orally administered and well tolerated.

A recent randomized open-label study compared sildenafil with nitric oxide and with epoprostenol in patients with pulmonary hypertension secondary to lung fibrosis, showing a significant reduction in the pulmonary vascular resistance index with sildenafil.[57] In this preliminary study sildenafil appeared to be more potent than nitric oxide and was associated with less systemic hypotension than was epoprostenol. Sildenafil also has been used as adjunctive or rescue therapy in selected patients.[58–62] Studies of the role of sildenafil in pulmonary hypertension are currently under way in the United States and Europe.

L-Arginine is a precursor of nitric oxide in the presence of nitric oxide synthase and is a readily available nutritional supplement that can be taken orally. In a placebo-controlled study of 19 patients with PAH,[63] supplemental L-arginine produced decreases in mean pulmonary artery pressure and pulmonary vascular resistance, an increase in oxygen consumption, a decrease in CO_2 production, and a small but statistically significant decline in mean systemic arterial pressure. Further study is needed to better define the role of oral supplementation of this simple amino acid for the treatment of PAH.

■ ANTICOAGULATION AND OTHER THERAPIES

Anticoagulants. The rationale for anticoagulant therapy for PAH is based on the development of in situ thrombosis seen pathologically in patients with plexogenic pulmonary arteriopathy.[12,64] These patients are at increased risk of thrombosis because of a variety of factors, including dilated right-sided heart chambers, sluggish pulmonary vascular flow, sedentary lifestyle, and venous insufficiency. A clear and significant survival benefit has been observed at 1 and 3 years for anticoagulated over nonanticoagulated patients with PAH.[12,64] The current recommendation is that all patients with PAH should receive anticoagulation therapy with coumarin derivatives to a target international normalized ratio of between 2 and 3[65] unless they have a contraindication.

Diuretic therapy reduces plasma volume and preload and helps treat right ventricular failure, reducing the right atrial pressure. Clinically there is an improvement in jugular venous distention, ascites, peripheral edema, and dyspnea, and thereby an improvement in quality of life. Patients are typically "volume dependent," and volume depletion from overdiuresis may result in significant hypotension and dizziness. Loop diuretics are used alone or in conjunction with a thiazide diuretic or spironolactone in patients with ascites. The role of ACE inhibitors is not completely clear in this population, but sympathetic and renin-angiotensin-aldosterone activation due to severe right heart failure argues in favor of some role. Interesting animal research suggests that pulmonary angiotensin-converting enzyme is important in the pathogenesis of PAH.[66,67]

Supplemental oxygen. Hypoxemia induces pulmonary vasoconstriction in patients with PAH,[68] and hypobaric conditions such as those associated with commercial air travel should be avoided without supplemental oxygen.[69] Although no study has looked specifically at the impact of oxygen therapy in patients with PAH, the Nocturnal Oxygen Therapy Trial showed improved quality of life and survival with oxygen therapy in patients with pulmonary hypertension due to chronic lung disease.[70] Some have argued that patients with PAH, other than those with intracardiac shunts, have only a mild degree of hypoxemia and that it is explained by minimal ventilation-perfusion mismatching and a low mixed venous oxygen level that is due to low cardiac output.[20] This argument maintains that oxygen supplementation rarely, if ever, improves quality of life in patients with PAH.[20] We have shown that patients with PAH may be significantly hypoxemic during sleep and require supplemental oxygen therapy.[71] We believe that all patients with PAH should be screened for hypoxemia with exertion and, if necessary, treated with supplemental oxygen while asleep.

Digoxin and other inotropes have been used to treat pulmonary hypertension, particularly in combination with calcium channel blockers to offset the latter drugs' negative inotropic effects and to increase cardiac output.[72] Catecholamines such as dopamine, dobutamine, and norepinephrine may be used in selected patients under careful hemodynamic monitoring in an attempt to temporarily augment contractility, systemic blood pressure, or both.

■ INDICATIONS FOR SURGICAL THERAPY

Lung transplantation should be the last option in patients with PAH.[73] Improvements in medical management have lowered rates of lung transplantation for PAH and extended the time to transplantation or eliminated the need altogether.[32] Patients in WHO functional class IV or those not responding to medical therapy should be referred for transplant evaluation. International guidelines have been published to direct this process.[74] Heart-lung transplants tend to be reserved for patients with structural cardiac abnormalities. In some circumstances a bridging procedure, such as atrial septostomy, can be used while the patient awaits lung transplantation, but such procedures are associated with significant risk.[75,76]

OTHER MANAGEMENT ISSUES

Perioperative risk. We recently reported in abstract form[77] that untreated patients with moderate to severe PAH had increased perioperative morbidity and mortality rates. Most of the complications were related to the surgical procedure or the underlying disease and not directly to PAH. The few available reports on perioperative risks in patients with PAH are case studies or series[78–80] that have looked predominantly at patients with portopulmonary hypertension undergoing liver transplantation with mixed results. We recommend perioperative pulmonary artery catheter monitoring for all patients undergoing surgery under general anesthesia.

Exercise. Pulmonary artery pressure may increase with exercise in PAH patients, precipitating dyspnea, chest pain, and syncope. The increase may be out of proportion to the rise in cardiac output, owing to exercise-induced pulmonary vasoconstriction[81] and elevated pulmonary vascular resistance.[82] We recommend that patients with PAH not lift objects heavier than 25 pounds or anything that might cause them to strain, causing elevation in intrathoracic pressure. We do encourage low-level cardiovascular, aerobic exercise to prevent deconditioning.

Immunization. Although no studies have specifically addressed the role of immunization in patients with PAH, we believe that routine pneumococcal vaccination and annual influenza vaccination are indicated. Hepatitis A vaccination should be considered in patients with congestive hepatopathy or portopulmonary hypertension.[83,84]

Pregnancy. Patients with PAH must avoid becoming pregnant. The physiologic changes associated with pregnancy severely stress an already overloaded right ventricle.[85] Some form of birth control is mandatory for women of childbearing age who have PAH. There has been concern that the estrogens in oral contraceptives might exacerbate in situ thrombosis,[86] but recent evidence suggests that there is no increased risk from the newer oral contraceptives with a lower estrogen content.[20] Which form of birth control is best remains unknown, but surgical sterilization is the safest and most effective method.

Treatment costs. Formal cost analyses have not been published for the management of PAH. In 2002, *The Medical Letter* addressed cost issues for the three FDA-approved drugs for PAH. According to that analysis,[87] the yearly costs of therapy may be $72,000 for epoprostenol, $93,000 for treprostinil, and $36,000 for bosentan. These numbers do not reflect device-related charges for epoprostenol or treprostinil, nor do they reflect the lab charges for mandatory ongoing liver function tests for bosentan. Additional costs for warfarin, digoxin, or diuretics seem minor in comparison.

Anecdotally, some patients with PAH have quit their jobs, legally separated from their spouses, or moved to other counties to become eligible for Medicaid and obtain coverage for these drugs. Nevertheless, in light of the significant clinical or mortality benefits, these drugs are recommended despite their costs.[88]

Prognosis. Discussing prognosis and end-of-life issues with patients who have PAH is often difficult. The only three therapies associated with a mortality benefit in patients with PAH to date are warfarin, calcium channel blockers, and epoprostenol, and only epoprostenol has been shown to improve survival in a prospective, randomized trial.[18] The cause of death in patients with primary pulmonary hypertension is usually progressive right heart failure or sudden death.[2] A recent study showed dismal results in the outcomes of PAH patients who underwent a circulatory arrest protocol.[89] Intense research for newer and better treatment options and continued outcomes research will help address these issues over time.

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